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Drugs used in the management of heart disease and cardiac arrhythmias

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BACKGROUND

Heart disease is an acquired or congenital abnormality of the cardiovascular system that can be structural, infective, degenerative, inflammatory and often genetic. Many heart diseases have a prolonged preclinical stage characterized by the presence of underlying cardiac disease and the absence of any clinical signs attributable to heart disease. During this stage the cardiovascular system adapts and compensates for the underlying abnormality in an effort to maintain a state that is free from clinical signs of cardiovascular disease. However, more often than not these adaptive mechanisms contribute to the eventual development of clinical signs and can thus be considered maladaptive. When heart disease is severe it overwhelms the ability of the heart and body to compensate and clinical signs of heart failure appear. Although not all heart diseases progress to a degree of severity that result in clinical signs, many do. The development of clinical signs attributable to heart disease identifies the development of heart failure and the onset of the clinical stage of heart disease.

Independent of underlying etiology (see Table 17.1) and species, heart failure is generally defined as the inability of the heart to deliver adequate quantities of blood to meet metabolic tissue demands with normal ventricular diastolic or atrial ('filling') pressures. Heart failure can be clinically classified as backward heart failure and forward heart failure. Backward heart failure almost always predominates and refers to elevated diastolic intraventricular and atrial pressures resulting in increased venous and capillary pressures causing the transudation of fluid into interstitial spaces (edema) or body cavities (ascites). Patients with backward heart failure often have increased systemic and pulmonary blood volumes and so are hypervolemic. They may be euphemistically called 'WET'. Backward heart failure can be subdivided into right, left and biventricular backward heart failure. The clinical presentations suggestive of left-sided congestive heart failure (CHF) are those commensurate with cardiogenic pulmonary edema in dogs and cats and pleural effusion in cats. Clinical signs consistent with right-sided CHF are those commensurate with ascites and pleural effusion. Forward heart failure refers to a lower than normal cardiac output resulting in poor peripheral perfusion. Patients with forward heart failure may be euphemistically called 'COLD'. Clinical presentations suggestive of forward heart failure are those commensurate with poor peripheral perfusion such as exercise intolerance, cold extremities and collapse.

Some medical therapies for heart failure are used independent of the underlying etiology (nonspecific) and some target specific abnormalities associated with the underlying etiology. For example, any patient with cardiogenic pulmonary edema will benefit from rest, oxygen and furosemide but only patients with diastolic dysfunction, such as feline hypertrophic cardiomyopathy, would be expected to benefit from a drug that improves relaxation, such as diltiazem. In addition, many drugs have more than one mechanism of action and so may be used for a variety of indications in different patients. For example, diltiazem is also used in the treatment of atrial fibrillation because as a Class IV antiarrhythmic it can slow down AV node conduction and slow ventricular response rate (heart rate). Finally, consideration must be given to potential side effects and drug interactions as well as client (cost and ease of administration) and patient (suspension, tablet) preferences.

THERAPEUTIC APPROACH TO HEART FAILURE

Clinically we predominantly manage patients with signs of backward heart failure. Isolated forward heart failure is rare. However, patients with signs of backward heart failure are at risk for forward heart failure and thus management of backward heart failure should include therapies targeting preservation of perfusion. In general,

Table 17.1 Causes of heart failure – pathophysiological classification

Heart failure can occur as a result of:

- **Primary reduction of myocardial contractility**
  - Dilated cardiomyopathy
  - Taurine deficiency
  - Chronic myocarditis (rare)
- **Systolic mechanical overload**

Pressure overloading

  - Aortic stenosis and pulmonic stenosis (rare)
  - Pulmonary hypertension

Volume overloading

  - Chronic degenerative valve disease
  - Mitral (rare) and tricuspid dysplasia (relatively rare)
  - Aortic or pulmonic insufficiency (rare)
  - Congenital left-to-right shunts, e.g. patent ductus arteriosus, ventricular septal defect (rare)
- **Diastolic mechanical inhibition**

Pericardial disorders, e.g. pericarditis, cardiac neoplasms

Ventricular myocardial disorders, e.g. feline hypertrophic and restrictive cardiomyopathies (rare)

- **Altered electrical function**

Dysrhythmias

the goal of heart failure therapies is to relieve/reduce clinical signs of backward heart failure, improve/preserve clinical signs of forward heart failure and prolong survival. Some medications work in more than one category, enhancing their potential clinical utility. For example, pimobendan reduces preload and afterload through mixed arterial and venous dilation, augments ventricular systolic function, may help palliate clinical signs attributed to pulmonary artery hypertension and have salutary effects on the maladaptive cytokine profile in heart failure.

Table 17.2 contains an overview of cardiovascular pharmacology. Agents are classified into categories based on mechanism of action. Table 17.3 contains a summary of cardiovascular medications used in the management of common small animal heart disease and is broken down by stage of disease, e.g. clinical versus preclinical. Tables 17.4a and 17.4b provide an overview of the common drugs and their indications in the management of cardiac disease in dogs (17.4a) and cats (17.4b).

Many drugs have more than one mechanism. For example, spironolactone is an aldosterone antagonist that acts as a potassium-sparing diuretic and a neuroendocrine modulator. Enalapril is an angiotensin converting enzyme (ACE) inhibitor with vasodilatory and neuroendocrine modulation properties. For the purpose of this chapter, an agent that has more than one effect will be mentioned in every appropriate section but the majority of the discussion and dosing recommendations will be covered in the section that represents its primary use. In addition, formulations and dose rates are not included for agents that currently have little to no clinical use in small animal veterinary medicine.

Therapeutic approach to backward heart failure (WET)

Relieve clinical signs of congestion

1. Abdominocentesis (dog) and pleurocentesis (cat, rarely dog) as required
2. Preload reduction
   a. Plasma volume reduction
      i. Diuretics such as furosemide, hydrochlorothiazide, spironolactone (especially right heart failure)
   b. Venodilation
      i. Nitroglycerine (topical), pimobendan
   c. Dietary sodium restriction
3. Inhibition of the renin-angiotensin-aldosterone system (RAAS)
   a. ACE inhibitors such as enalapril or benazepril
   b. Aldosterone antagonist such as spironolactone
4. Improve diastolic dysfunction if present
   a. Feline hypertrophic cardiomyopathy
      i. Calcium channel blocker such as diltiazem

Therapeutic approach to forward heart failure (COLD)

Improve forward cardiac output

1. Afterload reduction
   a. Contraindicated in feline obstructive cardiomyopathy and canine subaortic stenosis
      i. ACE inhibitors, hydralazine, amlodipine, pimobendan, Na nitroprusside (IV)
2. Augment systolic myocardial function in diseases characterized by systolic myocardial dysfunction
   a. Canine and feline dilated cardiomyopathy (DCM)
   b. Canine chronic valve disease (CVD)
      i. Pimobendan, dobutamine (IV), digoxin (weak inotrope)
3. Treat clinically important (hemodynamically significant) arrhythmias
   a. Tachyarrhythmias
      i. Ventricular
         Lidocaine (IV), procainamide, sotalol, amiodarone
      ii. Supraventricular (excluding sinus tachycardia)
         Digoxin, β-blocker, calcium channel blocker, amiodarone, sotalol
   b. Bradyarrhythmias
      i. Pacemaker

Table 17.2 Cardiovascular pharmacology overview

Category	Common drugs	Common indications
Afterload reducers	1. Hydralazine [0;****;2] 2. ACE inhibitor [0;*;2]: e.g. enalapril, benazepril 3. Calcium channel blocker: amlodipine [0;****;4] 4. Pimobendan [0;***;2] 5. Nitroprusside [I;*****;1]	1. Systemic hypertension 2. Systolic dysfunction: – Dilated cardiomyopathy (DCM) – Chronic valvular disease (CVD)
Preload reducers	A. Diuretics: 1. Furosemide [0,I,S,M;*****;5] 2. Spironolactone [0;*;1] 3. Thiazides [0;**;2] B. Venodilators 1. Nitroglycerin [I;T;*;1] 2. Pimobendan [0,**,2]	1. Left-sided and right-sided congestive heart failure (CHF) Note: spironolactone may be more useful in right heart failure
Positive inotropes (↑ strength of contraction)	1. Digoxin [0;1/4*;1] 2. Pimobendan [0; ****;5] 3. Adrenergic agonists: e.g. dobutamine [I;*****;4], epinephrine [I;***,2]	1. Systolic dysfunction: – DCM – CVD
Positive lusiotropes (improve relaxation)	1. Ca channel blocker: diltiazem [0;***;2] 2. β-blocker: atenolol [0;**;3], carvedilol [0;**;1]	1. Diastolic dysfunction: – Hypertrophic cardiomyopathy (HCM)
Positive chronotropes (↑ heart rate)	1. Adrenergic agonists: dobutamine [I;***;2], isoproterenol [I,****;2] 2. Anticholinergics [I,S,M;****;4]: atropine, glycopyrrolate	1. Hemodynamically important bradyarrhythmias, e.g. sinus bradycardia, AV block
Negative chronotropes	1. β-blocker [0;***;2]: atenolol, carvedilol 2. Ca channel blocker: diltiazem [0;***;3] 3. Digoxin [0;**;2] 4. Amiodarone [0;***;4]	1. Tachycardia: atrial fibrillation and other hemodynamically significant supraventricular arrhythmias Note: often require combination therapy, e.g. digoxin and diltiazem
Vasopressors (peripheral vasoconstriction)	1. Adrenergic agonists: dopamine, [I,***,2], epinephrine [I;***;2] 2. Vasopressin [I;***;3]	1. Hypotension that is unrelated to low cardiac output, e.g. shock, endothelial dysfunction
Neurohumoral modulators	1. β-blockers: carvedilol [0;***;4] 2. ACE inhibitors [0;****;5]: enalapril 3. Aldosterone antagonist: spironolactone [0;**;4] 4. Digoxin [0;**;2]	1. This category of medication is used in an attempt to delay the progression of both preclinical and clinical heart disease and combination therapy may be superior to monotherapy, e.g. ACE inhibitor + β-blocker Dog: DCM and CVD Cat: cardiomyopathies
Antiarrhythmics: Class I (#1–4) Class II (#5) Class III (#6&7) Class IV (#8) Other (#9)	1. Lidocaine [I;*****;5] 2. A Procainamide [I,M;***;4] B Procainamide [0;**;2] 3. Quinidine [0,I;***;2, only horses) 4. Mixelitine [0;***;2] 5. β-blockers [0;**;2] 6. Amiodarone [0,I;****;4] 7. Sotalol [0;****;4] 8. Ca channel blocker: diltiazem [0,I;***;4] 9. Digoxin [0;**;2]	1. Acute ventricular arrhythmias (VA) 2. A Acute supraventricular arrhythmias (SVA) B Chronic VA 3. Atrial fibrillation 4. Chronic VA (better in combination with 5) 5. Chronic SVA and VA (usually in combination) 6. Chronic and acute SVA and VA 7. Chronic VA (especially boxers) 8. Acute and chronic SVA 9. Chronic SVA (best in combination with 5 or 8)

[Route of delivery; Relative potency in category as monotherapy; Author preference/frequency of use within category], where route of administration (O, oral; I, IV; S, SQ; M, intramuscular; T, topical), Relative drug potency by effect within a category when used as monotherapy (****high, *low). Authors' preference by category (5 high, 1 low). If [0,**,4] is for the whole class it follows the class, e.g. ACE inhibitors, but if it is for a specific drug within a class it follows each drug, e.g. diuretics. Note potencies are for category that drug is listed in and authors' preference is for category effect and some drugs appear in more than one category because they have polypharmacy effects. For example, pimobendan is a strong positive inotrope and is our first preference in this category as an oral drug and although it is an afterload reducer and this is a desirable property, if we need to select an afterload reducer we would pick amlodipine empirically as it is more potent but we would still use pimobendan for its combination of effects in canine CHF.
Note: Most common SVA = atrial fibrillation.

Table 17.3 Summary of cardiovascular medications used in the management of common heart disease

Species		Disease	Preclinical Stage	Clinical Stage
Dog	Chronic valve disease	Sinus rhythm	NT [3], ACEI [2], β-blocker [2]	Diuretic (furosemide) [5]*, Pimobendan [5]*, ACEI [5], spironolactone [3], β-blocker [1]
		Atrial fibrillation or other supraventricular arrhythmias	NT [2], β-blocker [2]	As per sinus rhythm and add: amiodarone [3], digoxin [3], β-blocker [3], CCB [3] *Note: combination therapy may be necessary*
		Ventricular arrhythmias	NT [2], β-blocker [3]	As per sinus rhythm and add: sotalol [3], β-blocker & mexilitine [1]
		Left atrial enlargement causing left main stem bronchus compression	NT [2], ACEI [2], β-blocker [1–2]	As per sinus rhythm and add: theophylline SR [4], hydrocodone [3]
		Pulmonary artery hypertension		As per sinus rhythm: increase pimbendan dosing frequency to 3 times daily [4] and/or add sildenafil [3]
	Dilated cardiomyopathy	Sinus rhythm	NT [1], ACEI [4]*, β-blocker [2]	Diuretic (furosemide) [5]*, Pimobendan [5]*, ACEI [5]*, spironolactone [3], β-blocker [1]
		Atrial fibrillation or other supraventricular arrhythmias	NT [1], β-blocker [3], CCB [2]	As per sinus rhythm and add: amiodarone [3], digoxin [3], β-blocker [2], CCB [2] *Note: combination therapy may be necessary*
		Ventricular arrhythmias	ACEI [4], β-blocker [3]	As per sinus rhythm and add: amiodarone [3], sotalol [3], β-blocker & mexilitine [2], mexilitine [1]
Cat	Hypertrophic cardiomyopathy		ACEI [3], CCB [2], β-blocker [3]	Diuretic (furosemide) [5]*, ACEI [4]*, CCB [1], β-blocker [1–2]
	Intermediate or restrictive cardiomyopathy		ACEI [3], CCB [1], β-blocker [1]	Diuretic (furosemide) [5]*, ACEI [5]*, CCB [1], β-blocker [1]
	Dilated cardiomyopathy		ACEI [4], β-blocker [1] +/– taurine	Diuretic (furosemide) [5]*, ACEI [5]*, β-blocker [1]
	Arrhythmogenic right ventricular cardiomyopathy		ACEI [3–4], β-blocker [1]	Diuretic (furosemide) [4], ACEI [5], sotalol [3]

Note: *Clinical disease* is defined as the stage of disease when a patient ***has or had*** clinical signs attributable to their cardiovascular disease (e.g. cough due to cardiogenic pulmonary edema and or left atrial enlargement causing left main stem bronchial compression either at the time of the current exam or previously). Thus dogs with clinical disease may not have current clinical signs of disease if they are stable on medication. ***Preclinical disease*** is defined as the stage of disease when a patient has evidence of cardiovascular disease but currently or previously has no clinical signs that can be attributed to their underlying cardiovascular disease e.g. clinically normal dogs with heart murmurs characteristic of chronic valve disease or evidence of radiographic or echocardiographic left atrial enlargement who historically and currently have no clinical signs of cardiovascular disease. There is no definitive proof that any medication used during the preclinical stage of any listed disease can prolong the preclinical stage thus the numbers in [ ] represent the authors' views of current recommendations and no therapy is always an option.

Drugs are listed by class (e.g. angiotensin converting enzyme inhibitor) and if there is a preferred drug within a class it follows in brackets. Each class or specific drug listed is scored between 1 and 5 where [1] means rarely used and [5] means always used unless there is a clinical contraindication. Diuretic (furosemide) is always used if congestion is or was present. * denotes which medication should be used if number or medications to be used is limited. This summary is based on professional opinion/experience and currently available peer reviewed data and can be expected to evolve over time.

Angiotensin converting enzyme inhibitor (ACEI); beta-blocker (β-blocker); calcium channel blocker (CCB); no therapy (NT).

Table 17.4a Drugs commonly used for the therapy of canine heart failure

Drug	Preparation	Dosage	Indications (I) and potential toxicity (T)
AMIODARONE	Cordarone or generic (cheaper): 200, 400 mg tablets	DOG: 10-20 mg/kg q.24 h for 7-10 days then reduce to 3-15 mg/kg q.24-48 h chronically	I: hemodynamically significant ventricular or supraventricular arrhythmias (SVT, atrial fib) T: anorexia and elevated liver enzymes, neutropenia, etc. and potential proarrhythmic
AMLODIPINE Note: gradual uptitration required	Norvasc: 2.5, 5 mg tablets	DOG: 0.01-1 mg/kg PO q.12-24 h	I: hypertension T: hypotension
ATENOLOL Note: gradual uptitration required	Tenormin: 25, 50, 100 mg tablets	DOG: 6.25-12.5 mg q.12 h	I: diastolic dysfunction and hemodynamically significant ventricular or supraventricular arrhythmias (SVT, atrial fib) T: negative inotrope and chronotrope, beware decompensation
BENAZEPRIL	Lotensin: 5, 10, 20, 40 mg tablets	DOG: 0.3-0.5 mg/kg q.12-24 h	I: CHF (CVD, DCM), systemic hypertension T: beware azotemia and potential for interaction with NSAIDS
CARVEDILOL Note: gradual uptitration required	Coreg: 3.125, 6.25, 12.5, 25 mg tablets Note: can split in two but hard to split in 4. Can be formulated into suspension	DOG: 0.1-1 mg/kg PO q.12 h Note: 1 mg/kg is target dose and you will need to uptitrate to achieve this dose safely	I: occult systolic dysfunction (CVD, DCM) T: negative inotrope and chronotrope, beware decompensation
DIGOXIN	Lanoxin, Cardoxin, Digoxin USP: 0.125, 0.25, 0.5 mg tablets; 0.05 mg/mL and 0.15 mg/mL elixirs	DOG: 0.0055-0.011 mg/kg q.12 h or 0.22 mg/meter sq.body surface area q.12 h Note: err on low dose side to limit toxicity	I: heart failure, supraventricular tachyarrhythmias (SVT, atrial fib) T: GI (anorexia and vomiting), arrhythmias Note: toxicity potentiated by renal insufficiency
DILTIAZEM Note: gradual uptitration required	A. Nonsustained release: Cardizem: 30, 60, 90, 120 mg tablets B. Sustained release: Dilacor XR	DOG: 0.5-1.3 mg/kg orally q.8 h DOG: 2-4 mg/kg orally q.12 h	I: hemodynamically significant supraventricular arrhythmias (SVT, atrial fib) T: negative inotrope and chronotrope, beware decompensation
DOBUTAMINE	Dobutrex: 250 mg (20 mL) vial for injection	DOG: 2.5-20 μg/kg/min, constant rate IV infusion	I: severe systolic dysfunction (CVD, DCM) T: tachyarrhythmias
ENALAPRIL	Enacard: 1, 2.5, 5, 10 mg tablets	DOG: 0.25-0.5 mg/kg orally once or twice daily	I: CHF (CVD, DCM), systemic hypertension T: beware azotemia and potential for interaction with NSAIDS
FUROSEMIDE	Lasix: 12.5 [Vet] mg, 20, 40, 50 [Vet], 80 mg tablets; 1% syrup (10 mg/mL)	DOG: 2-6 mg/kg repeated q.2-12 h as needed (IV, IM, SQ, oral)	I: CHF T: hypotension, dehydration, hypokalemia, metabolic alkalosis
HYDRALAZINE Note: gradual uptitration required	Apresoline: 10, 25, 50 mg tablets	DOG: 0.5-3 mg/kg orally q.12 h (initial dose 0.5 mg/kg, titrate to effect or to at least 1 mg/kg q.12 h)	I: CHF, hypertension T: hypotension, GI
HYDROCHLOROTHIAZIDE (HCT) and SPIRONOLACTONE	Hydrodiuril, USP: 25, 50 mg tablets; Aldactazide: 25 mg HCT combined with 25 mg spironolactone	DOG: 2-4 mg/kg twice daily of either HCT or combined product Note: these are monotherapy doses	I: CHF T: hypotension, dehydration, hypokalemia, azotemia Note: reduce furosemide dose by 50% when starting HCT
LISINOPRIL	Zestril, Prinavil	DOG: 0.5 mg/kg PO q.24 h	I: CHF (CVD, DCM), systemic hypertension T: beware azotemia and potential for interaction with NSAIDS

Table 17.4a Drugs commonly used for the therapy of canine heart failure (*continued*)

Drug	Preparation	Dosage	Indications (I) and potential toxicity (T)
MEXILETINE	Mexitil: 150, 200, 250 mg capsules	DOG: 4–8 mg/kg PO q.8 h	I: hemodynamically significant ventricular arrhythmias T: anorexia and liver toxicity and potential proarrhythmic Note: may work best when combined with atenolol
PIMOBENDAN	Vetmedin: 1.25, 2.5, 5 mg capsules Note: not available in USA yet	DOG: 0.25–0.3 mg/kg PO q.12 h	I: CHF (CVD, DCM), pulmonary artery hypertension T: potential proarrhythmic?, hypotension
CLOPIDOGREL	Plavix 75 mg tablet	DOG: 1–2 mg/kg PO q.24 h Chronic (after 3 weeks) 1 mg/kg q.24 h Loading for acute effects (with in 90 min) 10 mg/kg PO	I: antiplatelet T: potential bleeding Note: If von Willebrand's deficiency is possible a VMB level should be determined before starting Plavix. Bleeding times are not sufficient
PROCAINAMIDE (sustained release)	Pronestyl SR or generic procainamide SR 250, 500, 750, 1000 mg oral 100 mg/mL, 10 mL vial or 500 mg/mL, 2 mL vial	DOG: 10–20 mg/kg PO q.8 h 5–25 mg/kg slow IV (10 min) 25–50 µg/kg/min as CRI to effect	I: hemodynamically significant ventricular and supraventricular (IV only) arrhythmias T: oral– anorexia, coat color change; IV –hypotension and potential proarrhythmic
NITROGLYCERIN	Nitrol, Nitro-bid, Nitrostat: one inch = 15 mg NTG; Minitran transderm patches 2.5, 5, 10, 15 mg/24 h	DOG: 4–12 mg (up to 15 mg) topically q.12 h	I: CHF T: hypotension
SILDENAFIL Note: gradual uptitration required	Viagra: 25, 50, 100 mg tablets	DOG: 0.25–3 mg/kg PO q.12 h	I: end-stage pulmonary artery hypertension T: hypotension Note: slow uptitration preferred but may be rapid in acute situation
SOTALOL	Betapace: 80, 160, 240 mg tablets	DOG: 0.5–2 mg/kg PO q.12 h	I: hemodynamically significant ventricular arrhythmias T: negative inotrope and chronotrope, beware decompensation, and potential proarrhythmic
SPIRONOLACTONE	Aldactone: 25, 50, 100 mg tablets	DOG: 0.25–1 mg/kg PO q.12 h antifibrotic effects DOG: 1–2 mg/kg PO q.12 h for diuretic effect	I: reverse remodeling, K-sparing diuresis, RAAS inhibition T: hyperkalemia especially when combined with an ACEI in the absence of furosemide

Echo sedation: (1) Preclinical young dog: combination of buprenorphine (0.007 mg/kg, IV or IM) and acepromazine (0.02–0.03 mg/kg, never >1 mg total, IV or IM). (2) Older or clinical dog: buprenorphine (0.007 mg/kg, IV or IM). (3) Dyspneic or very old clinical dog: butorphanol 0.2 mg/kg, IV or IM.
Taurine supplementation: Medium dog: 500 mg q.12 h; large dog: 1000 mg q.12 h.
L-carnitine supplementation: 1–3 g q.12 h.
Note: Therapeutic recommendations reflect the authors' opinion and are based on review of available data.

   ii. Anticholinergics
      Propantheline bromide
      Atropine sulfate (IV)
   iii. Sympathomimetics
      Terbutaline
   iv. Other
      Theopylline
4. Treat pulmonary artery hypertension if present and contributing to clinical signs
   a. Phosphodiesterase V inhibition
      i. Sildenifil, pimobendan

Therapeutic approach for all heart failure (WET or COLD)

Agents in this category have the potential to prolong survival in all patients with clinical heart disease or heart failure. Medications that improve perfusion and/

Table 17.4b Feline cardiovascular medication chart

Drug	Class	Dose (per cat)	Dose (mg/kg)
Enalapril* or benazepril*	ACEI	PO: 1-2.5 mg q.12-24 h	PO: 0.2-0.7 mg/kg q.12-24 h
1. Diltiazem 2. Cardizem CD 3. Dilacor XR	Calcium channel blocker	1. PO: 7.5 mg q.8 h 3. PO: 30-60 mg q.12-24 h	2. PO: 10 mg/kg q.24 h
Atenolol*	β-blocker	PO: 3.125-12.5 mg q.12-24 h	PO: 1.1-2.5 mg/kg q.12-24 h
Atenolol, low dose*	β-blocker	PO: 1-3.125 mg q.24 h Uptitrate if well tolerated	
Furosemide*	Diuretic	PO: 3.125-12.5 mg q.12-48 h	PO: 1-2 mg/kg q.12-48 h IV/IM/SQ: 0.5-2 mg/kg PRN
Hydrochlorothiazide*	Diuretic	PO: 6.25-12.5 mg q.12 h	PO: 2-4 mg/kg q.12 h
Spironolactone*	Aldosterone antagonist	PO: 6.25 mg q.12 h	PO: 1-2 mg/kg q.12 h
Digoxin	Cardiac glycoside	PO: 0.031 mg q.24-48 h ¼ of 0.125 mg tablet	
Aspirin	NSAID	PO: 81 mg q.3 d	PO: 25 mg/kg q.3 d
Sotalol*	Antiarrhythmic β-blocker	PO: 10 mg q.12 h	
Nitroglycerin paste	Vasodilator	Topical: 1/8-1/4 inch q.6-8 h	
Low molecular weight heparin	Antithrombotic		SQ: 100 IU/kg q.12-24 h
Butorphanol	Anxiolytic		IV/IM/SQ: 0.2 mg/kg PRN
Taurine	Amino acid	PO: 250-500 mg q.12 h	
Clopidogrel (Plavix)	Thienopyridine	18.75-75 mg PO q.24 h	

Can be formulated as a suspension by a formulation pharmacy.
Echo sedation medetomadine 20 μg/kg IM.
Note: Therapeutic recommendations reflect the authors' opinion and are based on review of available data.

or reduce congestion can be expected to reduce euthanasia-associated mortality.

Prolong survival

1. Inhibition of the RAAS
   a. ACE inhibitors
      i. Enalapril, benazepril
   b. Aldosterone antagonism
      i. Spironolactone
2. Inhibition of the sympathetic nervous system
   a. β-Blockers
      i. Atenolol and metroprolol (selective), propranolol (nonselective; unproven in dogs and cats)
   b. Adrenergic blockers (α- and β-blockade)
      i. Carvedilol
3. Improve diastolic function
   a. Feline hypertrophic cardiomyopathy (HCM)
      i. Calcium channel blocker such as diltiazem
      ii. β-Blocker such as atenolol (prolongs diastolic filling period)
4. Other
   a. Modulation of cytokine maladaption
      i. Pimobendan
   b. Prevention of thrombosis in heart diseases associated with increased risk
      i. Feline hypertrophic cardiomyopathy
         Antiplatelet agents such as clopidogrel
         Anticoagulants such as coumadin, heparin (IV, SQ) and low molecular weight heparin (IV, SQ)
   c. Antioxidants
      i. Carvedilol
      ii. Omega 3 fatty acid supplementation
   d. Complementary therapy
      i. Taurine
      ii. L-carnitine

Therapeutic approach for preclinical heart disease

Agents in this class target primarily mechanisms involved in the progression of heart disease. However, to date, no therapeutic agent has been demonstrated to delay the progression of any canine or feline preclinical heart disease and thus agents listed in this section are candidate therapies.

Prolong preclinical stage of disease

1. Inhibition of the RAAS
   a. ACE inhibitors
      i. Enalapril, benazepril
   b. Aldosterone antagonism
      i. Spironolactone

2. Inhibition of the sympathetic nervous system
   a. β-Blockers
      i. Atenolol and metroprolol (selective), propranolol (nonselective)
   b. Adrenergic blockers (α- and β-blockade)
      i. Carvedilol
3. Improve diastolic function
   a. Feline hypertrophic cardiomyopathy
      i. Calcium channel blocker such as diltiazem
      ii. β-Blocker such as atenolol
4. Other
   a. Prevention of thrombosis in heart diseases associated with increased risk
      i. Feline hypertrophic cardiomyopathy
         Antiplatelet agents such as clopidogrel
         Anticoagulants such as coumadin, heparin (IV, SQ) and low molecular weight heparin (IV, SQ)
   b. Antioxidants
      i. Carvedilol
      ii. Omega 3 fatty acid supplementation
   c. Complementary therapy
      i. Taurine
      ii. L-carnitine

WHICH THERAPY FOR WHICH CONDITION?

To date, there are few adequately powered prospective veterinary clinical studies to support definitive therapeutic recommendations regarding the treatment of clinical and preclinical heart disease secondary to any etiology. Evidence-based therapeutic recommendations for most cardiac diseases await adequately powered prospective clinical trials. Until that time, therapeutic decisions in patients with clinical signs of heart disease should be based on specific clinical signs, characterization of the underlying heart disease and individual response to therapy. In patients with preclinical heart disease therapeutic recommendations should be made based on the presence, severity and prognosis for the underlying cardiac disease. Finally, all therapeutic recommendations should be made in light of any important comorbidities and should be guided by follow-up evaluations as well as client and patient preferences.

The following classification system was modified from that of the American College of Cardiology and the American Heart Association.

Grade A evidence: Recommendations derived from multiple randomized clinical trials

Grade B evidence: Recommendations derived from small randomized trials and careful analysis of descriptive retrospective and case–control studies

Grade C evidence: Recommendations based on expert opinion and extrapolation from human and experimental literature

However, it is of interest to note that diuretics are inarguably useful to ameliorate clinical signs of congestion despite the absence of Grade A and Grade B data and remain a cornerstone of conventional CHF therapy independent of underlying etiology.

Canine dilated cardiomyopathy (DCM)

Preclinical

ACE inhibitors have been demonstrated to prolong the preclinical stage of DCM in some Doberman pinschers and may be more beneficial in males than females (Grade B evidence). There is overwhelming support for their use in human preclinical DCM and they are commonly used in preclinical canine DCM (Grade C evidence). As there is strong support in the human literature for the use of gradual β-blockade in human DCM, scientific rationale supports their potential utility in preclinical canine DCM (Grade C evidence). One small clinical trial, however, did not show any benefit.

Clinical

In addition to diuretics for the amelioration of clinical signs of congestion, there is strong evidence to support the use of ACE inhibitors and pimobendan in clinical canine DCM (Grade A and C evidence). Other agents may be useful in certain cases such as carnitine and taurine supplementation in cocker spaniels with clinical DCM (Grade B evidence). Gradual β-blockade improves mortality in people with DCM but has not been prospectively evaluated in the dog and carries a relative risk of decompensation in all patients with heart failure (Grade C evidence). Spironolactone has been demonstrated to reduce mortality in human patients with DCM and thus may be useful in clinical canine DCM but remains unevaluated in the veterinary literature at this time (Grade C evidence).

Canine chronic degenerative AV valve disease (CVD)

Preclinical

ACE inhibitors have been demonstrated *not* to prolong the preclinical stage of CVD (Grade B evidence). There is some scientific rationale and short-term canine clinical trials that suggest that gradual β-blockade may prolong the preclinical stage of CVD (Grade C evidence). Thus currently no medication has been proven to prolong the preclinical stage of canine CVD.

Clinical

In addition to diuretics for the amelioration of clinical signs of congestion, there is strong evidence to support the use of ACE inhibitors and pimobendan in clinical canine CVD (Grade A and C evidence). Gradual β-blockade may be useful, but has not been prospectively evaluated, in the dog and carries a relative risk of decompensation in all patients with heart failure (Grade C evidence). Digoxin and spironolactone have been demonstrated to reduce mortality and/or morbidity in human patients with clinical DCM. They therefore may be useful in clinical canine CVD but remain unevaluated in the veterinary literature (Grade C evidence).

Feline cardiomyopathies

Given the absence of clinical trial data on specific cardiomyopathies, comments will be made in general and any exceptions will be mentioned.

Preclinical

There are no definitive recommendations for any cardiomyopathy. In general, recommendations reflect the underlying severity of the cardiomyopathy in combination with an agent's safety, tolerability (dosing form and frequency) and potential to prolong the preclinical stage based on scientific rationale (Grade C evidence).

- There is no evidence that hypertrophic cardiomyopathy (HCM) benefits from diltiazem or an ACE inhibitor.
- Patients with hypertrophic obstructive cardiomyopathy (HOCM) may benefit from a β-blocker.
- There is no evidence that any drug alters the natural history of arrhythmogenic right ventricular cardiomyopathy (ARVC).
- If dilated cardiomyopathy (DCM) is due to taurine deficiency, taurine supplementation is generally curative (Grade B evidence). There is no evidence that any other intervention is beneficial.

Clinical

In addition to diuretics for the amelioration of clinical signs of congestion, there is evidence to support the use of ACE inhibitors in all feline cardiomyopathies (Grade B and C evidence). In addition, all cats with significant left atrial enlargement have an increased risk of thromboembolic complications and may benefit from thrombotic prophylaxis such as clopidogrel (Grade C evidence). Additional therapies may be indicated on an individual basis.

DRUGS USED TO TREAT HEART FAILURE

DIURETICS

EXAMPLES

Loop diuretics: furosemide, bumetanide, ethacrynic acid
Thiazide diuretics: hydrochlorothiazide, chlorothiazide
Potassium-sparing diuretics: spironolactone, triamterene, amiloride

Clinical applications

In most patients with heart failure, edema is primarily the direct consequence of an increase in blood volume. Blood volume may be increased by as much as 30% in dogs with severe heart failure. Diuretics decrease edema formation by decreasing this excess blood volume. The decrease in blood volume results in decreases in diastolic intraventricular, venous and capillary pressures.

Diuretics, especially the loop diuretics, are the most important and most efficacious class of drugs used for treating heart failure. Most heart failure patients, if left untreated, would die of severe edema or effusions. Consequently, the primary goal in these patients is to control the formation of edema and effusion. Although other agents, such as ACE inhibitors, nitrates and pimobendan, and sodium-restricted diets may be used for this purpose, their ability to control edema formation is at least one order of magnitude less than the loop diuretics such as furosemide.

Mechanism of action

Diuretics increase urine flow by increasing renal plasma flow or by altering nephron function. Diuretics that increase renal plasma flow by expanding plasma volume (e.g. mannitol, hetastarch) are contraindicated in patients with heart failure because they increase venous and capillary pressures and thus increase edema formation. Agents that alter nephron function increase urine production by interfering with ion transport or the action of aldosterone or antidiuretic hormone (ADH) within the nephron.

Agents that interfere with ion transport do so by altering (1) intracellular ionic entry, (2) energy generation and use for ion transport, or (3) ion transfer from the cell to the peritubular capillaries through the antiluminal membrane. Agents that interfere with ion transport also differ as to their site of action within the nephron. In general, agents that act on the loop of Henle are the most potent.

Three classes of diuretics are used clinically in dogs to treat heart failure: loop diuretics, thiazide diuretics and potassium-sparing diuretics. They differ in their

ability to promote sodium and thus water excretion and in mechanism of action. The loop diuretics are the most potent and can be used in small doses in patients with mild to moderate heart failure and in higher doses in patients with severe heart failure. They can be administered orally for chronic administration or can be administered parenterally to patients with acute, severe heart failure. Thiazide diuretics are mildly to moderately potent agents. They are most commonly used in conjunction with a loop diuretic in patients with severe CHF that have become refractory to loop diuretics over time. Historically, the use of potassium-sparing diuretics has been reserved for those patients that become hypokalemic secondary to the use of other diuretics and for patients refractory to other agents because of an elevated plasma aldosterone concentration. In the latter situation, potassium-sparing diuretics are administered in conjunction with another diuretic, usually a loop diuretic. More recently, the potassium-sparing diuretic and aldosterone antagonist spironolactone has been used as an inhibitor of the renin-angiotensin-aldosterone system alone or in combination with an ACE inhibitor. If it is used in combination with an ACE inhibitor there is a risk of clinically significant hyperkalemia. This is minimized if furosemide is administered concurrently.

Adverse effects

Diuretic therapy has the potential to cause undesirable effects, primarily electrolyte disturbances, dehydration and prerenal and renal azotemia. The relative risks of azotemia are heightened when they are used concurrently with ACE inhibitors and/or nonsteroidal anti-inflammatories (NSAIDs) and other potential renal toxins. Diuretics may also increase the risk of digoxin toxicity.

Electrolyte abnormalities

- Electrolyte disturbances are less common in dogs and cats than they are in humans. However, they can occur, especially in those canine and feline patients that are not eating and/or drinking normally, or in patients administered acute, high-dose therapy.
- Cats appear to be more susceptible than dogs to becoming electrolyte depleted and dehydrated with diuretic therapy. This may be because of a species difference in drug effect but is more probably caused by the fact that cats tend to stop eating and drinking more readily when they are unwell.
- Hypokalemia is one of the more common undesirable effects. However, two studies have documented that the incidence of hypokalemia is low in dogs administered furosemide chronically and who are eating and drinking normally. Hypokalemia is always a significant risk, even in dogs that eat, when sequential nephron blockade is initiated with a rescue diuretic such as hydrochlorothiazide. Dogs that are hypokalemic and hypomagnesemic may not respond to potassium supplementation alone.
- Hyponatremia may occur in patients on high dose diuretic therapy. Patients with severe heart failure may also become hyponatremic through inappropriate antidiuretic hormone secretion and resultant water retention. It may be impossible to distinguish between these two causes in some heart failure patients. No primary corrective therapy is recommended.
- Hypomagnesemia may occur but the incidence in dogs with heart failure receiving diuretics is very low. In one study, there was no significant difference in serum magnesium concentration between control dogs and dogs with heart failure treated with diuretics ± digoxin. In another study of 113 dogs with heart failure, only four had a low serum magnesium concentration. Hypomagnesemia may accompany hypokalemia. Dogs that are hypokalemic and hypomagnesemic may not respond to potassium supplementation alone.

Note: electrolyte abnormalities can be profound when sequential nephron blockade is employed. Potassium supplementation may help with normalization of potassium concentrations. Hypochloremia and hyponatremia should not be corrected via supplementation of parenteral fluids.

Dehydration and prerenal azotemia

Subclinical hypovolemia (dehydration) is probably common in patients with severe heart failure that require maximum doses of diuretics to treat their heart failure. At times patients can become clinically dehydrated and, in some, prerenal azotemia will be present. If the patient is clinically affected (e.g. not eating), the diuretic dose must be reduced or discontinued temporarily and in some cases judicious intravenous fluid therapy must be employed. However, in patients that are not clinically affected by their dehydration and azotemia, the prerenal azotemia can be safely ignored as long as it is not severe or obviously progressive on serial analysis (e.g. urea <30 mmol/L).

Diuretic resistance

There are numerous factors that determine the response to diuretic therapy. These include the potency of the drug, the dosage administered, the duration of action of the drug, the route of administration, renal blood flow, glomerular filtration rate and nephron function. For example, furosemide must be delivered to its site of action in the loop of Henle to produce its effect. The number of molecules of furosemide that reach the site

of action depends on the concentration of the drug in plasma and renal blood flow. The plasma concentration depends on the route of administration (intravenous administration will produce a higher concentration than oral administration) and the dose. The duration of effect will also determine the total diuretic effect produced in a certain time period.

Patients with CHF may become refractory to furosemide because of decreased delivery of the drug to the nephron as a result of reduced renal blood flow or hormonal stimulus for sodium and water retention. Drug delivery may be increased by administering a drug that may increase renal blood flow, such as an arterial dilator (e.g. hydralazine). However, afterload reduction with an arterial dilator must be done cautiously in patients with heart failure because of the risk of hypotension. Alternatively, a potent inotrope such as dobutamine (short term) or pimobendan (chronic) may improve cardiac output and thus renal blood flow. Delivery can also be increased by increasing plasma concentration. This is most readily accomplished by administering the drug parenterally (e.g. intravenous, intramuscular, subcutaneous). Administering the drug as a constant rate infusion (CRI) may be superior in the acute situation because it provides continual nephron delivery over the duration of the CRI, optimizing diuresis. However, a thoughtful bolus administration protocol works very well and does not require the special equipment that is needed for a CRI.

Heart failure and diuretic administration stimulate the RAAS, resulting in a marked increase in plasma aldosterone concentration. Aldosterone counteracts the effects of a diuretic and may contribute to diuretic resistance. Consequently, the administration of an ACE inhibitor will be beneficial if tolerated. Furosemide administration produces hypertrophy of the distal convoluted tubular cells and increases ion transport capacity in this region in rats. This shifts the dose–response curve to the right and downward in humans. If this also occurs in cats and dogs, it may also contribute to diuretic resistance.

It is possible that oral bioavailability of furosemide is decreased in patients with right heart failure. Gastrointestinal edema is the reputed offender in this scenario. However, it was documented in humans that massive fluid accumulation due to heart failure does not alter the pharmacokinetics of furosemide.

Loop diuretics

EXAMPLES

Furosemide (authors' preference), bumetanide, torsemide (torasemide), ethacrynic acid (not in dogs and cats)

Furosemide

Furosemide is a loop diuretic and the most commonly used diuretic for treating heart failure in the dog and cat. Other loop diuretics include ethacrynic acid, torsemide and bumetanide. Ethacrynic acid is not used. Bumetanide is a newer agent that is 25–50 times as potent as furosemide. Torsemide is also more potent than furosemide and has at least twice the duration of effect. There is little clinical experience with the latter two drugs in veterinary medicine. Furosemide remains the diuretic of choice in dogs and cats with heart failure.

Clinical applications

Furosemide is used as first-line therapy for treating all stages of acute and chronic heart failure secondary to all cardiac diseases except pericardial disease causing cardiac tamponade. However, pericardial effusion secondary to biventricular heart failure is managed in part with furosemide as required to control other clinical signs of congestion such as pulmonary edema. It is also used in noncardiac disease including treatment of hypercalcemia, management of ascites and edema associated with hepatic disease or nephrotic syndrome and in acute oliguric renal failure.

Mechanism of action

All loop diuretics inhibit sodium, potassium and chloride reabsorption in the thick portion of the ascending loop of Henle. In so doing, they inhibit sodium and obligatory water reabsorption in the nephron. The loop diuretics are capable of increasing the maximal fractional excretion of sodium from a normal of approximately 1% of filtered load to 15–25% of the filtered load, making them the most powerful natriuretic agents available.

Furosemide is a sulfonamide-type loop diuretic which, in addition to inhibiting sodium, potassium and chloride reabsorption in the loop of Henle, also decreases reabsorption of sodium and chloride in the distal renal tubule. Furosemide diuresis results in enhanced excretion of sodium, chloride, potassium, hydrogen, calcium, magnesium and possibly phosphate. Chloride excretion is equal to or exceeds sodium excretion. At a dose of 1.0 mg/kg to normal anesthetized dogs, furosemide increases sodium excretion approximately 17-fold. Potassium excretion is much less affected in dogs, at most twofold following furosemide administration. Magnesium excretion increases by a factor of 4 while calcium excretion increases 50-fold. Enhanced hydrogen ion excretion without a concomitant increase in bicarbonate excretion can result in metabolic alkalosis in dogs. This effect is rarely clinically significant, although it could be beneficial in dogs with pre-existing

metabolic acidosis due to poor perfusion. Despite the increase in net acid excretion, urinary pH falls slightly after furosemide administration, while urine specific gravity is generally reduced to around 1.006–1.020.

In addition to its diuretic effects, furosemide acts as a mild systemic venodilator, decreasing systemic venous pressure before diuresis takes place (especially after intravenous administration). Furosemide decreases renal vascular resistance. Thus, it acutely increases renal blood flow (in the order of 50%) without changing glomerular filtration rate.

Furosemide increases thoracic duct lymph flow in dogs following high doses (8–10 mg/kg IV). This effect is independent of renal function as it occurs in nephrectomized animals. The basis for this effect is unexplained.

Furosemide acts as a bronchodilator in humans, horses and guinea-pigs. It can be administered as an inhalant in humans with asthma. Its bronchodilatory effects in dogs and cats are unknown. If it does have bronchodilatory effects in cats and dogs, it could have beneficial effects in cats with asthma and in dogs with chronic bronchitis but its use should not replace conventional therapy for these diseases. It does, however, offer an explanation for why some dogs with chronic valve disease that are not truly in heart failure and are coughing due to chronic bronchitis (small airway disease) may experience a reduction in their cough when treated with furosemide. Thus resolution or improvement of a cough following trial therapy with furosemide does not prove the patient was in heart failure. One needs to document radiographic resolution of a characteristic infiltrate in the therapeutic trial of this nature. It is important that dogs with heart disease (preclinical) that will not benefit from furosemide are not administered the drug chronically.

Formulations and dose rates

Furosemide is available in oral (tablets, suspensions) and parenteral formulations.

CANINE

Chronic heart failure

1 mg/kg PO q.12 h for mild heart failure to 5 mg/kg q.8 h (doses should be separated by at least 3 h but do not have to be exactly 8 h) for severe heart failure. When this dose fails to keep the patient free of clinical signs of congestion a second diuretic may be added (see hydrochlorothiazide). The need for the addition of a rescue diuretic is clinically relatively rare. In general, the goal with furosemide is to use the minimum dose necessary to keep the patient free of clinical signs of congestion. Dogs with mitral regurgitation secondary to CVD that are refractory to furosemide administration may also benefit from the administration of a systemic arteriolar dilator, such as amlodipine or hydralazine.

Acute heart failure

Severe pulmonary edema requires immediate intensive intravenous or intramuscular administration in dogs. Intravenous is preferred if feasible.

FUROSEMIDE DOSE SCHEDULE FOR SEVERE LIFE-THREATENING CARDIOGENIC PULMONARY EDEMA IN THE DOG

- Dependent on severity of respiratory clinical signs
- Guided by resting respiration rate with oxygen supplementation and thoracic radiographs when available
- For *severe life-threatening cardiogenic pulmonary edema* in the dog:

Initial dose: 4–6 mg/kg IV (IM if IV not feasible)
Then: 2–4 mg/kg IV q.1 h (or 1 mg/kg min CRI) until resting respiration rate (RR) ↓ by 20%
Then: 2–4 mg/kg IV q.2 h (or 0.5 mg/kg min CRI) until resting RR ↓ by 50%
Then: 2–4 mg/kg IV q.6–8 h (discontinue CRI at this time)
Then: switch to oral 2–4 mg/kg q.8–12 h

Note: For less severe edema use the lower end of the dose range and in older patients who are concurrently azotemic reduce the lower range doses in the schedule by 50%.

If dogs with respiratory distress fail to demonstrate a trend for improvement (reduced respiration rate) following 4–6 doses or 4–6 h of a furosemide CRI alternative differentials for respiratory distress should be considered and/or additional heart failure therapy should be initiated.

FELINE

Chronic heart failure

1 mg/kg PO every 1–3 d (mild heart failure) to 2 mg/kg twice to three times daily (severe heart failure) in most cases (doses should be separated by at least 3 h but do not have to be exactly 8 h). In general the goal with furosemide is to use the minimal dose necessary to keep the patient free of clinical signs of congestion. Some cats that are not amenable to oral administration may benefit from chronic client-administered subcutaneous injections. A higher oral dose may be considered in some cats that are not responding to a conventional dose. The need for the addition of rescue diuretics in the cat is exceedingly rare.

Acute heart failure

Severe pulmonary edema requires immediate intensive intravenous or intramuscular administration in cats. Intravenous is preferred if feasible.

FUROSEMIDE DOSE SCHEDULE FOR SEVERE LIFE-THREATENING CARDIOGENIC PULMONARY EDEMA IN THE CAT

- Dependent on severity of respiratory clinical signs
- Guided by resting respiration rate with oxygen supplementation and thoracic radiographs when available
- For *severe life-threatening cardiogenic pulmonary edema* in the cat:

Initial dose: 2–4 mg/kg IV (IM if IV not feasible)
Then: 1–2 mg/kg IV in 1–2 h
Then: 1–2 mg/kg IV in 2–4 h if resting respiration rate is not ↓ by 50%
Then: switch to oral at 1–2 mg/kg q.8–12 h once RR reduced by 50%

Formulations and dose rates—cont'd

Note: In general the doses at the lower end of the range are sufficient to resolve most cases of pulmonary edema in the cat. If cats do not stabilize or demonstrate a trend in respiratory rate reduction and effort following 2–3 doses of furosemide then alternative differentials for respiratory distress should be considered. For example, if asthma is possible start corticosteroids and/or bronchodilators and if pleural effusion is possible perform diagnostic/therapeutic pleurocentesis.

In general most cats with respiratory distress due to cardiogenic pulmonary edema can be stabilized with furosemide and good supportive care and will not require additional cardiovascular therapy until a safe echocardiogram can be performed. An echocardiogram can usually be safely performed, if available, 12–24 h after the respiratory rate has decreased by 30–50%.

Finally, a cat's initial response to the above therapeutic plan can be considered prognostic. That is, cats with cardiogenic pulmonary edema that fail to stabilize as outlined above often have a poorer long-term prognosis.

Pharmacokinetics

Furosemide is highly protein bound (86–91%). The ratio of kidney to plasma concentration is 5:1. A small amount of furosemide (1–14%) is metabolized to a glucuronide derivative in dogs but this metabolism does not take place in the liver. In dogs about 45% of furosemide is excreted in the bile and 55% in the urine. After intravenous administration, furosemide has an elimination half-life of approximately 1 h. Intravenously, furosemide's onset of action is within 5 min, peak effects occur within 30 min and duration of effect is 2–3 h. Also after intravenous administration, about 50% of the drug is cleared from the body within the first 30 min, 90% is eliminated within the first 2 h and almost all is eliminated within 3 h.

Furosemide is rapidly but incompletely absorbed after oral administration with a bioavailability of 40–50%. The terminal half-life after oral administration is biexponential. The initial phase has a half-life of approximately 30 min, the second a half-life of approximately 7 h. The initial disposition phase has the most effect on plasma concentration, with concentration decreasing from therapeutic to subtherapeutic within 4–6 h of oral administration. After oral administration, onset of action occurs within 60 min, peak effects occur within 1–2 h and duration of effect is approximately 6 h. In normal dogs, a dose of 2.5 mg/kg furosemide intramuscularly results in maximum natriuresis (beyond that dose there is no further increase in sodium excretion). This occurs at a plasma concentration of approximately 0.8 μg/mL. Because the diuretic effect of furosemide is dependent on its hematogenous delivery to the kidney, patients with decreased renal blood flow (e.g. those with heart failure) need a higher plasma concentration (higher dose) to produce the same effect observed in normal dogs. This is achieved by administering higher oral doses or administering the drug intravenously.

Experimentally induced moderate renal failure approximately doubles the serum half-life of furosemide in dogs and decreases renal clearance to 15% of control. Experimentally induced renal failure also markedly attenuates the diuretic effect of the drug to approximately one-third of control. A higher concentration of furosemide is required to produce the same diuretic effect in dogs with renal failure. However, the relationship between the rate of urinary furosemide excretion and diuresis remains constant. Consequently, the decrease in diuresis in dogs with renal failure appears to be due to a decrease in delivery of furosemide to the nephron. In canine patients with renal failure, two discordant effects interact on the diuretic effects of furosemide. First, the prolongation in half-life increases the serum concentration for any given chronically administered dose. This increases diuresis. Second, the diuretic effect for any given serum concentration is reduced. This complex interaction makes it much more difficult to determine an effective dose for furosemide in a patient with renal failure.

Cats are more sensitive to furosemide than dogs. The increase in urine volume is comparable between normal cats and normal dogs in doses from 0.625 mg/kg to 10 mg/kg IM. However, in cats sodium excretion is between 1.3 and 2.2 times (average 1.7 times) that seen in dogs at each dosage. The slope of the regression equation between furosemide dose and sodium excretion (mmol/kg) for cats is about twice that for dogs. Clinically, cats commonly require no more than 1–2 mg/kg q.12–24 h PO chronically for the treatment of pulmonary edema. However, higher doses may be needed in feline patients with severe heart failure because of reduced renal blood flow.

Adverse effects

Adverse effects shared with other diuretics are presented above.

- Furosemide has the potential for ototoxicity. However, when administered as the sole agent, doses in excess of 20 mg/kg IV are required to produce any loss in hearing ability in dogs. Doses in the 50–100 mg/kg range produce profound loss of hearing.
- Furosemide can potentiate the ototoxic and nephrotoxic effects of other drugs such as the aminoglycosides. Furosemide does not have direct nephrotoxic effects when administered by itself.
- Owners must be warned that high-dose furosemide therapy can produce profound dehydration in patients that stop drinking and so to markedly decrease the dose or stop the administration until they can talk to a veterinarian.

- Intensive intravenous dosing commonly results in mild to moderate hypokalemia (serum K^+ concentration 3.0–3.5 mmol/L), mild to moderate hyponatremia (serum Na^+ concentration 135–145 mmol/L) and mild to moderate dehydration. These may need to be addressed after the life-threatening pulmonary edema has been controlled. However, in dogs, electrolyte disturbances and dehydration are usually corrected when the dog feels well enough to eat and drink once the pulmonary edema has resolved. In addition, the electrolyte abnormalities and dehydration are usually not clinically significant unless severe overdosing has occurred. Consequently, aggressive fluid therapy for these abnormalities is not required and is often contraindicated because such fluid therapy can result in recrudescence of the heart failure. In cats, judicious administration of fluids may be required to rehydrate the patient after intensive diuresis because cats often do not restart eating and drinking as readily as dogs. Clinically significant electrolyte disturbances and dehydration are rare in dogs receiving long-term furosemide therapy unless maximal doses are employed and/or anorexia is present. These abnormalities may be more common in cats.

Known drug interactions

The natriuretic effect of furosemide is attenuated by aspirin administration in dogs. This drug interaction is possible with any NSAID by way of prostaglandin inhibition leading to reduced renal papillary blood flow. Indomethacin and aspirin completely inhibit the increase in renal blood flow observed after furosemide administration in dogs.

Special considerations

Furosemide injection contains the sodium salt of furosemide that is formed by the addition of sodium hydroxide during manufacturing. It should be stored at a temperature of 15–30°C and protected from light. Injections having a yellow color have degraded and should not be used. Exposure of furosemide tablets to light may cause discoloration. Discolored tablets should not be used. Furosemide injection can be mixed with weakly alkaline and neutral solutions having a pH of 7–10, such as 0.9% saline or Ringer's solution. A precipitate may form if the injection is mixed with strongly acidic solutions such as those containing ascorbic acid, tetracycline, adrenaline (epinephrine) or noradrenaline (norepinephrine). Furosemide injection should also not be mixed with most salts of organic bases, including lidocaine, alkaloids, antihistamines and morphine.

Thiazide diuretics

EXAMPLES

Hydrochlorothiazide, chlorothiazide

Clinical applications

The relative potency of thiazide diuretics when compared to furosemide is low in the dog and cat when they are used as monotherapy and thus they are rarely used as first-line diuretics in the dog and cat. Thiazides are primarily used in canine patients that have developed furosemide resistance. Dogs in heart failure are considered resistant to furosemide therapy when chronic oral furosemide at 4–5 mg/kg q.8 h fails to relieve clinical signs of congestion. In these cases the addition of a thiazide diuretic results in a synergistic drug–drug interaction as a result of sequential nephron blockade. This commonly results in restoration of diuresis and resolution of clinical signs. Sequential nephron blockade results from potentiation of thiazide diuretic effects due to upregulation of the specific exchange mechanism that is inhibited by thiazides in the distal convoluted tubule. This potentiation is the result of adaptations arising secondary to chronic furosemide therapy. Thus thiazides are commonly referred to as rescue diuretics.

Mechanism of action

The thiazides act primarily by reducing membrane permeability to sodium and chloride in the distal convoluted tubule. They promote potassium loss at this site and produce large increases in the urine sodium concentration but only mild to moderate increases in urine volume. Consequently, moderate renal sodium loss is produced. Thiazide diuretics increase renal sodium excretion from a normal value of about 1% to 5–8% of the filtered load. Thiazide diuretics also inhibit carbonic anhydrase in the proximal tubules but this effect varies considerably among the various agents. The thiazides are ineffective when renal blood flow is low, which may explain their lack of efficacy as a sole agent in patients with severe heart failure.

Thiazide diuretics decrease glomerular filtration rate, which may explain their lack of efficacy in patients with renal failure. It is unknown whether this is due to a direct effect on renal vasculature or is secondary to the decrease in intravascular fluid volume.

Thiazides are sometimes used to decrease the polyuria associated with diabetes insipidus; this effect is mediated through plasma volume reduction resulting in decreased glomerular filtration rate and enhanced proximal reabsorption of NaCl. Dietary sodium restriction can potentiate their beneficial effects in this setting.

Formulations and dose rates

Chlorothiazide is available in tablet and suspension formulations, hydrochlorothiazide in tablet form.

DOGS

Hydrochlorothiazide (preferred)

- 2–4 mg/kg PO q.12 h (monotherapy dose)

Note the authors' rescue diuretic of choice (see Diuretic resistance and furosemide formulation and dose rates) is hydrochlorothiazide, regardless of whether or not concurrent spironolactone therapy is employed. This is rarely required in the clinical setting (<15% of cases in the authors' experience)

Chlorothiazide (monotherapy dose)

- 20–40 mg/kg PO q.12 h

CATS

Hydrochlorothiazide (preferred)

- 1–2 mg/kg PO q.12 h

RULE OF THUMB: when a maximum chronic dose of furosemide (5 mg/kg PO q.8 h) alone or in combination with spironolactone fails to keep the patient free of cardiogenic edema or effusion, then hydrochlorothiazide can be initiated at 2 mg/kg q.12 h. However, when hydrochlorothiazide is initiated it is recommended by the author (Gordon) to reduce the daily dose of furosemide by approximately 50% (3 mg/kg q.12 h) and add a potassium supplement. The dose of spironolactone can be added at 0.5–1 mg/kg q.12 h to minimize potassium wasting.

Pharmacokinetics

In dogs, thiazides are well absorbed after oral administration. The action of chlorothiazide begins within 1 h, peaks at 4 h and lasts 6–12 h. Hydrochlorothiazide has an onset of action within 2 h, peaks at 4 h and lasts 12 h. The newer, more lipid-soluble thiazides (trichlormethiazide, cyclothiazide) have not been studied in the dog or cat.

Adverse effects

In addition to their effects on sodium and chloride, the thiazides also increase potassium excretion because of the increased sodium that reaches the distal tubular site of sodium-potassium exchange. Long-term thiazide administration can result in mild metabolic alkalosis associated with hypokalemia and hypochloremia in human patients. The effects in dogs and cats are less clear. These effects are potentiated when they are used concurrently with other loop diuretics such as furosemide. Although little can or should be done to normalize Na and Cl serum concentrations in this setting, K supplementation is often required to maintain the serum potassium concentration within the normal range. In addition, magnesium supplementation may be beneficial due to its positive correlation with potassium concentration.

Because thiazides are most commonly used as rescue diuretics in dogs with furosemide resistance, their relative potencies are profoundly augmented and they can cause marked diuresis resulting in prerenal azotemia. Therefore caution should be used when initiating rescue diuretic therapy, particularly in dogs with pre-existing azotemia. To minimize this risk when initiating thiazides as rescue therapy the author (Gordon) reduces the total daily dose of furosemide by approximately 50% (see Rule of Thumb). Follow-up re-evaluation should occur in 7–14 days or sooner if the patient is not doing well clinically and should include the revaluation of renal parameters and serum potassium concentration.

Potassium-sparing diuretics

EXAMPLES

Spironolactone (preferred), triamterene, amiloride

Clinical applications

This class of diuretics acts by inhibiting the action of aldosterone on distal tubular cells or blocking sodium reabsorption in the latter regions of the distal tubule and collecting tubules. In normal dogs, they can only increase the maximal fractional excretion of sodium to 2% of the filtered load. In dogs with heart failure, particularly those with ascites secondary to right heart failure, an increased plasma aldosterone concentration may be present and the effect of these diuretics may be enhanced. However, potassium-sparing diuretics are weak diuretics when used alone as diuretics and thus should never be used as sole agents in patients with heart failure. One should never rely on a potassium-sparing diuretic, such as spironolactone, to produce additional diuresis in a patient that is refractory to other diuretics. When potassium-sparing diuretics are administered with other diuretics, potassium loss is decreased, representing an additional benefit. Consequently, they can be administered to patients that become hypokalemic because of the administration of other diuretic agents.

Spironolactone

Spironolactone can be used in combination with other diuretics, primarily furosemide, to produce additional diuresis (generally a mild increase) or to decrease potassium excretion. In addition, as an aldosterone antagonist, spironolactone is considered a neuroendocrine modulator (aldosterone receptor blocker). One human study reported that low-dose spironolactone (subdi-

uretic doses) reduced heart failure mortality by approximately 18–40% and this effect was attributable to its neuroendocrine modulatory effects. Spironolactone is also used in the management of fluid retention associated with noncardiac disease such as hepatic disease and nephrotic syndrome. Spironolactone might be particularly useful as a diuretic in the setting of right heart failure causing ascites.

Triamterene

Triamterene is rarely used in dogs and cats and almost never as a sole diuretic agent. It is generally administered in combination with other diuretics, usually furosemide, to decrease potassium excretion in a patient that develops hypokalemia while on furosemide.

Mechanism of action

Spironolactone

Spironolactone is structurally similar to aldosterone and binds competitively to aldosterone's binding sites in the distal tubule. Due to its aldosterone antagonism spironolactone is also considered an inhibitor of the RAAS and thus a neuroendocrine modulator.

Triamterene

Triamterene is a potassium-sparing diuretic that is structurally related to folic acid. It acts directly on the distal tubule to depress reabsorption of sodium and decrease the excretion of potassium and hydrogen. It does not competitively inhibit aldosterone.

Formulations and dose rates

Spironolactone

Spironolactone is supplied as tablets. It is also supplied in a fixed combination with hydrochlorothiazide. The diuretic spironolactone dose for dogs is 2–4 mg/kg/d. Lower doses (0.5–1 mg/kg q.12 h) may be considered for inhibition of the RAAS.

Triamterene

Triamterene is supplied as capsules. It is also supplied in a fixed combination with hydrochlorothiazide. The oral canine dose is 2–4 mg/kg/q.24 h.

Pharmacokinetics

Spironolactone has a long half-life and so its onset of action is slow. In dogs its peak effect does not occur until 2–3 d after administration commences. The drug is extensively and rapidly metabolized to conrenone and other metabolites in plasma. These metabolites are pharmacologically active but much less so than the parent compound. The duration of effect for spironolactone is 2–3 d after cessation of drug administration.

Triamterene's action begins within 2 h, peaks at 6–8 h and lasts 12–16 h.

Adverse effects

The diuretic effects of potassium-sparing diuretics are generally too mild to produce any untoward effects. However, when combined with an ACE inhibitor whose mechanism of action also includes anti-aldosterone effects, the relative risk of hyperkalemia is increased. However, it is only clinically significant in patients who are not receiving furosemide concurrently.

Known drug interactions

The potassium-sparing property of spironolactone does not result in clinical hyperkalemia even when used in combination with an ACE inhibitor as long as furosemide is also given. However, in the authors' experience the combination of spironolactone and an ACE inhibitor (without concurrent furosemide administration) can result in clinically significant hyperkalemia and should thus be avoided.

POSITIVE INOTROPIC DRUGS

EXAMPLES

Oral: pimobendan (preferred), digoxin
IV: dobutamine (preferred), dopamine, epinephrine (adrenaline), milrinone, amrinone

As a class, with the exception of calcium-sensitizing aspect of agents such as pimobendan, the final common pathway for positive inotropy is dependent on increased concentrations of cytosolic calcium in cardiomyocytes. All drugs with this property have the potential to cause arrhythmias and increase myocardial oxygen consumption, negative properties which may be exaggerated in long-term therapy for the management of chronic heart failure. Thus any potential benefit must be weighed in relationship to these potential negative side effects.

Positive inotropy that is mediated through calcium sensitization (e.g. pimobendan) might thus be considered the safest form of positive inotropy. Positive inotropes include digitalis glycosides, sympathomimetics such as epinephrine (adrenaline), dobutamine and dopamine. Pure phosphodiesterase inhibitors such as milrinone and pimobendan, a calcium sensitizer/phosphodiesterase inhibitor, will be discussed in the section on inodilators.

Digitalis glycosides

Clinical applications

Historically, the digitalis glycosides were indicated for the treatment of heart failure characterized by systolic dysfunction (i.e. decreased myocardial contractility) and for the treatment of supraventricular tachyarrhythmias.

In dogs with heart failure, digitalis does not result in a clinically significant increase in myocardial contractility and currently there are more potent oral positive inotropes available (e.g. pimobendan). The current primary clinical indication for digoxin is for the management of clinically significant supraventricular arrhythmias such as atrial fibrillation where it is often used in combination with other antiarrhythmics such as β-blockers or diltiazem. Thus further discussion of digoxin will be covered in the antiarrhythmic section of this chapter.

Sympathomimetics

EXAMPLES

Dobutamine (preferred for acute inotropic support), adrenaline (epinephrine), dopamine

Clinical applications

Sympathomimetics are used to provide inotropic support for patients in acute cardiac failure. Most sympathomimetics have the ability to increase contractility about 100% above baseline, but many are unsuitable for treating heart failure because of other drug properties. Sympathomimetics such as dopamine, and particularly dobutamine, are less arrhythmogenic, produce a smaller heart rate increase and are more suitable for heart failure therapy than the classic sympathomimetics such as adrenaline (epinephrine) and noradrenaline (norepinephrine). The arrhythmogenic potential for all catecholamines is increased when dogs are anesthetized with drugs such as thiamylal and halothane. In this setting, the arrhythmogenic potential of adrenaline (epinephrine), dopamine and dobutamine is similar.

One of the major limitations of using sympathomimetics to treat patients with heart failure is the major alterations that occur in β-receptor density and sensitivity during subacute to chronic stimulation by endogenous or exogenous catecholamines such as occurs in the setting of chronic heart failure or prolonged use of the agent in question. Typically, the inotropic response to sympathomimetics decreases to 50% of baseline after a day or two of constant stimulation because of the decrease in β-receptor number and sensitivity. Consequently, one should generally not consider using a sympathomimetic for longer than 2 or 3 days for inotropic support and their effects may be reduced in chronic heart failure requiring higher doses.

Mechanism of action

In the heart, sympathomimetic amines increase contractility, conduction velocity and heart rate primarily by binding to cardiac β-adrenergic receptors. The increase in contractility is brought about by activation of adenyl cyclase within the cell. Adenyl cyclase cleaves adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP), which stimulates a cellular protein kinase system. Protein kinases phosphorylate intracellular proteins, such as phospholamban on the sarcoplasmic reticulum (SR), allowing the SR to bind more calcium during diastole and thereby release more calcium during systole. Cyclic AMP also affects L-type calcium channels to increase calcium entry into the cell during systole.

Dobutamine

Clinical applications

Dobutamine is preferred for acute or short-term inotropic support in heart failure characterized by systolic dysfunction.

In clinical situations, dobutamine can be used to treat acute or decompensated heart failure characterized by systolic dysfunction, such as DCM and most CVD, until inotropic support is no longer needed or until other longer-acting drugs have taken effect. It is also often used in anesthetized patients requiring inotropic support.

Mechanism of action

Dobutamine is a synthetic catecholamine. It stimulates β_1-adrenergic receptors, increasing myocardial contractility. It also weakly stimulates peripheral β_2- and α_1-adrenergic receptors. As this response is balanced, systemic arterial blood pressure is usually unchanged. Dobutamine is less arrhythmogenic than most of the other sympathomimetics in conscious animals. In vagotomized experimental dogs under anesthesia, dobutamine is as arrhythmogenic as adrenaline (epinephrine).

Formulations and dose rates

Dobutamine is supplied as 12.5 mg/mL in a 20 mL single use vial (250 mg/vial) and should be diluted appropriately for administration.

DOGS AND CATS (RARE)

- CRI = 2-40 μg/kg/min IV. Typically the CRI is initiated at the lower dose and increased every 2–10 min until desired effect (increase in systemic blood pressure) or toxicity is detected (worsening arrhythmias or clinically significant tachycardia)
- Doses of 5–20 μg/kg/min are generally adequate for conscious dogs in heart failure. Infusion rates of greater than 20 μg/kg/min often produce tachycardia and vomiting
- Lower doses 1–5 μg/kg/min IV are usually used in anesthetized patients who are not in heart failure
- Dobutamine can be used in combination with pimobendan in acute emergency situations
- Cats may be administered 5–15 μg/kg/min. It is however, rarely indicated because systolic dysfunction is rare in the majority of feline heart diseases
- The positive inotropic effect is dose dependent

Pharmacokinetics

Dobutamine must be administered as a CRI. A plateau plasma concentration is achieved within approximately 8 min of starting the infusion. Upon cessation of the infusion, dobutamine rapidly clears from the plasma with a terminal half-life of 1–2 min. The rapid clearance is due primarily to degradation of the drug by catechol-*O*-methyltransferase.

In experimental dogs, dobutamine produces dose-related increases in myocardial contractility, cardiac output, stroke volume and coronary blood flow, with no change in systemic arterial blood pressure. When administered to a patient with acute or chronic myocardial failure, it should increase contractility and cardiac output and decrease ventricular diastolic pressures, leading to a decrease in edema formation and normalization of systemic blood pressure if it is low. This has been poorly documented in dogs and cats with chronic myocardial failure but has been well documented in human patients. Failing myocardium responds much less avidly to positive inotropic agents than normal myocardium. Consequently, it is not unusual for echocardiographic measures of left ventricular function to change minimally following dobutamine administration in dogs with severe systolic dysfunction (e.g. DCM). This statement is true of all positive inotropes.

Dobutamine's effects on heart rate are generally less than those of other catecholamines. When studied in normal dogs and in dogs with experimental myocardial infarction, the heart rate did not increase at infusion rates less than 20 μg/kg/min. Dobutamine, however, does increase heart rate in a dose-dependent manner in dogs that are anesthetized.

Adverse effects

Dobutamine can exacerbate existing arrhythmias, especially ventricular arrhythmias. It can also produce new arrhythmias and increase heart rate.

Special considerations

The 12.5 mg/mL solution must be further diluted into at least 50 mL for administration. Once in an intravenous solution, the compound is stable at room temperature for 24 h.

Dobutamine should not be mixed with bicarbonate, heparin, hydrocortisone sodium succinate, cefalothin, penicillin or insulin.

Dopamine

Clinical applications

In cardiovascular medicine, dopamine is recommended for short-term use in animals with systolic dysfunction and in the management of acute oliguric renal failure, particularly in the dog. In addition, dopamine is often used as a pressor agent to manage inappropriate hypotension in both conscious and anesthetized patients.

Mechanism of action

Dopamine is the precursor of noradrenaline (norepinephrine). It stimulates cardiac α- and β-adrenergic receptors as well as peripherally located dopaminergic receptors. The reported effects of dopamine are dose dependent: where dopaminergic effects on renal blood flow occur at low doses 1–1.5 μg/kg/min, positive inotropic responses predominate at doses 5–10 μg/kg/min and pressor effects dominate at infusion rates greater than 10 μg/kg/min. The pressor effects are undesirable in the setting of decompensated heart failure and thus dobutamine is preferred in this setting. Dopaminergic receptors appear to be located most prevalently in the renal and mesenteric vascular beds, where they produce vasodilation and improve blood flow. As with dobutamine, all effects are attenuated over time and are reduced in dogs with heart failure relative to normal dogs.

Formulations and dose rates

Dopamine is supplied as 40 mg/mL in a 10 mL single use vial (400 mg/vial) and should be diluted appropriately for administration.

DOGS

- 1–10 μg/kg/min IV
- Low doses (1.0–1.5 μg/kg/min) cause renal vasodilation via specific dopaminergic receptors; therefore, dopamine is often used in the management of acute oliguric renal failure
- Medium doses (3–10 μg/kg/min) cause increased cardiac output with little effect on peripheral resistance or heart rate
- Doses higher than 10 μg/kg/min can be used but result in noradrenaline (norepinephrine) release and increased peripheral vascular resistance and heart rate (pressor effect)
- An initial dose of 2 μg/kg/min may be started and titrated upward to obtain the desired clinical effect (improved hemodynamics)

Pharmacokinetics

All sympathomimetics have a very short half-life (1–2 min). When administered orally, they experience rapid and extensive first-pass hepatic metabolism before they reach the circulation. Consequently, they must be administered intravenously as a CRI.

Special considerations

Dopamine is inactivated when mixed with sodium bicarbonate or other alkaline intravenous solutions. The solution becomes pink or violet. The product should not be used if it is discolored.

INODILATORS

EXAMPLES

Oral: pimobendan
IV: milrinone, amrinone

This class of agents has both positive inotropic and vasodilatory properties and they have been labeled inodilators as a reflection of the term 'inodilation' (coined by Lionel H Opie in 1989). Historically, short-term management of acute or decompensated heart failure characterized by systolic dysfunction benefited from a combination of dobutamine (inotrope) and sodium nitroprusside (vasodilator). Agents in this class combine these properties but are not as potent as a combination of dobutamin and nitroprusside. However, pimobendan is available in an oral formulation, making chronic therapy possible.

Pimobendan

Clinical applications

Pimobendan is a novel agent with properties that are desirable in the clinical management of canine heart failure secondary to both DCM and chronic CVD in dogs.

The efficacy of pimobendan in the treatment of heart failure arising from DCM and CVD has been evaluated thoroughly in dogs. Available prospective data support its ability to significantly reduce morbidity in dogs with heart failure secondary to these conditions. A prospective blinded placebo-controlled study by O'Grady et al demonstrated a doubling of overall survival in Doberman pinschers with heart failure secondary to DCM, from a mean of 63 ± 14 days (mean ± standard deviation) with furosemide, an ACE inhibitor and placebo, to 128 ± 29 days with furosemide, an ACE inhibitor and pimobendan at 0.25 mg/kg by mouth twice daily (P = 0.04). Additional studies suggest a survival benefit with the combination of pimobendan and furosemide when compared to an ACE inhibitor and furosemide (with or without digoxin) in dogs with heart failure secondary to DCM or CVD.

Other studies offer conflicting evidence with respect to the superiority of pimobendan over an ACE inhibitor for the treatment of heart failure secondary to CVD. Preliminary analysis of an ongoing study by O'Grady et al showed no survival advantage using pimobendan and furosemide compared to an ACE inhibitor and furosemide in dogs with heart failure due to CVD. Conversely, Smith et al and Lombard et al (VetScope study) demonstrated superiority of a combination of pimobendan and furosemide over an ACE inhibitor (ramipril or benazepril respectively) and furosemide for the treatment of heart failure due to CVD. Smith's study reported a significant reduction of overall adverse outcomes, including death from the CHF (euthanized or died) and treatment failure when furosemide and ramipril (48%) were compared to furosemide and pimobendan (18%) over 6 months of treatment. Lombard's study reported that the median survival (i.e. death or treatment failure) for dogs receiving pimobendan and furosemide was 415 days versus 128 days for those receiving benazepril and furosemide (P = 0.0022). In all three studies no significant adverse consequences occurred, which suggests that the combination of pimobendan and furosemide is superior to furosemide and an ACE inhibitor for the treatment of heart failure due to CVD.

To date, pimobendan appears to be safe and well tolerated in dogs with heart failure associated with CVD. Pimobendan in combination with an ACE inhibitor and furosemide has not been prospectively evaluated in comparison to an ACE inhibitor and furosemide in heart failure due to CVD. However, when used with concurrent therapy such as furosemide, an ACE inhibitor, digoxin, spironolactone, etc., it appears to be beneficial.

One of the authors (Gordon) has been using pimobendan (0.25–0.3 mg/kg PO) in addition to background heart failure therapy for > 6 years in over 300 dogs for the treatment of CHF from both DCM and CVD. In one unpublished study from these 300 dogs, survival and hemodynamic effects were reviewed in a subset of dogs with advanced heart failure due to CVD. In addition to pimobendan these dogs received furosemide (100%, at least 3 mg/kg PO q.12 h) and an ACE inhibitor (100%), spironolactone (>75%), a β-blocker (20%), digoxin (11%) and hydrochlorothiazide (3%). Hemodynamic effects were evaluated prior to initiation of pimobendan and approximately 45 days later. No significant changes in indirect systemic blood pressures, bodyweight, hematocrit, total solids, serum creatinine or electrolytes (P = 0.05) were detected. Blood urea nitrogen concentration increased significantly in some dogs (pre-pimobendan 29 mg/dL vs post-pimobendan 33 mg/dL, P < 0.05). Heart rate and respiratory rate were reduced and no changes occurred in the combined frequency of arrhythmias (i.e. ventricular premature beats, ventricular tachycardia, supraventricular premature beats, supraventricular tachycardia and atrial fibrillation) on electrocardiograms. A trend (P = 0.059) was noted in reduction of the dosage of furosemide administered to the dogs.

Certain echocardiographic parameters suggested improvement in systolic function, namely a reduction in left ventricular (LV) internal dimension in systole, reduction of LV end-systolic area and an increase in the percentage of LV area shortening. Reduction in the regurgitant fraction was suggested by a decrease in the

radiographic vertebral heart score, a reduction in systolic left atrial diameter on echocardiography and a decrease in the M-mode derived ratio of left atrial to aortic size.

Taken together, these findings suggested that the addition of pimobendan to background heart failure therapy had no negative side effects and it enhanced systolic function, as well as reducing filling pressures. Although these beneficial effects were observed (on average) 45 days after initiating pimobendan, more recent experience and abstract data suggest that these effects may be apparent as soon as 24 h after starting the drug, which suggests a potential application in the treatment of acute, decompensated heart failure. The median survival of the dogs in the authors' 6-year study was 17 months (range 2–50 months). The median was estimated from a Kaplan Meier curve where mortality was the outcome variable and dogs were censored if still alive at the time of analysis (30% were censored).

The authors' clinical experience is in agreement with currently available prospective data supporting the efficacy of adjunctive pimobendan therapy in improving the quality and length of life in dogs with heart failure arising from both CVD and DCM. Pimobendan is easy to use clinically, requiring no additional monitoring, and enjoys excellent client compliance. Pimobendan works very rapidly and can be used during the initial, acute phase of heart failure treatment. Peak hemodynamic effects following oral administration on an empty stomach are achieved in 1 h and last 8–12 h. The rapid onset of action, low rate of side effects and decreased time of hospitalization with use of the drug have had a positive impact on the willingness of clients to pursue the treatment of heart failure in the clinic, as well as overall client satisfaction with chronic heart failure therapy. Ongoing studies will further define the survival benefits associated with the use of pimobendan in dogs with heart failure due to CVD.

Pimobendan has been licensed for use in dogs with CHF since 2000 in many countries around the world, including countries in Europe, Great Britain, Australia, Canada and Mexico and most recently the USA (2007). Pimobendan is produced and marketed under the trade name Vetmedin.

In summary, pimobendan is a novel agent with properties that are desirable in the clinical management of CHF secondary to both DCM and CVD in dogs. Review of available data supports that pimobendan is safe, well tolerated and leads to enhanced quality of life in dogs when used in combination with furosemide and other conventional heart failure therapies. Pimobendan prolongs survival in dogs with CHF from DCM and CVD and an ongoing study will offer additional insight into its effects on mortality in dogs with CHF due to CVD.

Mechanism of action

Inotropy

Pimobendan is a benzimidazole pyridazinone derivative and is classified as an inodilator (i.e. positive inotrope and balanced systemic arterial and venous dilator). In failing hearts it exerts its positive inotropic effects primarily through sensitization of the cardiac contractile apparatus to intracellular calcium. As a phosphodiesterase (PDE) III inhibitor it can potentially increase intracellular calcium concentration and increase myocardial oxygen consumption. However, the cardiac PDE effects of pimobendan are reportedly minimal at pharmacological doses in dogs with heart disease, which is a major advantage relative to other inotropic PDE inhibitors such as milrinone. Pimobendan's calcium sensitization of the contractile apparatus is achieved by enhancement of the interaction between calcium and the troponin C complex, resulting in a positive inotropic effect that does not increase myocardial oxygen consumption.

Overall, pimobendan enhances systolic function by improving the efficiency of contraction, limiting the potential arrhythmogenic side effects of other positive inotropes whose sole mechanism of action is to increase myocardial intracellular calcium. Calcium sensitizers such as pimobendan may thus represent the only class of inotropic agents that 'safely' augment contractility.

Vasodilation

Phosphodiesterase III and V are found in vascular smooth muscle. Inhibitors of PDE III such as pimobendan result in balanced vasodilation (combination of venous and arterial dilation) leading to a reduction of both cardiac preload and afterload, a cornerstone of therapy in heart failure. In addition, pimobendan may have some PDE V inhibition effects. PDE V concentrations are relatively high in the vascular smooth muscle of pulmonary arteries, so PDE V inhibition might help ameliorate elevations in pulmonary artery pressure (pulmonary hypertension) that tend to parallel longstanding elevations in left atrial pressure, a clinically important complication of CVD.

Cytokine modulation

The significance of alterations in proinflammatory cytokine concentrations such as tumor necrosis factor-β, interleukins 1β and 6 on the progression of heart failure has been documented in many forms of heart disease. Maladaptive alterations in these cytokine concentrations are associated with increased morbidity and mortality and pimobendan has demonstrated beneficial modulation of several such cytokines in various models of heart failure.

Antiplatelet effects

Pimobendan reportedly may have some platelet inhibitory effect in the dog. The clinical significance of this property is not yet clear.

Positive lusitropic effect

Positive lusitropic effects occur via PDE III inhibition in cardiomyocytes. Pimobendan increases intracellular cAMP, which facilitates phosphorylation of receptors on the sarcoplasmic recticulum and enhances the diastolic re-uptake of calcium and the speed of relaxation – a positive lusitropic property.

Formulations and dose rates

Pimobendan is supplied as hard gelatin capsules (most countries) containing 1.25, 2.5 mg or 5 mg pimobendan. In 2007 a new chewable formulation was released in the USA and Australia in the same sizes. Pimobendan is not stable in suspension and should not be reformulated in this manner. The labeled dose recommendation is 0.25–0.3 mg/kg q.12 h. Initial efficacy may be enhanced by administration on an empty stomach but once steady state is reached (a few days) it can be administered with food.

Pharmacokinetics

Bioavailability is reduced by food until steady state is reached in a few days. Consequently, the drug should be administered on an empty stomach at least 1 h before feeding for maximal effects when starting therapy. Peak hemodynamic effects following oral administration on an empty stomach are achieved in 1 h and last 8–12 h. Therefore it can provide rapid short-term support to dogs with acute or decompensated heart failure even though it is an oral preparation.

Adverse effects

Pimobendan is well tolerated clinically in dogs with heart failure.

- In the treatment of more than 300 dogs one of the authors (Gordon) has recognized systemic hypotension and sinus tachycardia once, which was resolved by dose reduction.
- Gastrointestinal signs including anorexia and vomiting are not statistically different in frequency from those reported with ACE inhibitor treatment in the same patient population.
- One case report documented chordal rupture in two dogs while using pimobendan for an off-label indication.
- One additional case report documented ventricular hypertrophy but the dogs in this study did not have heart failure and thus do not represent the patient population pimobendan is licensed to treat.
- No prospective randomized controlled blinded study in either human or veterinary medicine has reported an increase in the frequency of arrhythmias. Recently one small unpublished study suggested that pimobendan increases the number and complexity of ventricular tachyarrhythmias in dogs with DCM and one small prospective placebo controlled study reported no increase in arrhythmias (Holter) in dogs with CVD receiving pimobendan versus enalapril.
- According to the Canadian package insert:
  - suspected adverse effects that have been reported following clinical use in dogs include: systemic hypotension and tachycardia (usually dose dependent and avoided by reducing the dose), gastrointestinal problems (inappetence, anorexia, vomiting), nervous system/behavioral problems (uneasiness, inco-ordination, convulsions) and polyuria and polydypsia.
  - Arrhythmias and chordal rupture represent two additional potential adverse effects.
  - In addition, as for all positive inotropic agents, pimobendan should not be administered to patients with hypertrophic cardiomyopathy or patients with any type of outflow tract obstruction (e.g. subaortic stenosis, pulmonic stenosis).
  - There are no data on the safety of pimobendan in pregnant or lactating dogs.

Milrinone and amrinone

Mechanism of action

Milrinone and amrinone are bipyridine compounds. Bipyridine compounds increase myocardial contractility and produce mild systemic arteriolar dilation. Milrinone is about 30–40 times as potent as amrinone.

Bipyridine compounds primarily act as inhibitors of phosphodiesterase fraction III. Phosphodiesterase III is an intracellular enzyme that specifically hydrolyzes cAMP in myocardial and vascular tissue. When phosphodiesterase III is inhibited, intracellular cAMP concentration increases. This increase results in the same type of inotropic effect in the myocardium as is produced by sympathomimetics. The major difference is that bipyridine compounds 'bypass' the β-receptors and so there is no decrement in inotropic effect over time. Bipyridine compounds also produce arteriolar dilation, probably also mediated by phosphodiesterase inhibition. Milrinone also increases left ventricular relaxation and distensibility in human heart failure patients.

Cardiovascular effects of the bipyridine compounds are species dependent. Myocardial contractility increases to a similar degree as is observed following the administration of a β-agonist in dogs and cats (i.e. approximately 100% above baseline). Myocardial contractility increases only about 50% above baseline in nonhuman primates and presumably in humans. When amrinone is administered to rats, contractility only increases about

25% above baseline. Because of this marked species difference, data obtained from human patients given amrinone or milrinone cannot be extrapolated to dogs or cats.

Milrinone

Clinical applications

Milrinone is the preferred bipyridine compound but is rarely used clinically; for acute cardiovascular support, dobutamine is preferred. It is a bipyridine compound with pharmacological effects and clinical indications that are almost identical to amrinone. Milrinone is currently marketed for intravenous administration only. No clinical studies of the effects of intravenous milrinone administration for acute myocardial failure in dogs or cats have been performed. Clinical studies of the effects of chronic oral administration have been performed but this form of the drug has not been approved for veterinary use and is not available for human use.

Formulations and dose rates

Milrinone lactate is supplied in 10 mL and 20 mL single-dose vials containing 1 mg/mL. It can be diluted in 0.45% and 0.9% sodium chloride and 5% dextrose in water.

DOGS

- In normal anesthetized dogs, milrinone 30–300 μg/kg IV increases contractility by 40–120% while decreasing diastolic blood pressure by 10–30%
- Constant-rate intravenous infusions (1–10 μg/kg/min) increase contractility by 50–140%, with peak effect in 10–30 min
- Dogs with systolic dysfunction (predominantly from DCM) displayed improved echocardiographic parameters with milrinone 0.5–1.0 mg/kg q.12 h PO during a 4-week treatment regimen

Pharmacokinetics

Peak effect occurs within 1–2 min of starting an intravenous infusion and is reduced to 50% of maximum within 10 min of stopping the infusion. The effects are essentially gone in 30 min.

Adverse effects

Ventricular arrhythmias worsen in a small percentage of dogs.

Known drug interactions

Milrinone is chemically incompatible with furosemide and thus should not be administered in the same intravenous line without flushing adequately in between.

Amrinone

Clinical applications

Amrinone is used for short-term inotropic support in small animal patients with myocardial failure. It may be useful to supplant a sympathomimetic once β-receptor downregulation has become a problem. It is not commonly used as a first-line agent because of its expense.

Formulations and dose rates

Amrinone is supplied in 20 mL ampoules in a concentration of 5 mg/mL for administration as supplied or for dilution in 0.9% or 0.45% saline.

DOGS AND CATS

- Amrinone is marketed only as a solution for intravenous administration and so is useful only for short-term administration
- In dogs, the initial dose should be 1–3 mg/kg, administered as a slow intravenous bolus, followed by a CRI of 10–100 μg/kg/min. One-half the initial bolus may be administered 20–30 min after the first bolus
- The same regimen may be effective in the cat

Pharmacokinetics

In normal anesthetized dogs, an intravenous bolus of amrinone (1.0–3.0 mg/kg) causes contractility to increase 60–100%, systemic arterial blood pressure to decrease 10–30% and heart rate to increase 5–10%. The maximal contractility increase occurs within 5 min after injection and decreases 50% by 10 min. Effects are dissipated within 20–30 min. This short duration of effect necessitates administering the drug by constant intravenous infusion following the initial bolus injection. Infusion rates of 10–100 μg/kg/min in anesthetized experimental dogs increase contractility by 30–90% above baseline and in unanesthetized dogs by 10–80%.

In anesthetized dogs, an infusion of 10 μg/kg/min does not decrease systemic blood pressure, whereas 30 μg/kg/min decreases it by 10% and 100 μg/kg/min decreases it by 30%. Heart rate does not increase at 10 μg/kg/min but elevates by 15% at 30 μg/kg/min and increases by 20% at 100 μg/kg/min. In anesthetized dogs with drug-induced myocardial failure, amrinone infusions increase contractility by 40–200% above baseline and increase cardiac output by 80%. Constant infusions in dogs take about 45 min to reach peak effect. In experimental cats, amrinone infused at 30 μg/kg/min causes contractility to increase by 40% above baseline. Peak effect occurs 90 min after starting an infusion.

Studies have not been performed to determine the hemodynamic changes brought about by amrinone administration in dogs or cats with naturally occurring heart failure. On the basis of the information from normal dogs, however, clinical recommendations can be made. The drug has a wide margin of safety and the risk of toxicity is low. With milrinone (which has similar

toxic effects in dogs as amrinone), exacerbation of ventricular arrhythmias may occur in about 5% of dogs treated for heart failure.

Special considerations

- Amrinone is incompatible with dextrose.
- The drug is prepared with the aid of lactic acid as a sterile solution of the drug in water. The commercially available injection is a clear yellow solution that is stable for 2 years from the date of manufacture.
- When the drug is diluted, it is stable for up to 24 h at room temperature or at 2–8°C under usual lighting conditions.
- Amrinone is chemically incompatible with furosemide and thus should not be administered in the same intravenous line without flushing adequately in between.

VASODILATORS

EXAMPLES

Pure vasodilators
Oral: calcium channel blocker (amlodipine) (preferred), hydralazine (preferred), prazosin, isosorbide mononitrate and dinitrate (nitrate)
IV: nitroprusside (nitrate; preferred)
Topical: nitroglycerine (nitrate; most likely ineffective)
Vasodilators with additional properties
Oral: pimobendan, ACE inhibitors, sildenifil
IV: milrinone

Tolerable vasodilation (preload and afterload reduction) represents a cornerstone of heart failure therapy in human and veterinary medicine. Vasodilator therapy was first introduced in human medicine in the early 1970s after it was noted that the acute administration of nitroprusside resulted in marked improvement in hemodynamics. The first reports of vasodilator use in veterinary medicine were published in the late 1970s and early 1980s. In addition, vasodilators are useful in the management of systemic hypertension.

Mechanism of action

Vasodilators are drugs that act on arteriolar or venous smooth muscle to cause smooth muscle relaxation (i.e. vasodilation) through a variety of mechanisms. Their hemodynamic effects depend on the vascular beds they influence (arterial or venous or balanced/mixed), as well as relative drug potency. The effect of these drugs on the pulmonary vasculature is erratic or insignificant. This discussion is therefore focused on systemic vascular beds. Two agents will be discussed as they relate to pulmonary hypertension (pimobendan and sildenafil).

In patients with heart failure, systemic arterioles are constricted (enhanced total peripheral resistance) so that a normal blood pressure (perfusion pressure) can be maintained when cardiac output is reduced. In addition, systemic veins are constricted so that blood volume is shifted from the peripheral to the central compartment in order to increase ventricular preload, producing volume overload hypertrophy (eccentric hypertrophy or dilation) and, in so doing, improve stroke volume and cardiac output. In patients with heart failure, these adaptive compensatory mechanisms ultimately become detrimental and maladaptive, contributing to the development of clinical signs consistent with heart failure.

Although systemic vasoconstriction is able to maintain a normal systemic blood pressure the relative increase in resistance to blood flow contributes to increased afterload. The normal systemic blood pressure and increased afterload decreases the effective transfer of mechanical energy into blood propulsion into the aorta. The net result is a decrease in stroke volume and an increase in energy consumption by the heart to generate stroke volume. Systemic venoconstriction in heart failure patients contributes to the increase in central blood volume. In heart failure patients, the ventricular chambers are unable to grow larger in response to this increase in volume (eccentric hypertrophy or dilation). Consequently, the increase in central blood volume and venoconstriction contributes to the increase in ventricular diastolic pressures and hence to the increase in edema and ascites formation.

Vasodilators are generally classified as arteriolar dilators, venodilators or combination (i.e. balanced) arteriolar and venodilators. Arteriolar dilators relax the smooth muscle of systemic arterioles, decreasing peripheral vascular resistance and impedance. This usually results in decreased systemic arterial blood pressure, systolic intraventricular pressure and systolic myocardial wall stress (or afterload). Thus, the force that opposes myocardial fiber shortening is reduced. This allows the heart muscle to shorten further and increases stroke volume. That reduces the work the heart has to do and increases tissue perfusion.

Arteriolar dilators are especially useful in patients with left-sided valvular regurgitation and left-to-right shunts. For example, in CVD, the left ventricle pumps blood in two directions: forwards into the systemic circulation and backwards through a leaky mitral valve. The percentage of blood pumped into the systemic circulation versus the percentage pumped into the left atrium depends on the relative resistances to blood flow. If resistance to blood flowing into the left atrium (e.g. 1000 dyn.s.cm^{-5}.m^{2}) is one half of systemic vascular

resistance (e.g. 2000 dyn.s.cm^{-5}.m^2), twice as much blood will be ejected into the left atrium in systole as is ejected into the aorta (i.e. 67% of the stroke volume will be ejected into the left atrium and 33% will be ejected into the aorta). In dogs with severe CVD more than 75% of the total left ventricular stroke volume may go backward into the left atrium.

Resistance to blood flow into the systemic circulation depends primarily on the cross-sectional area of the systemic arterioles. Resistance to blood flow through a defect like a leaky mitral valve depends on the size of the defect. Defect size is relatively fixed (unless a surgeon intervenes) in the short term but does progress over time as the disease progresses. Systemic vascular resistance, however, is labile and can be manipulated with drugs. If an arteriolar-dilating drug is administered to a patient with CVD, the decrease in systemic vascular resistance (e.g. to 1000 dyn.s.cm^{-5}.m^2) will result in an increase in forward flow into the aorta and systemic circulation. This will result in a decrease in backward flow into the left atrium and so a decrease in left atrial and pulmonary capillary pressures. In this example, the percentage of the stroke volume ejected into the left atrium will decrease from 67% to 50%, which would represent a large change, but even modest reductions in regurgitation fraction (5%) would be clinically significant.

Venodilators relax systemic venous smooth muscle, theoretically redistributing some of the blood volume into the systemic venous reservoir, decreasing cardiac blood volume and reducing pulmonary and hepatic congestion. The net result is reduced ventricular diastolic pressures, decreased pulmonary and systemic capillary pressures and diminished edema and ascites formation. Consequently, venodilators are used in the same situations as diuretics and sodium-restricted diets.

Vasodilators are also classified according to their mechanism of action (Table 17.5). ACE inhibitors not only produce vasodilation, they inhibit the RAAS and are thus neuroendocrine modulators resulting in less sodium and water retention.

Therapeutic endpoints

The therapeutic endpoint of vasodilator therapy is reduction in edema (reduced pulmonary capillary pressure and venous pressures) for venodilators and improved forward perfusion (elevation of cardiac output) for arteriolar dilators in patients with diseases such as DCM. When regurgitation or left-to-right shunting is present, arteriolar dilators reduce pulmonary edema formation and improve forward flow.

While it may not be feasible to measure these parameters directly, close monitoring of clinical signs and radiographic appearance of the lungs is realistic. Therapeutic response is seen as a decrease in cough, return of normal respiratory rate and effort, improved capillary refill time and color (sometimes hyperemic), improved distal extremity perfusion and temperature, improved attitude and possibly exercise tolerance, resolution of ascites and radiographic resolution of the pulmonary edema or pleural effusion. Mean or systolic systemic arterial blood pressure is usually reduced by 10–20 mmHg after the administration of a potent arteriolar dilator. Mean systemic arterial blood pressure should be maintained above 60 mmHg.

Adverse effects

While vasodilators enable one to achieve better therapeutic results, with their use comes the potential for adverse effects. These drugs are often used in critically ill canine or feline patients or patients with multiple problems that may be on several medications at the time of evaluation or during the course of treatment. These patients, in general, are at greater risk for experiencing adverse effects from a drug.

Table 17.5 Vasodilator drugs commonly used in veterinary medicine

Vasodilator	Type (mechanism)	Route	Dose	
			Dogs	***Cats***
Pimobendan*	Balanced (inodilator)	PO	0.25-0.3 mg/kg q.12 h	
Amlodipine**	Arterial (Ca channel blocker)	PO	0.01-3 mg/kg PO q.12-24 h (usually 12)	0.625 mg/cat q.24 h
Hydralazine	Arterial (↑ PGI_2)	PO	0.5–3 mg/kg q.12 h	2.5–10 mg/cat q.12 h
Prazosin	Balanced (α_1-blocker)	PO	0.5–2 mg/dog q.8–12 h	0.6 cm/cat q.6–8 h
Nitroglycerin	Venous (cGMP formation)	Cutaneous	0.6 cm per 5 kg q.6–8 h	
Nitroprusside	Balanced (cGMP formation)	IV	1–15 μg/kg/min	
Benazepril*	Balanced (ACE inhibitor)	PO	0.3–0.5 mg/kg q.24 h	0.2-0.7 mg/kg q.24 h
Enalapril*	Balanced (ACE inhibitor)	PO	0.5 mg/kg q.12–24 h (usually used q.12)	0.5 mg/kg q.12–24 h

* Authors' preferred agents for HF.
** Authors' preferred agent for systemic hypertension.

The primary major adverse effect of systemic arteriolar dilator therapy is clinically significant hypotension (i.e. mean systemic blood pressure <60 mmHg). This is uncommon and usually occurs as an isolated event following administration of the first doses of the drug or during titration of the dose. It may only warrant a decrease in the dose rather than discontinuation of the drug. The additive effects of a diuretic and a vasodilator may be a factor in producing hypotension. In the authors' clinical experience, this generally only occurs if the patient is clinically dehydrated and severely volume depleted. Hypotension is more common and often more severe when two arteriolar dilators are administered concurrently.

It is important to recognize systemic arterial hypotension. If it is misinterpreted as incomplete response to medication or progression of the disease, further doses could result in added complications. Acute-onset weakness and lethargy following drug administration are the most common clinical signs of hypotension.

Hypotension is poorly defined in the medical literature or only defined as any systemic arterial blood pressure less than normal. However, in clinical patients the term hypotension probably should not be used to denote a mild to moderate decrease in blood pressure. Rather, it should be reserved to denote a systemic arterial blood pressure low enough to result in clinical signs.

To produce clinical signs, systemic arterial blood pressure must decrease to a point where blood flow is markedly reduced through particular vascular beds. When mean systemic arterial blood pressure decreases to less than approximately 50–60 mmHg, flow to renal, myocardial and cerebral vascular beds becomes compromised. Normal mean arterial blood pressure is 100–110 mmHg. Therefore, there is a blood pressure reserve of about 50 mmHg. Arteriolar dilators take advantage of this reserve in patients with heart failure and cause mild to moderate decreases or tolerable reductions in blood pressure as a therapeutic effect. In patients with heart failure it is common to decrease mean systemic arterial blood pressure to 70–80 mmHg. This is an expected and therapeutic effect and causes no clinical signs of hypotension. On the contrary, clinical signs are generally improved because of the enhanced systemic blood flow (tissue perfusion) achieved through a tolerable reduction in afterload (blood pressure).

PURE VASODILATORS

Calcium channel blockers

Amlodipine

Amlodipine is a dihydropyridine calcium channel blocker that primarily affects the calcium channels in vascular smooth muscle, specifically in systemic arteriolar smooth muscle. Calcium channel blockers as a class are considered vasodilators but individual agents have different relative potencies and additional effects. Calcium channel blockers are also class IV antiarrhythmics and positive lusitropic agents. For further discussion of these properties please refer to the antiarrhythmic and positive lusitropic sections of this chapter respectively.

Amlodipine is the only calcium channel blocker used in veterinary practice that has potent vasodilatory properties. Amlodipine is similar to nifedipine. Both drugs have primarily arteriolar dilating properties with little effect on cardiac conduction and mechanical properties in the doses used clinically. Because of its ability to relax the smooth muscle of systemic arterioles, amlodipine imparts benefits similar to hydralazine to patients with mitral regurgitation (i.e. reduce the amount of regurgitation). These benefits may be realized without the reflex tachycardia seen with hydralazine and the drug appears to be better tolerated by the gastrointestinal tract.

Clinical applications

Amlodipine is an arteriolar dilator frequently used to treat systemic hypertension in cats and dogs. It can also be used to treat severe mitral regurgitation in dogs, in a similar manner to hydralazine. In heart failure the dose must be titrated to an effective endpoint using systemic arterial blood pressure as a guide. In general, systolic blood pressure should decrease by 10–15 mmHg when an effective dose is being administered. This systemic hypotension is a relative contraindication to initiation of amlodipine in the treatment of heart failure. If the dose is not titrated up to an effective endpoint, most often an effective dose will not be achieved, resulting in no clinical benefit. Benefits of amlodipine over hydralazine appear to be less reflex tachycardia, fewer gastrointestinal side effects and a lower incidence of clinically significant hypotension.

One short term study documented a reduction in regurgitant fraction (74% to 63%) after an average dose of 0.25 mg/kg (range 0.13–0.53 mg/kg) PO q.24 h in 16 dogs with left heart failure secondary to CVD short term. No adverse effects were noted. Systolic blood pressure decreased from 140 mmHg to 134 mmHg.

Mechanism of action

Amlodipine is a calcium channel blocker that affects primarily the calcium channels in vascular smooth muscle, specifically in systemic arteriolar smooth muscle. It is similar to nifedipine. Both drugs have primarily arteriolar dilating properties, although amlodipine has even fewer negative inotropic effects than its parent compound.

Formulations and dose rates

Amlodipine is supplied as tablets containing the besylate salt of amlodipine (2.5, 5 and 10 mg tablets). To treat refractory pulmonary edema secondary to severe mitral regurgitation, the dose needs to be titrated. The starting dose can be as low as 0.1 mg/kg q.24 h and can peak as high as 0.5 mg/kg q.12 h. The same protocol can be used to treat systemic hypertension in dogs but the peak dose may be as high as 3 mg/kg q.12 h.

Pharmacokinetics

The pharmacokinetics of amlodipine have been studied in dogs. Bioavailability is about 90%, compared to bioavailability in humans of about 65%. Time to peak plasma concentration is 6 h in dogs and 8 h in humans. Following intravenous or oral administration, about 45% of the drug is excreted in the feces and 45% in the urine as metabolites. Only 2% of the drug is excreted unchanged. Initial metabolism involves oxidation of the dihydropyridine ring to the pyridine analog. Further metabolism involves side-chain oxidation and hydrolysis of one or both side-chain ester groups. Plasma half-life is similar to that in humans at about 30 h following intravenous administration. Volume of distribution is also similar to that in humans at 25 L/kg. Approximately 95% of amlodipine is protein bound in all species studied.

Adverse effects

Theoretically, amlodipine overdose can cause clinically significant systemic hypotension. In practice, this appears to be very uncommon. However, further experience with the drug is required before any definitive statements can be made. Amlodipine produces no electrocardiographic effects in humans administered the drug. Amlodipine and a β-blocker can be administered together. The drug has been too expensive to use in large dogs. However, a generic formulation has recently become available.

Hydralazine

Clinical applications

The primary indication for hydralazine administration in veterinary medicine is severe mitral regurgitation that is refractory to conventional therapy. Hydralazine is also very effective for treating canine and feline patients with severe aortic regurgitation and patients with a large ventricular septal defect. Hydralazine can also be used to decrease systemic blood pressure in dogs with systemic hypertension. Administration of an α-adrenergic blocking drug is frequently required when the drug is used to treat systemic hypertension to block the reflex increase in cardiac output brought about by the sympathetically mediated increase in contractility and heart rate.

Mechanism of action

Hydralazine directly relaxes the smooth muscle in systemic arterioles, probably by increasing the prostacyclin concentration in systemic arterioles. It also increases aortic compliance. Hydralazine has no effect on systemic venous tone. It decreases vascular resistance in renal, coronary, cerebral and mesenteric vascular beds more than in skeletal muscle beds. Hydralazine also reflexly increases myocardial contractility. This is most probably secondary to hydralazine-induced histamine release resulting in noradrenaline (norepinephrine) release.

Hydralazine is a very potent arteriolar dilator. In dogs it is able to decrease systemic vascular resistance to less than 50% of baseline in comparison to captopril, which can only decrease systemic vascular resistance by about 25%. Hydralazine's potency can be both beneficial and detrimental to its use. Its potency is of benefit because it results in good to profound improvement in the majority of patients in which it is indicated. Its potency can be detrimental if it results in systemic hypotension.

In small dogs with severe mitral regurgitation refractory to the administration of furosemide, regurgitant flow may constitute 75–85% of cardiac output. Left ventricular contractile function is usually normal or only mildly depressed. Consequently, the major hemodynamic abnormalities are caused by marked regurgitant flow through an incompetent mitral valve. The ideal treatment would be mitral valve repair but currently this is not technically feasible. Consequently, the theoretical treatment of choice is arteriolar dilator administration.

ACE inhibitors are usually the first choice for achieving mild arteriolar dilation. Hydralazine is more potent and is reserved for patients that are refractory to ACE inhibitors. Hydralazine decreases regurgitant flow, increases forward aortic flow and venous oxygen tension and decreases radiographic evidence of pulmonary edema. A therapeutic dosage decreases mean arterial blood pressure from 100–110 mmHg to 60–80 mmHg. These effects improve the quality of life and appear to prolong survival time.

In dogs with dilated cardiomyopathy, hydralazine also improves cardiac output but does not usually appreciably reduce edema formation. Consequently, the drug does not seem to improve the quality of life for the patient nor does it usually result in appreciable prolongation of life.

Formulations and dose rates

Hydralazine is available as tablets. The author (Kittelson) has witnessed a lack of response to some generic hydralazine products and does not recommend their use.

The effective dose is 0.5–3.0 mg/kg q.12 h PO. This dose must be titrated, starting with a low dose and titrating upward to an effective endpoint.

Dose titration

In dogs that are not being administered an ACE inhibitor, the starting dose of hydralazine should be 1.0 mg/kg. This can then be titrated up to as high as 3.0 mg/kg if no response is observed at lower doses. Titration in these animals can be performed with or without blood pressure measurement. If blood pressure cannot be monitored, titration is performed more slowly and clinical and radiographic signs are monitored. Baseline assessments of mucous membrane color, capillary refill time, murmur intensity, cardiac size on radiographs and severity of pulmonary edema are made.

A dose of 1 mg/kg is administered q.12 h PO and repeat assessments are made in 12–48 h. If no response is identified, the dose is increased to 2 mg/kg q.12 h and then to 3 mg/kg q.12 h if no response is seen at the previous dose. Mucous membrane color and capillary refill time will become noticeably improved in about 50–60% of dogs. In most dogs with heart failure due to mitral regurgitation, the severity of the pulmonary edema will improve within 24 h. In many of these dogs the size of the left ventricle and left atrium will decrease. In some dogs, improvement will not be great enough to identify with certainty. In those dogs the titration may continue, with the realization that some dogs will be mildly overdosed and clinical signs of hypotension may become evident.

Owners should be warned to watch for signs of hypotension and notify the clinician if they are identified. If a dog becomes weak and lethargic following hydralazine administration, the dog should be rechecked by a veterinarian but in almost all situations the dog should only be observed until the drug effect wears off 11–13 h later. The drug dose should then be reduced. In the rare event that signs of shock become evident, fluids and vasopressors may be administered. In human medicine, there has never been a death recorded that was secondary to the administration of hydralazine alone. The dosage record is 10 g. The authors have observed dogs becoming very weak following an overdose of hydralazine but have never observed a serious complication when the drug was not administered in conjunction with another vasodilator such as an ACE inhibitor.

More rapid titration can be performed if blood pressure monitoring is available. In this situation, baseline blood pressure is measured and 1.0 mg/kg hydralazine administered. Blood pressure measurement should then be repeated 1–2 h later. If blood pressure (systolic, diastolic or mean) has decreased by at least 15 mmHg, the dose administered (1.0 mg/kg) is effective and should be administered q.12 h from then on. If no response is identified, another 1.0 mg/kg dose should be administered (cumulative dose of 2.0 mg/kg) and blood pressure measured again 1–2 h later. This can continue until a cumulative dose of 3.0 mg/kg has been administered within a 12 h period. The resultant cumulative dose then becomes the dose administered q.12 h.

In dogs that are already receiving an ACE inhibitor, hydralazine must be added to the treatment regimen cautiously. ACE inhibition depletes the body's ability to produce angiotensin II in response to hydralazine-induced vasodilation. Severe hypotension can occur if the hydralazine dose is not titrated carefully. In general, the dosage should start at 0.5 mg/kg and the dose should be titrated at 0.5 mg/kg increments until a response is identified. Blood pressure monitoring is strongly encouraged in this situation. Referral to a specialist cardiologist or internist is also encouraged if feasible.

In dogs with acute, fulminant heart failure due to severe mitral regurgitation that are not already receiving an ACE inhibitor, hydralazine titration can be more aggressive. An initial dose of 2.0 mg/kg may be administered along with intravenous furosemide. This dose should produce a beneficial response in more than 75% of dogs. It may produce hypotension but the hypotension is rarely fatal, whereas fulminant pulmonary edema is commonly fatal.

Pharmacokinetics

Hydralazine is well absorbed from the gastrointestinal tract but undergoes first-pass hepatic metabolism. Although the kidney does not excrete hydralazine, its biotransformation is affected by renal failure, which may increase serum concentration. The vasodilating effect of hydralazine occurs within 30–60 min after oral administration and peaks within 3 h. The effect is then stable for the next 8–10 h, after which it rapidly dissipates. The net duration of effect is about 12 h.

Adverse effects

The most common side effects include first-dose hypotension and anorexia, vomiting and diarrhea.

- **Gastrointestinal.** Anorexia and/or vomiting occur in approximately 20–30% of patients. They are often intractable as long as the drug is being administered. Consequently, discontinuation of the drug may be necessary. Reducing the dose to 0.25–0.5 mg/kg

q.12 h for 1–2 weeks and then increasing the dose to its therapeutic range may be effective in some cases.

- **Hypotension**. The most serious adverse effect is hypotension, indicated by signs of weakness and depression. In most cases, this does not require treatment and the signs will abate within 10–12 h after the last dose of hydralazine. The dose should then be reduced.
- **Reflex tachycardia**. When hydralazine is used as the only agent in patients with hypertension and normal cardiac function, hydralazine induces a reflex increase in sympathetic nervous system tone. The increased sympathetic drive increases myocardial contractility and heart rate. Consequently cardiac output increases dramatically, offsetting the effect of the arteriolar dilation. The net result is no change in systemic arterial blood pressure. When an α-adrenergic receptor blocker is added to the therapeutic regimen, the reflex effect is blocked and systemic arterial blood pressure decreases.

  Although hydralazine is not commonly used to treat hypertension in veterinary medicine, this same response would be expected in a patient that is misdiagnosed and receives hydralazine when it is not in heart failure.

  Reflex sympathetic tachycardia is not as common in heart failure patients as in patients with systemic hypertension. However, in one study, heart rate in dogs with mild to moderate heart failure increased from an average of 136 beats/min to 153 beats/min following hydralazine administration. In patients with heart failure, the sympathetic nervous system is already activated but the heart's ability to respond to the sympathetic nervous system is blunted or abolished. In fact, the heart's ability to respond to any type of stimulus is overwhelmed.

  Therefore, when hydralazine is administered to a patient with heart failure, systemic arterial blood pressure does decrease and a less profound increase in systemic blood flow is produced than that observed when the drug is administered to patients with systemic hypertension.

  Reflex tachycardia may be controlled by the addition of α-adrenergic blocking drugs or digoxin.
- **Increased renin release**. Rebound increases in renin and aldosterone secretion and decreased sodium excretion occur following hydralazine administration. The beneficial effect on regurgitant fraction usually outweighs these effects, however.

  One should remember that drugs like furosemide also increase renin release and so increase plasma aldosterone concentration. In people, systemic lupus erythematosus, drug fever and peripheral neuropathy have been reported.

Known drug interactions

Hydralazine administration may have beneficial effects on the pharmacokinetics and pharmacodynamics of other drugs.

- Increased renal blood flow caused by hydralazine administration can increase the glomerular filtration rate (if initially depressed) and thereby enhance digoxin excretion.
- Increased renal blood flow also improves furosemide delivery to the nephron. This increases furosemide's renal effects (increases natriuresis and diuresis), especially in patients that are refractory to furosemide administration because of decreased renal flow due to decreased cardiac output.

Prazosin

Clinical applications

Prazosin is an arteriolar and venodilatory agent. The hemodynamic effects of prazosin have not been documented in the dog or cat. In humans with heart failure, its administration decreases right and left ventricular filling pressures, edema and congestion and increases stroke volume and cardiac output. Prazosin is effective in reducing mean arterial blood pressure in some dogs with renal hypertension.

Mechanism of action

Prazosin acts primarily by blocking α_1-adrenergic receptors but also peripherally inhibits phosphodiesterase. Since prazosin does not block α_2-adrenergic receptors, noradrenaline (norepinephrine) release is still controlled via negative feedback. Reflex tachycardia is generally not seen. The vasodilating effects of prazosin become attenuated after the first dose in humans and in rats. This problem has markedly limited its use in human medicine. In rats, it is thought that this effect is brought about by stimulation of the RAAS.

Formulations and dose rates

Prazosin is supplied as capsules.

DOGS

- The starting dose is 1 mg q.8 h PO for dogs <15 kg and 2 mg q.8 h PO for dogs >15 kg
- The dose then needs to be titrated upward if the initial dose is ineffective, or reduced if hypotension occurs

CATS

- The preparation is not amenable for use in cats

Pharmacokinetics

Elimination and metabolism are primarily hepatic. No adjustment is made for renal insufficiency.

Adverse effects

Prazosin may cause first-dose hypotension, anorexia, vomiting, diarrhea and syncope.

Nitrates

EXAMPLES

IV: nitroprusside
Topical: nitroglycerin

The organic nitrates, such as nitroglycerin, are esters of nitric oxide. Nitroprusside is a nitric oxide-containing compound without an ester bond. There are important differences in the biotransformation of these compounds but it is generally accepted that they share a common final pathway of nitric oxide (endothelium-derived relaxing factor) production and a common therapeutic effect. Organic nitrates, such as nitroglycerin, are explosive. They are rendered nonexplosive by diluting the compound with an inert recipient, such as lactose.

Mechanism of action

Nitrates relax vascular smooth muscle. They do this through a complex series of events. Nitrates are denitrated in smooth muscle cells to form nitric oxide (NO), which binds with the heme moiety on the enzyme guanylate cyclase. This causes activation of guanylate cyclase, which enzymatically forms cGMP from GTP. Cyclic GMP activates a serine/threonine protein kinase, which phosphorylates myosin light chains, resulting in smooth muscle relaxation. Cyclic GMP also stimulates calcium efflux and uptake by intracellular proteins and may inhibit calcium influx.

Clinical applications

Nitrates have been advocated as agents to produce systemic venodilation in dogs and cats with heart failure. Few studies have been performed to document the pharmacodynamics or establish the therapeutic dosage of the nitrates in dogs or cats. Nitrates can be administered orally, intravenously or transcutaneously to patients with heart failure. When administered transcutaneously or orally to humans, a low plasma concentration is achieved. Nitrates act primarily as venodilators at low plasma concentrations. When administered intravenously, a higher concentration is achieved and arteriolar dilation also occurs. Intravenous nitroglycerin is a potent venodilator with moderate arteriolar dilating properties.

Nitrates are well absorbed from the gastrointestinal tract but are rapidly metabolized by hepatic organic nitrate reductase. Consequently, bioavailability of orally administered nitrates is very low, typically less than 10%. In humans, the duration of effect after transcutaneous administration is 3–8 h.

Nitrate tolerance

The phenomenon of nitrate tolerance dates back to the 1940s. Munitions workers exposed to nitroglycerin commonly developed a headache on Monday that abated over the week as they developed tolerance. Over the weekend, their tolerance abated and on Monday, re-exposure again resulted in headache.

Tolerance to the organic nitrates is a common problem in human patients, occurring in up to 70% of individuals exposed to intravenous infusions of nitroglycerin. The exact mechanism is poorly understood, although two possible explanations have been proposed. The most popular theory is that sulfhydryl groups (thiols) are depleted with repeated exposure. Sulfhydryl groups are required for the metabolic conversion of nitroglycerin to nitric oxide. The second theory involves neurohormonal activation resulting in vasoconstriction and increased renal sodium retention.

Intermittent administration of nitrates prevents tolerance in human patients. However, this approach is limited by the fact that the hemodynamic benefit is interrupted. Concurrent administration of hydralazine with a nitrate appears to prevent nitrate tolerance in human heart failure patients. Hydralazine also prevents tolerance in a rat model of heart failure and in vitro in rat aortas rendered tolerant to nitrate in vivo. The results of the in vitro experiment suggested that the effect was due to inhibition of a pyridoxyl-dependent reaction, such as the catabolism of cysteine and methionine, which could enhance the availability of sulfhydryl groups.

Nitroglycerin

Clinical applications

In human patients with heart failure, transdermal administration of nitroglycerin primarily results in systemic venodilation. This effect results in a redistribution of blood volume from the central to the peripheral vascular compartments resulting in a decrease in diastolic intraventricular pressures and a reduction in the formation of edema fluid. Systemic vascular resistance is lowered to a lesser degree. The dosage required to produce a beneficial effect is highly variable from patient to patient and some patients are refractory to the drug. Tolerance develops quickly, within 18–24 h. A rebound increase in systemic vascular resistance is observed when nitroglycerin is withdrawn, which results in a decrease in cardiac output. There is no rebound effect on ventricular diastolic and atrial pressures.

Transdermal administration of nitroglycerin has been advocated for use in dogs and cats with heart failure. All references in the veterinary literature to the use of

nitroglycerin, including dosing, are anecdotal. Nitroglycerin is most commonly administered in conjunction with furosemide, usually to patients with severe heart failure. Beneficial effects in this situation cannot be directly ascribed to nitroglycerin because it is well known that furosemide by itself can produce dramatically beneficial effects in these patients.

In our clinic, transdermal nitroglycerin is only rarely used in patients with heart failure. However, we have on occasion observed beneficial effects in dogs that were not responding or had become unresponsive to other cardiovascular drugs. Consequently, there may be a limited role for this drug in veterinary patients. Nitroglycerin is not a very effective drug and should never be administered as the sole agent to a patient with moderate to severe heart failure.

Formulations and dose rates

Nitroglycerin ointment is available in a 2% formulation to be spread on the skin for absorption into the systemic circulation. Numerous manufacturers also supply it in a transcutaneous patch preparation. Nitroglycerin is diluted with lactose, dextrose, alcohol, propylene glycol or another suitable inert excipient so that the medical-grade material usually contains about 10% nitroglycerin. It appears as a white powder when diluted with lactose or as a clear, colorless or pale yellow liquid when diluted with alcohol or propylene glycol. Nitroglycerin is also supplied as a liquid for intravenous administration. Extended-release preparations are supplied as capsules or scored tablets.

In dogs and cats, 2% nitroglycerin cream has been used (12 mm per 2.5 kg bodyweight q.12 h for dogs, 3–6 mm q.4–6 h for cats) but efficacy has not been documented. If transcutaneous nitroglycerin cream is used, it should be applied on a hairless area (usually inside the ear flap), using gloves, since transcutaneous absorption will occur in the clinician or owner as well as in the patient. Cutaneous absorption in a human can cause a profound headache and a very unhappy client. Transdermal patches have been used successfully in large dogs with dilated cardiomyopathy.

When nitroglycerin is administered intravenously it acts as a potent arteriolar dilator and venodilator. The onset of action after intravenous administration is similar to nitroprusside. Duration of effect is minutes so the drug must be administered by CRI. The recommended administration rate to start with in humans is 5 μg/min. This dose is increased in increments of 10–20 μg/min until an effect is identified. There is no fixed optimum dose. Effective doses in small animals have not been identified. To use this drug, a low starting dose would have to be identified and titrated upward as blood pressure was monitored.

In cats and dogs, extended-release nitroglycerin can be used to treat refractory heart failure alone or in conjunction with other vasodilators. Most experience has been garnered in dogs and cats with refractory ascites or pleural effusion. Anecdotal evidence would suggest that the time between fluid removal can be increased by several weeks if extended-release nitrogylcerin is used and in some cases use of the drug may eliminate the need for fluid removal altogether. The dose should be titrated, starting at 2.5 mg q.12 h orally in cats up to a maximum of 6.5 mg q.8 h PO. Small dogs can be treated the same as cats. In medium to large dogs, the dose is started at 6.5 mg q.12 h PO. The maximum dose is 9.0 mg q.8 h PO.

Mechanism of action

Nitroglycerin is an organic nitrovasodilator that possesses a nitrate ester bond. The biotransformation of nitroglycerin to nitric oxide is complex and not completely understood. Thiols (compounds containing sulfhydryl groups) appear to be important as intermediary structures.

Pharmacokinetics

Nitrates are metabolized in the liver by nitrate reductase to two active major metabolites: 1,2- and 1,3-dinitroglycerols. Although less active than their parent compounds, they may be responsible for some of the pharmacological effect.

Nitroglycerin has a very short half-life of 1–4 min. It is metabolized to 1,3-glyceryl dinitrate, 1,2-glyceryl dinitrate and glyceryl mononitrate. The parent compound is approximately 10–14 times as potent as the dinitrate metabolites but the metabolites have longer half-lives and are present in substantial plasma concentrations. The mononitrate metabolite is inactive. The onset of action with the transdermal route of administration is delayed and the duration of effect is prolonged. Transdermal systems are designed to provide continuous, controlled release of nitroglycerin to the skin, from which the drug undergoes absorption. The rates of delivery and absorption of the drug to the skin vary with the specific preparation. Individual manufacturers' information for a drug should be consulted for this information. However, one must remember that this information pertains to human skin and probably does not translate into the actual rate of delivery for a dog or a cat.

Special considerations

Nitroglycerin ointment should be stored in airtight containers at 15–30°C. Owners should be instructed to close the container tightly immediately after each use. Intravenous nitroglycerin solutions should be stored only in glass bottles because nitroglycerin migrates readily into many plastics. About 40–80% of the total amount of nitroglycerin in a diluted solution for IV administration is absorbed by the polyvinyl chloride (PVC) tubing of IV administration sets. Special non-PVC-containing administration sets are available.

Isosorbide mononitrate and dinitrate

Clinical applications

Isosorbide mononitrate and dinitrate are organic nitrates that can be administered orally, primarily to patients

with severe, refractory heart failure. One study has documented that isosorbide mononitrate did not produce the expected shift in blood volume from the central thoracic space to the splanchnic space. As with other nitrates, one should never rely on the isosorbides to produce a clinically meaningful change in hemodynamics or produce clinically significant improvement.

Mechanism of action

This is the same as for other organic nitrates.

Formulations and dose rates

- Isosorbide dinitrate is supplied as 5, 10, 20, 30 and 40 mg tablets. Isosorbide mononitrate is supplied as 10 and 20 mg tablets
- The dose for both nitrates is in the 1–2 mg/kg q.12 h range

Pharmacokinetics

Isosorbide mononitrate has been studied in experimental dogs. In one study, a dose of approximately 1–2 mg/kg PO to dogs subjected to transmyocardial direct current shock produced acute hemodynamic effects that lasted only 2 h. This dose when administered over days, however, resulted in a chronic decrease in pulmonary capillary wedge pressure and a decrease in left ventricular volume and mass when compared to control dogs.

Nitroprusside

Clinical applications

Nitroprusside is a potent venodilator and arteriolar dilator. It may also increase left ventricular compliance. It is administered intravenously and is used only for short-term treatment of dogs with severe or fulminant heart failure. In one study in normal dogs, nitroprusside decreased systemic arterial blood pressure by 23% and increased cardiac output by 39%. This effect became attenuated over time. Because tolerance does not occur with nitroprusside, this attenuation of effect is probably due to reflex changes. As expected, left ventricular end-diastolic and end-systolic diameters decreased in one study, as did left ventricular end-diastolic pressure.

Nitroprusside is beneficial in dogs with experimentally induced acute mitral regurgitation (comparable to a patient with a ruptured chorda tendinea). In one study, a dose of 5 μg/kg/min reduced left ventricular systolic pressure 16% and decreased left ventricular end-diastolic pressure from 23 mmHg to a normal value of 10 mmHg. Left atrial pressure, left atrial diameter and left ventricular diameter also decreased. The left atrial 'v' wave decreased from 41 mmHg to 16 mmHg.

In humans with severe heart failure, nitroprusside can produce beneficial effects that are as good as or better than administration of intravenous furosemide. In one study, nitroprusside reduced pulmonary capillary pressure from 31 mmHg to 16 mmHg while increasing the cardiac index from 2.33 L/min/m^2 to 3.62 L/min/m^2. Furosemide (200 mg IV) in these same patients decreased pulmonary capillary pressure to 27 mmHg while the cardiac index did not change.

Nitroprusside, in combination with dobutamine, has been shown to be effective in dogs with severe heart failure due to DCM. Otherwise, all information is anecdotal. Available information suggests that nitroprusside can be very effective at improving the clinical signs of heart failure. Of course, nitroprusside only produces a temporary improvement that is readily reversible. When administration is discontinued, vasodilation rapidly disappears and a rebound increase in vasoconstriction, above that observed prior to drug administration, may occur. In human patients, when nitroprusside is discontinued after 24–72 h, pulmonary capillary and systemic arterial pressures return to pre-treatment values within 5 min. This occurs despite increases in urine volume and sodium excretion while on the drug. Consequently, other, longer-acting drugs must be administered while patients are weaned off the nitroprusside in order to maintain the improvement in hemodynamics.

Mechanism of action

Nitroprusside (sodium nitroferricyanide) produces nitric oxide in vascular smooth muscle. Unlike the organic nitrates, nitroprusside releases nitric oxide when it is nonenzymatically metabolized directly via 1-electron reduction. This may occur on exposure to numerous reducing agents and tissues such as vascular smooth muscle. The major difference between nitroprusside and the organic nitrates is that tolerance to nitroprusside does not develop.

Formulations and dose rates

Sodium nitroprusside is supplied as vials containing 50 mg of lyophilized dry powder for dilution in 5% dextrose in water.

The dose of nitroprusside is highly variable from patient to patient. In addition, the hemodynamic response can be varied depending on the amount of change in filling pressures and cardiac output desired. Consequently, the dosage range is large. Doses from 2–25 μg/kg/min reduce systemic arterial blood pressure in a dose-dependent manner in experimental dogs. However, the decrease in blood pressure with 25 μg/kg/min is only about 5 mmHg more than that observed with 10 μg/kg/min. Consequently, it does not appear that doses greater than 10 μg/kg/min provide much more benefit than those less than 10 μg/kg/min. In humans, the dosage rarely exceeds 10 μg/kg/min.

Pharmacokinetics

Nitroprusside is rapidly metabolized after intravenous administration, with a half-life of a few minutes. Consequently, no loading dose is required and any untoward effects of the drug can be rapidly reversed by discontinuing drug administration. When nitroprusside is metabolized, cyanogen (cyanide radical) is produced. This is converted to thiocyanate in the liver by the enzyme thiosulfate sulfurtransferase (rhodanase).

Adverse effects

- Adverse effects of nitroprusside are hypotension and cyanide toxicity.
- Nitroprusside-induced hypotension can be rapidly (1–10 min) reversed by discontinuing drug administration.
- Sodium nitroprusside infusions in excess of 2 µg/kg/min generate cyanogen in amounts greater than can be effectively buffered by the normal quantity of methemoglobin in the body. Deaths due to cyanogen toxicity can result when this buffering system is exhausted. In humans, this has only been reported in patients receiving infusion rates of 30–120 µg/kg/min. However, increased circulating cyanogen concentration, metabolic acidosis and clinical deterioration have been observed at infusion rates within the therapeutic range.
- In humans, it has been recommended that an infusion rate of 10 µg/kg/min should not last for longer than 10 min. Cyanogen toxicity can be manifest as venous hyperoxemia (bright red blood as a result of the inability of oxygen to dissociate from hemoglobin), lactic acidosis and dyspnea. Administration of thiosulfate and of hydroxycobalamin have been reported to prevent cyanide toxicity. In the presence of thiosulfate, cyanogen is converted to thiocyanate, which is excreted in the kidneys.
- Thiocyanate toxicity can occur, especially in patients that have a decrease in GFR, are on prolonged infusions or are receiving thiosulfate. Neurological signs occur in humans at a serum concentration of 60 µg/mL and death can occur at concentrations above 200 µg/mL. As for other hypotensive agents, nitroprusside increases plasma renin activity.

Special considerations

Sodium nitroprusside is sensitive to light, heat and moisture. Exposure to light causes deterioration that may be observed as a change in color from brown to blue caused by reduction of the ferric ion to a ferrous ion. If not protected from light, approximately 20% of the drug in solution in glass bottles will deteriorate every 4 h when exposed to fluorescent light.

The drug deteriorates even faster in plastic containers. Consequently, sodium nitroprusside should be protected from light by wrapping the bottle with aluminum foil. When adequately protected from light, the solution is stable for 24 h. Nitroprusside reacts with minute quantities of a variety of agents including alcohol, forming blue, dark red or green products. The solution should be discarded if this occurs.

VASODILATORS WITH ADDITIONAL PROPERTIES

Inodilators

EXAMPLES

Oral: pimobendan
IV: milrinone, amrinone

This class of agents has both positive inotropic and vasodilatory properties and has been labeled inodilators as a reflection of the term ‘inodilation’ coined by Lionel H Opie in 1989. All properties of this class are discussed in detail in the inodilator section of this chapter (p. 398).

Angiotensin-converting enzyme (ACE) inhibitors

EXAMPLES

Enalapril (preferred), benazepril (preferred), ramipril (preferred), lisinopril, captopril

In general, all ACE inhibitors have similar effects on hemodynamics. ACE inhibitors are modest balanced venodilators with important neuroendocrine modulatory effects. Thus further discussion of ACE inhibitors will be covered in the neuroendocrine modulation section of this chapter.

Sildenafil

Sildenafil (Viagra®) is an orally active phosphodiesterase V inhibitor (PDE Vi). Phosphodiesterase V is found in a relatively high concentration in lung and erectile penile tissue and is elevated in humans with pulmonary hypertension. Pulmonary hypertension (PH) is a clinically important disease in the dog with high morbidity and mortality rates. Canine PH is most often a sequel of other disease processes and thus requires a balanced therapeutic approach which targets the underlying etiology as well as palliation of clinical signs. An important goal of therapy is to reduce pulmonary artery pressure. Conventional systemic arteriolar dilators have no preferential effect on pulmonary vasculature and thus have

no benefit and may worsen clinical signs. PDE Vi prevents degradation of cGMP resulting in relaxation of pulmonary vascular smooth muscle and, to a lesser degree, systemic vasodilation (preferential pulmonary vasodilation). Sildenafil is currently the most extensively researched of the PDE V inhibitors and has been shown to improve both exercise tolerance and quality of life in humans with pulmonary hypertension resulting in its FDA approval for treatment of this disorder in humans.

Viagra® was recently re-released as Revatio® (which is more expensive). Sildenafil is now available as a generic preparation in some countries further reducing its cost although documentation of efficacy of the generic formulations has not been reported. Clinical improvement in humans has been documented at multiple doses ranging from 20 mg to 80 mg three times a day. Because higher doses do not increase the efficacy, the currently recommended dose in humans is 20 mg every 8 h.

Formulations and dose rates

CANINE

- 0.25–3.0 mg/kg PO

Empirically, the authors start at a dose of approximately 5 mg/dog and titrate. In oxygen-dependent dogs, initiation of the target dose of approximately 3 mg/kg may be indicated and well tolerated based on the authors experience. Uptitration can occur over days to weeks if patients are not oxygen dependent. Due to cost the authors have not used doses greater then 25 mg/dog. Oral sildenafil liquid dosage forms have been reported to be stable and have been used in people. Therefore suspension formulations can be used in dogs and greatly facilitate cost effective accurate dosing.

Adverse effects

None have been documented in the dogs managed by the author (>25 dogs). One retrospective canine study also reported no adverse side effects and clinical improvements in 10 dogs with PH receiving a median dose of approximately 2 mg/kg every 8–24 h.

Known drug interactions

Due to the nature of canine PH, sildenafil has been used in combination with many other medications including conventional heart failure medications (diuretics, ACE inhibitors, pimobendan) with no recognized adverse effects.

NEUROENDOCRINE MODULATION

Agents in this group address the maladaptive changes associated with the progression of heart disease in the RAAS and sympathetic nervous system.

EXAMPLES

Oral: ACE inhibitors (preferred), aldosterone antagonist (e.g. spironolactone) (preferred), β-blockers (preferred), digoxin, neutral endopeptidase inhibitors, angiotensin receptor blockers

Angiotensin-converting enzyme (ACE) inhibitors

EXAMPLES

Enalapril (preferred), benazepril (preferred), ramipril (preferred), lisinopril, captopril

There are five ACE inhibitors that have been used in dogs and cats: captopril, enalapril, lisinopril, benazepril and ramipril. Generally these drugs have similar effects. The primary difference is in duration of effect and potential side effects. Captopril, the original ACE inhibitor, is short-acting, lasting less than 3–4 h, and has more side effects than the other ACE inhibitors. It is therefore now rarely used. The effects of enalapril and ramipril last 12–14 h. Lisinopril and benazepril are thought to be the longest-acting ACE inhibitors; once-daily use is advocated in humans and animals. Benazepril is excreted primarily via hepatic metabolism versus renal filtration (others) and thus may be better tolerated in patients with pre-existing renal disease particularly when a low dose is required.

Clinical applications

The primary clinical indication for ACE inhibitors is for the treatment of heart failure in dogs, cats and people. ACE inhibitors are also frequently used for the management of systemic hypertension in people. However, their efficacy in systemic hypertension in dogs and cats when used as monotherapy has been disappointing.

A more recent indication for ACE inhibitors in dogs, cats and people is in the treatment of a variety of renal diseases with emphasis on protein-losing glomerulopathy. Given the subject matter of this chapter, these indications will not be discussed in detail but the reader is directed to additional reading on the subject including the *ACVIM consensus statement on management of proteinuria in dogs and cats*. In brief, there is evidence that use of ACE inhibitors (benazapril) will attenuate the progression of renal failure in cats with significant proteinuria. However, the evidence that they are beneficial in cats with little proteinuria (the majority of cats) has not yet been established by appropriate large-scale clinical trials. There is probably no disadvantage to using ACE inhibitors in cats with renal failure as there may be some benefit provided the cat can be pilled easily

and the owner can afford the treatment. However, dietary change (reduction in phosphate) carries significantly greater potential benefits in slowing the progression of renal failure and ACE inhibitor therapy should not be regarded as a substitute for it. Treating cats and dogs that are severely azotemic or that have prerenal azotemia with ACE inhibitors may actually speed their demise.

Mechanism of action

The RAAS plays an important role in regulating cardiovascular homeostasis in normal individuals and patients with heart failure. Renin is released from the juxtaglomerular apparatus in response to sympathetic stimulation and to decreased sodium flux by the macula densa. In the plasma, renin is a protease that acts on the glycoprotein angiotensinogen to form the polypeptide angiotensin I. Angiotensin converting enzyme (ACE) cleaves two amino acids from the decapeptide angiotensin I to form the octapeptide angiotensin II. This conversion primarily occurs in the vascular endothelium of the lung although other vascular beds are involved.

ACE inhibitors bind to the same site on ACE as angiotensin I, effectively arresting its action. This site contains a zinc ion and ACE inhibitors contain a sulfhydryl, carboxyl or phosphoryl group that interacts with this site. The relative potency of these compounds depends on the affinity of the compound for the active site. ACE inhibitors that are more tightly bound to the active site tend to be more potent. They also tend to have a longer duration of effect.

The effects of ACE inhibitors occur as a result of the decreased concentration of circulating angiotensin II. Angiotensin II has several important effects in patients with heart failure.

- It is a potent vasopressor.
- It stimulates the release of aldosterone from the adrenal gland.
- It stimulates vasopressin (ADH) release from the posterior pituitary gland.
- It facilitates the central and peripheral effects of the sympathetic nervous system.
- It preserves glomerular filtration when renal blood flow is decreased via glomerular efferent arteriolar constriction.
- It stimulates hypertrophy and thus contributes to maladaptive remodeling in heart failure.

ACE inhibitors have several effects in patients with heart failure. Balanced vasodilation (arteriolar and venodilation) occur as a direct result of the decreased concentration of angiotensin II. Consequently, ACE inhibitors are generally classified as vasodilators. ACE inhibitors also decrease activation of the RAAS and this is their most important role.

The effects of ACE inhibitors become evident at different times following the onset of administration. Arteriolar dilation is observed after the first dose is administered, while the lessening of sodium and water retention takes days to become clinically significant. Since most dogs presenting for severe heart failure are dying from pulmonary edema, the ACE inhibitors are poor emergency heart failure drugs and their potential to cause adverse renal effects is enhanced when aggressive parenteral furosemide is used. Thus this author does not initiate or continue ACE inhibitor therapy when intravenous furosemide is being used.

The ability of ACE inhibitors to decrease plasma aldosterone secretion may become attenuated or lost with time. In one study of cavalier King Charles spaniels with severe mitral regurgitation, enalapril significantly decreased plasma aldosterone concentration after 3 weeks of administration. However, 6 months later the plasma aldosterone concentration had increased to an even higher level than at baseline. These dogs were also on furosemide at 6 months, which may have contributed to the increase. However, it is known that other enzymes, such as chymase, are capable of converting angiotensin I to angiotensin II and so may contribute to the lack of prolonged effect.

In most canine patients the arteriolar dilating effect of ACE inhibitors is relatively mild when compared to the more potent arteriolar dilators like amlodipine and hydralazine. In general, ACE inhibitors can decrease systemic vascular resistance by 25–30% while hydralazine can decrease it by 50%.

Benefits

Clinical cardiovascular disease

The clinical benefits of ACE inhibitors in heart failure are well documented in human and canine studies and are considered a class effect. Thus if enalpril has been shown to be beneficial one could use benazepril and expect the same effect. In human medicine there are currently head to head ACE inhibitor trials under way that may address potential differences in efficacy between ACE inhibitors. In general, ACE inhibitors improve clinical signs and improve quality of life in dogs and cats with heart failure due to diverse causes. The improvement in clinical signs is primarily due to reduction in capillary pressures and edema formation and to increased perfusion of vascular beds. ACE inhibitors are one of the few drug types used to treat heart failure that have been proved to both improve symptoms and prolong life in humans and to prolong the time until treatment failure in dogs.

A number of studies have evaluated enalapril's efficacy in dogs with dilated cardiomyopathy and with primary mitral regurgitation and heart failure. In the first study (IMPROVE: **i**nvasive **m**ulticenter **pro**spective

veterinary evaluation of enalapril study) it was shown that measurements of acute hemodynamic variables in dogs in heart failure generally did not change but chronic measures of clinical status did. A second study (COVE: co-operative veterinary enalapril study group) examined 211 dogs at 19 centers. In this blinded and placebo-controlled clinical trial, dogs on enalapril again improved clinically when compared to those on placebo over a 28-day period. There were 141 dogs with primary mitral regurgitation and 70 with dilated cardiomyopathy as the primary diagnosis.

A third study (LIVE: long-term investigation of veterinary enalapril study) continued to examine 148 dogs from the COVE and IMPROVE studies for up to 15.5 months. Dogs remained in the study until they developed intractable heart failure (n = 48), died of heart failure (n = 17), died suddenly (n = 10), died of a non-cardiac cause (n = 4), dropped out of the study for other reasons (n = 48) or the study ended (n = 21). Dogs administered enalapril remained in the study significantly longer (169 days) than dogs administered the placebo (90 days). Most of this benefit occurred in the first 60 days. After that, dogs in both groups either developed intractable heart failure or died at a similar rate. When divided into dogs with mitral regurgitation and those with dilated cardiomyopathy, the dogs with dilated cardiomyopathy receiving enalapril remained in the study significantly longer than those receiving placebo while the dogs with mitral regurgitation did not. Enalapril has been shown to be beneficial in dogs with mitral regurgitation but of less benefit for the group as a whole than might have been expected. In general, some dogs with mitral regurgitation have dramatic responses to an ACE inhibitor, many improve clinically but a significant number have little response.

A more recent clinical trial compared the effects of benazepril to placebo in 162 canine patients (37 with dilated cardiomyopathy and 125 with primary mitral regurgitation) with mild to moderate heart failure. Most dogs were already being treated for heart failure with diuretics and vasodilators, including other ACE inhibitors. Benazepril (0.25–0.5 mg/kg/day) increased time to treatment failure or death (428 days) when compared to placebo (158 days). The percentage of dogs surviving without being withdrawn from the study because of worsening heart failure 1 year after the onset of the study was 49% in the benazepril group and 20% in the placebo group. From these data it appears that benazepril produces benefits similar to other ACE inhibitors in dogs with heart failure.

The results of these studies are quite clear. ACE inhibitors, despite the fact that they produce minimal hemodynamic change, result in clinical improvement in dogs with heart failure due to mitral regurgitation or dilated cardiomyopathy. ACE inhibitors appear to perform better in dogs with DCM but are clearly efficacious in many dogs with mitral regurgitation. However, in general and in both diseases, the clinical response is not profound. Rather, in most cases ACE inhibition results in mild and gradual improvement, which helps to stabilize the clinical course of the patient and improve the quality of life.

More recently, pimobendan has been demonstrated to be superior to a variety of ACE inhibitors for the treatment of canine heart failure (see p. 398). Based on all currently available data it is one of the author's (Gordon) opinion that optimum canine heart failure therapy from 2007 involves a combination of an ACE inhibitor and pimobendan as well as furosemide at a dose that controls signs of congestion.

Preclinical cardiovascular disease

Studies have been performed in humans to determine if starting ACE inhibitor therapy with enalapril in patients with left ventricular dysfunction but without evidence of heart failure is beneficial. Benefit has been defined as reduction in mortality, reduction in the incidence of heart failure and reduction in the hospitalization rate. In a study of human patients with chronic cardiac disease, 4228 patients with ejection fractions less than 35% (comparable to a shortening fraction below 15%) were randomized to receive either placebo or enalapril. They were followed clinically for an average of 37 months. During this time there was no reduction in mortality associated with enalapril administration. There was a reduction in the incidence of heart failure and in hospitalizations for heart failure (the drug delayed the onset of heart failure). These latter findings should be expected for any drug meant to effectively treat heart failure.

A recent study examined the effects of administering either enalapril or placebo to 237 cavalier King Charles spaniels with myxomatous mitral valve disease and mitral regurgitation over 2 years. Dogs at entry had to have a heart murmur due to mitral regurgitation, with or without radiographic evidence of cardiomegaly. Enalapril, when compared to placebo, had no effect on how soon these dogs went into heart failure. Consequently, there is no current indication for administering an ACE inhibitor to dogs with mitral regurgitation prior to the development of heart failure. These results were more recently confirmed in an all breed study.

Adverse effects

The potential risks of interfering with angiotensin II formation lie in its role of preserving systemic blood pressure and glomerular filtration rate (GFR) as renal flow decreases. Blocking angiotensin II action on peripheral arterioles can result in hypotension that leads to cerebral hypoperfusion. Dizziness is seen in 15%

of humans taking ACE inhibitors. The incidence of clinically significant hypotension in dogs appears to be much less, probably because dogs do not walk upright.

The second risk is seen in patients that are very dependent on angiotensin II to maintain GFR. Glomerular efferent arteriolar constriction maintains normal GFR in mild to moderately severe heart failure when renal blood flow is reduced. The primary stimulus for this vasoconstriction is increased plasma angiotensin II concentration, which is elaborated in response to the decrease in renal blood flow. Glomerular capillary pressure provides the force for filtration and glomerular capillary pressure is determined by renal plasma flow and efferent arteriolar resistance.

When renal plasma flow is low (as in heart failure) and potentiated by concurrent diuretic use, angiotensin II causes efferent arterioles to constrict, bringing glomerular capillary pressure back to normal. GFR is then preserved despite the decrease in renal blood flow and normal serum urea and creatinine concentrations are maintained. The filtration fraction (ratio of GFR to renal plasma flow) is increased. When an ACE inhibitor is administered, efferent arteriolar dilation must occur. In some patients this dilation appears to be excessive, resulting in a moderate to marked reduction in GFR and subsequent azotemia.

Those human patients that are at greatest risk for developing azotemia include patients with high plasma renin activity, low renal perfusion pressure, hyponatremia and excessive volume depletion. When angiotensin II concentration is decreased in at-risk patients, GFR becomes decreased and azotemia results. The azotemia is generally mild but occasionally can be severe in both human and canine patients.

Functional azotemia can occur secondary to the administration of any ACE inhibitor. The longer-acting agents (e.g. enalapril) may more frequently produce azotemia in human patients than the shorter-acting agents (e.g. captopril). However, in one study in rats, captopril produced a marked reduction in GFR while perindopril did not. Treatment consists of reducing the diuretic dose or stopping the administration of the ACE inhibitor. Although this functional azotemia may develop with greater frequency in at-risk patients, it should be stressed that azotemia sometimes develops in a canine patient that appears to have no risk factors other than heart failure.

Decreased GFR and an increase in serum urea and creatinine concentration are seen in 35% of human patients receiving ACE inhibitors. In most cases the increase in urea is mild and requires no intervention. In dogs, the incidence of clinically significant azotemia (plasma urea >35 mmol/L) is low. However, it occurs frequently enough that any veterinarian using these drugs should be aware of the potential occurrence of azotemia. Mild to moderate increases in plasma urea concentration (between 12 and 21 mmol/L) also occur at a low rate. In these patients, urea concentrations may increase without a concomitant increase in serum creatinine, or the increase in creatinine may be milder. As long as these patients continue to eat and act normally, these changes can generally be ignored.

Recommended guidelines for ACE inhibitor therapy with regards to azotemia based on human studies include the following.

- Identify high-risk patients (patients with moderate to severe dehydration, hyponatremia) before therapy.
- Ensure that the patient is not clinically dehydrated and ensure adequate oral fluid intake throughout therapy.
- Evaluate renal function at least once within 1 week after commencing therapy.
- Decrease the dose of furosemide if moderate azotemia develops or discontinue the ACE inhibitor if the azotemia is severe or if a reduction in furosemide dose does not improve renal function.
- Do not initiate or continue ACE inhibitor therapy when parenteral furosemide is required for severe or decompensated heart failure.
- Be cautious when combining an ACE inhibitor with agents that have potential renal toxicity or drugs that have the potential to also reduce GFR in susceptible patients such as all NSAIDs (see Chapter 13 for mechanism).

The prescribing information for one ACE inhibitor states that if azotemia develops the dose of diuretic should be reduced and if azotemia persists the dose should be reduced further or discontinued. This implies that diuretic administration should be discontinued permanently. Recommendations to permanently discontinue furosemide therapy in a patient with a clear history of moderate to severe heart failure are not tenable. In human medicine, the recommendation is to discontinue diuretic therapy for 24–48 h if needed, not permanently.

It is important to warn owners of the clinical signs of severe azotemia (usually anorexia and other gastrointestinal signs) and to measure serum creatinine and/or urea concentrations within the first week of ACE inhibitor therapy.

If a patient develops severe azotemia, it is usually wise to discontinue ACE inhibitor therapy and ensure that the patient is not significantly dehydrated.

If dehydration is moderate to severe, it is advisable to reduce the furosemide dose or discontinue its administration for 1–2 days and administer intravenous fluids cautiously.

Once the dog is stable, reassess the need for an ACE inhibitor. If the ACE inhibitor was being administered because of its potential (rather than actual) benefits and the patient does not require its administration it is advised not to attempt to readminister the ACE inhibitor.

If the patient is refractory to furosemide administration there are several options

- Initiate pimobendan if the patient is not already receiving it.
- Readminister the ACE inhibitor but at a lower dose and then try to gradually titrate the dose into the therapeutic range.
- Use a short-acting ACE inhibitor, such as captopril, if a longer-acting agent, such as enalapril, lisinopril, or benazepril, was administered initially.
- Add a thiazide diuretic.
- Add hydralazine or amlodipine.

One study of human patients with heart failure has documented that captopril acutely decreases the natriuretic and diuretic effects of furosemide. In this study, furosemide increased sodium excretion 623% above baseline while captopril plus furosemide only increased it 242% above baseline. Urine volume increased 225% above baseline with furosemide but only 128% above baseline in patients receiving both furosemide and captopril. This was an acute study. The chronic effects of administering captopril to patients stabilized on furosemide are unknown. This finding suggests that an ACE inhibitor should not be administered to a patient with severe, acute heart failure that needs the diuretic effect of furosemide to maintain life.

Known drug interactions

The arteriolar dilating effect of enalapril, and probably other ACE inhibitors, is attenuated by the concomitant administration of aspirin in humans. ACE inhibitors also decrease the breakdown of bradykinin, which stimulates prostaglandin synthesis. The predominant effect of prostaglandins in the systemic circulation is vasodilation. In one study in humans, the normal decrease in systemic vascular resistance induced by an ACE inhibitor was blocked by the concomitant administration of aspirin. However, a study has been performed in experimental dogs with heart failure in which low-dose aspirin produced no decrease in hemodynamic response to enalaprilat. In addition, the potential renal adverse effects associated with ACE inhibition may be potentiated by concurrent use of any NSAID particularly in dogs with heart failure receiving furosemide.

The combination of an ACE inhibitor and spironolactone has the potential to cause clinically significant hyperkalemia. There is only one retrospective report of the relative safety of this combination in dogs with heart failure who are also receiving concurrent furosemide. However, the author (Gordon) has observed clinically significant hyperkalemia when an ACE inhibitor and spironolactone were administered to a dog not receiving concurrent furosemide.

Enalapril

Enalapril is structurally and pharmacologically similar to captopril but contains a disubstituted nitrogen rather than the sulfhydryl group. The lack of the sulfhydryl group may result in decreased risk of certain side effects in humans, such as taste disturbances and proteinuria. These adverse effects have not been documented in dogs or cats administered ACE inhibitors.

Formulations and dose rates

The veterinary formulation of enalapril maleate is supplied as tablets. The human formulation is also supplied as tablets. There is also a formulation of enalapril maleate and hydrochlorothiazide that contains 10 mg enalapril maleate and 25 mg hydrochlorothiazide in one tablet. Enalaprilat is available for intravenous injection as enalaprilat in 0.9% alcohol at a concentration of 1.25 mg/mL of anhydrous enalaprilat.

DOGS

- Dose range studies have been performed with enalapril in dogs with surgically induced mitral regurgitation and heart failure. In these dogs, a dose of 0.5 mg/kg enalapril PO produced a greater decrease in pulmonary capillary pressure than a dose of 0.25 mg/kg. A dose of 0.75 mg/kg produced no better response. After 21 days of administration, the 0.5 mg/kg q.24 h dose produced a significant decrease in heart rate while the 0.25 mg q.24 h dose did not. Consequently, the enalapril dose is 0.5 mg/kg
- Whether this dose should be administered q.12 h or q.24 h is debatable. The package insert recommends starting with dosing q.24 h, increasing to q.12 h if the clinical response is inadequate
- Based on the pharmacodynamics presented below, we generally start the drug by administering it twice a day to dogs in heart failure, at approximately 12 h intervals

CATS

- PO: 1–2.5 mg/cat q.12–24 h
- PO: 0.2–0.7 mg/kg q.12–24 h

Pharmacokinetics

Enalapril is the ethyl ester of enalaprilat. It has little pharmacological activity until it is hydrolyzed in the liver to enalaprilat. Enalapril is available commercially as the maleate salt. Enalapril maleate is absorbed better from the gastrointestinal tract in dogs than enalaprilat. The affinity for enalaprilat for the angiotensin I binding

sites on ACE is approximately 200,000 times that of ACE.

In dogs, enalapril maleate achieves peak concentration within 2 h of administration. Bioavailability is approximately 60%. Enalapril is metabolized to enalaprilat. Peak serum concentration of this active form occurs 3–4 h after an oral dose. The half-life of accumulation is approximately 11 h and duration of effect is 12–14 h. Steady-state serum concentration is achieved by the fourth day of administration. Excretion of enalapril and enalaprilat is primarily renal (40%) although 36% is excreted in the feces. Approximately 85% of an oral dose is excreted as enalaprilat.

The pharmacodynamics of enalapril have been examined in experimental dogs. A dose of 0.3 mg/kg administered per os results in approximately 75% inhibition of the pressor response to angiotensin I. This effect lasts for at least 6 h and is completely dissipated by 24 h after administration. A dose of 1.0 mg/kg produces only slightly better inhibition (approximately 80%) for at least 7 h. About 15% inhibition is still present 24 h after oral administration.

Adverse effects

The adverse effects of enalapril are the same as for all ACE inhibitors, as outlined above. Chronic high-dose enalapril toxicity appears to be confined to the kidneys. In healthy dogs administered doses up to 15 mg/kg/d over 1 year, drug-induced renal lesions are not seen. High-dose (30–60 mg/kg/d) enalapril administration to dogs results in dose-related renal toxicity. At 30 mg/kg/d, increasing degrees of renal damage are observed that are shown to be a direct nephrotoxic response of enalapril itself on proximal tubular epithelium. This damage is permanent only when potentiated by marked hypotension. The damage is confined to the proximal tubules, primarily to the juxtamedullary regions of the cortex where necrosis of the tubular cells, but not the basement membrane, is present. Dogs that survive the initial insult to the proximal tubules undergo regeneration. A dose of 90–200 mg/kg/d is rapidly lethal through renal failure. The renal toxicity appears to be due to a direct nephrotoxic effect of the drug and to an exaggerated decrease in systemic blood pressure. Saline administration ameliorates the toxicity.

Benazepril

Benazepril can be used in dogs or cats with heart failure as any other ACE inhibitor. Benazeprilat has been studied in dogs with experimentally induced acute left heart failure. Benazeprilat decreased left ventricular end-diastolic pressure by approximately 15%, peripheral resistance by approximately 30% and aortic pressure by 30%. Cardiac output did not increase in these anesthetized dogs.

Formulations and dose rates

Benazepril

Benazepril is supplied as tablets and can be made into suspension by a formulation pharmacy.

DOGS

- PO: 0.3 mg/kg and 0.5 mg/kg q.24 h (some clinicians use it in advanced heart failure)

CATS

- PO: 1–2.5 mg/cat q.12–24 h
- PO: 0.2-0.7 mg/kg q.12–24 h

Benazeprilat

- Dog: 30 μg/kg IV

Pharmacokinetics

Benazepril is a nonsulfhydryl ACE inhibitor. Like enalapril, it is a prodrug that is converted to benazeprilat by esterases, mainly in the liver. Benazeprilat is approximately 200 times more potent as an ACE inhibitor than is benazepril. The conversion of benazepril to benazeprilat is incomplete and other metabolites are formed in the dog.

Benazeprilat is poorly absorbed from the gastrointestinal tract whereas benazepril hydrochloride is well absorbed in the dog. Bioavailability increases by about 35% with repeated dosing. Following the administration of oral benazepril, plasma benazeprilat concentration reaches peak concentration in plasma within 1–3 h. Benazeprilat is rapidly distributed to all organs except the brain and placenta. Benazeprilat is excreted approximately equally in the bile and the urine in dogs. The terminal half-life is approximately 3.5 h. There may be an additional slow terminal elimination phase in dogs that may have a half-life between 55 and 60 h. This combined excretion may allow better dosing control in patients with pre-existing renal insufficiency however benazepril is no more renal protective than any other ACE inhibitors at equipotent doses.

The pharmacodynamics of benazepril have been studied in dogs by measuring plasma ACE activity before and after various doses of the drug. A dose of 0.125 mg/kg benazepril q.24 h appears to be too low. It only inhibits plasma ACE activity to approximately 80% of baseline. A dose of 0.25 mg/kg decreases plasma ACE activity to less than 10% of baseline within 3 h of administration. This effect lasts for at least 12 h. By 16 h plasma ACE activity is back to 20% of baseline and by 24 h it is approximately 30% of baseline. Doses of 0.5 and 1.0 mg/kg cause the >90% suppression to last at least 16 h. When benazepril is administered chronically, doses from 0.25 mg/kg to 1.0 mg/kg produce indistinguishable effects at the time of peak effect (2 h after oral administration) and at trough effect (24 h after oral administration).

Adverse effects

Anticipated adverse effects would be the same as for other long-acting ACE inhibitors.

Lisinopril

Lisinopril is a lysine derivative of enalaprilat. It does not require hydrolysis to become active. It has a higher affinity for ACE than either captopril or enalapril.

Formulations and dose rates

Lisinopril is supplied as tablets.

DOGS AND CATS

- A clinically effective dose of lisinopril has not been identified
- The generally used dose in dogs is 0.5 mg/kg q.24 h PO. From pharmacodynamic data, a dose of 0.25–0.5 mg/kg q.12 h or 1.0 mg/kg q.24 h may be more effective
- The primary benefit of lisinopril may be in dogs with impaired liver function
- The major factor that retards its use is the fact that the studies to document its pharmacodynamics and efficacy in the dog and cat have not been performed

Pharmacokinetics

Lisinopril's bioavailability is 25–50% and is unaffected by feeding. Peak plasma concentration occurs 4 h after oral administration in dogs. Peak inhibition of the pressor response to angiotensin I occurs 3–4 h after oral administration. Peak ACE inhibition occurs 6–8 h after administration. Elimination half-life of lisinopril in dogs is about 3 h.

Lisinopril's effects last for 24 h but are substantially attenuated 24 h after oral administration in dogs. A dose of 0.3 mg/kg orally to dogs results in approximately 75% inhibition of the pressor response to angiotensin I 3 h after administration. This response decreases to about 60% inhibition by 6 h and to approximately 10% at 24 h. When a dose of 1.0 mg/kg is administered PO, more than 90% inhibition of the pressor response to angiotensin I is achieved 4 h after drug administration. This response is effectively unchanged 6 h after administration and is still approximately 40% inhibited 24 h after administration.

Adverse effects

The adverse effects of lisinopril are the same as those of the other long-acting ACE inhibitors.

Captopril

Formulations and dose rates

Captopril is supplied as tablets but is no longer a recommended ACE inhibitor in dogs or cats as more suitable products are now available on the veterinary market.

DOGS

- 0.5–1.0 mg/kg q.8 h PO
- Doses of 3.0 mg/kg q.8 h have been associated with glomerular lesions and renal failure in experimental dogs and in clinical canine patients
- In one study, the onset of activity of captopril was within 1 h following the first dose. Drug effect lasted less than 4 h. A dose of 1 mg/kg produced slightly greater effects than a dose of 0.5 mg/kg. A dose of 2 mg/kg produced no additional benefit

CATS

- 0.5–1.5 mg/kg q.8–12 h, determined from clinical experience

Pharmacokinetics

Captopril's affinity for ACE is approximately 30,000 times greater than that of angiotensin I. Captopril has a half-life in dogs of about 3 h. It is about 75% bioavailable in fasted dogs and 30–40% in fed dogs. Approximately 40% of circulating captopril is protein bound. Captopril is metabolized in the liver but almost all of the captopril and its metabolites are eliminated by the kidneys, principally via tubular secretion. In patients with decreased renal function, a decrease in dose interval or dose is recommended. The average total body clearance and the renal clearance of captopril are 600 mL/kg in the dog. The volume of distribution of captopril in the dog is 2.6 L/kg; the volume of the central compartment is about 0.5 L/kg.

Adverse effects

- Captopril is generally well tolerated in most patients. However, side effects can occur and include anorexia, vomiting, diarrhea, azotemia and hypotension.
- Gastrointestinal side effects appear to be more common in dogs administered captopril than in dogs administered other ACE inhibitors.
- In human patients, captopril produces fewer instances of azotemia and hypotension than do the longer-acting ACE inhibitors. Doses in excess of 2.0 mg/kg q.8 h can produce renal failure, hence should be avoided.

ALDOSTERONE ANTAGONISTS

EXAMPLE

Spironolactone

Spironolactone is an aldosterone antagonist and potassium sparing diuretic. It has potential beneficial effects on the progression of heart disease. For a full discussion of spironolactone see the diuretic section of this chapter.

β-BLOCKERS

EXAMPLES

Selective
Oral: atenolol, metoprolol
IV: esmolol
Nonselective
Oral: carvedilol, propranolol

Clinical applications and mechanism of action

Traditionally, β-blockers were considered indirect positive lusiotropes and class II antiarrhythmics. Discussion of these properties can be found in the positive lusiotropes and antiarrhythmics sections of this chapter respectively. However, there are also data that shows that the administration of β-blockers to human patients with heart failure due to systolic myocardial dysfunction results in improved myocardial function, exercise capabilities and prolonged survival. This effect is counter-intuitive, because β-blockers are negative inotropic agents; historically negative inotropic agents have been relatively contraindicated in heart failure characterized by systolic dysfunction.

The mechanism for the reported improvement in human patients with DCM may involve limiting the effects of chronic excessive adrenergic stimulation on cardiomyocytes. Elevated levels of circulating catecholamines (norepinephrine) are characteristic of chronic heart failure in humans and have been documented in canine patients with symptomatic spontaneous CVD in a chronic canine model of experimental mitral regurgitation and in spontaneous DCM. Catecholamines have been shown to reduce viability and protein synthesis in isolated adult human cardiomyocytes offering insight into one potential mechanism for impaired systolic function with CVD and DCM.

The reported beneficial effects of gradual β-blockade represent a biological effect that is not immediate upon initiation of therapy. In fact, the negative inotropic and chronotropic properties of these agents make decompensation a relative risk, in the short term, and mandate gradual initiation of therapy in the form of an uptitration protocol. However, improved systolic function and LV remodeling have been demonstrated in every human study greater than 3 months in duration.

When β-blockers are used in human patients with heart failure due to DCM, a low initial dose is administered orally to determine if the patient can tolerate any short term negative inotropic effects of the drug. If the patient does not deteriorate on the low dose, the dose is gradually increased (uptitrated) over 1–3 months, with the dose being increased by approximately 50–100% weekly. Eventually, doses 4–15 times the starting dose are administered. β-Blockers that have been used in humans include metoprolol, labetolol, carvedilol, bisoprolol and bucindolol. The starting dose for adult humans range from 1.25 mg PO for bisoprolol to 3.125 for carvedilol and 6.25 mg PO for metoprolol. The target dose in humans ranges from 5–10 mg PO per day for bisoprolol to 25 mg PO for carvedilol and 50–100 mg PO per day for labetolol and bucindolol.

Early evaluations of β-blockade for the treatment of heart failure focused on second-generation β_1-selective agents (metoprolol, atenolol) to avoid increases in afterload characteristic of nonselective β-blockade. However, β_1 and β_2 receptors are present in the myocardium and both are important in mediating adrenergic effects in cardiomyocytes. Additionally, in human heart failure, cardiac β_1 receptors are down-regulated while β_2 receptor numbers remain unchanged. Therefore, due to the relative increase in β_2 receptors, more comprehensive cardiac adrenergic blockade can be achieved with the use of nonselective β-blockers.

Carvedilol (Coreg®) is a third-generation nonselective β-blocker with α_1-blocking properties and ancillary antioxidant effects and thus combining the potential benefit of a nonselective β-blocker with the vasodilatory effects of an α_1-blocker. Additionally, the antioxidant properties may decrease the oxidant stress associated with progressive heart failure. Carvedilol is currently the only β-blocker approved by the American FDA for the treatment of human heart failure but the benefits of β-blockade are considered a relative class effect and number of different β-blockers are currently used for the treatment of human heart failure.

β-Blockers in canine DCM

Selective and nonselective β-blockers including carvedilol have been shown to significantly increase systolic function and survival in human patients with heart failure secondary to DCM. More recently, carvedilol has been shown to be superior to metoprolol with respect to survival in human DCM. One small prospective veterinary study evaluated the effect of carvedilol on survival in heart failure due to DCM in a small number of Doberman pinschers. No benefit was observed. However, the study had low statistical power due to small numbers of patients and used a low dose of carvedilol relative to more recently published canine pharmacokinetic and pharmacodynamic data. There are currently no data available to allow comment on the potential utility of β-blockade in the preclinical stage of canine DCM but their potential utility is rational based on the human model.

β-Blockers in canine CVD

High-dose atenolol (2–5 mg/kg PO q.24 h), a second-generation selective β-blocker, improved LV function in an experimental canine model of chronic mitral regur-

gitation (MR). The improvement was associated with enhanced innate contractile function of isolated cardiomyocytes due to an increase in the absolute number of contractile elements.

The reported beneficial effects of gradual β-blockade represent a biologic effect that is not immediate upon initiation of therapy. In fact, the negative inotropic and chronotopic properties of these agents make decompensation a relative risk in the short-term and mandate gradual initiation of therapy in the form of an up-titration protocol. Improved systolic function and LV remodeling have been demonstrated in every human study greater than 3 months in duration.

The left ventricular (LV) work associated with mitral regurgitation (MR) represents a model of pure volume overload because the excess volume is ejected into the relatively low pressure of the left atrium. In contrast, LV work associated with other forms of volume overload such as aortic insufficiency represents a combination of pressure and volume overload because the LV ejects the excess volume against relatively high aortic diastolic pressures. Although patients with chronic MR develop compensatory LV remodeling in the form of eccentric hypertrophy (dilation), the hypertrophic response is reportedly inadequate contributing to increased LV wall stress with commensurate increases in myocardial oxygen consumption. Researchers have suggested that inadequate hypertrophy is the result of the relatively low LV afterload in this condition. This premise argues against the primary utility of afterload reduction in patients with MR, and perhaps offers insight to the failure of afterload reduction to delay its progression. Additionally, reduced LV systolic function has been demonstrated in an experimental canine model of chronic MR and in chronic spontaneous human MR.

Incomplete understanding of the incessant progression of heart failure underlines the need for prompt intervention in mildly symptomatic patients in an attempt to decrease morbidity and mortality. This premise has been validated repeatedly in human heart failure studies with a number of agents including carvedilol. It is difficult to routinely diagnose canine patients with early (Class I & II) clinical signs of heart failure such as mild exercise intolerance. However, it is not uncommon to evaluate 'relatively' asymptomatic dogs with CVD that on further evaluation are found to have cardiac remodeling including, left atrial enlargement +/– left ventricular eccentric hypertrophy (dilation). A subset of these patients also demonstrate systolic dysfunction crudely based on an increased LV end-systolic diameter. The combination of non-selective β-blockade and afterload reduction in concert with the antioxidant properties offered by carvedilol is rational in dogs with chronic MR that are not yet in heart failure and might delay the development of overt clinical signs of heart failure in this population of dogs. Given the relative risk of decompensation associated with β-blockade in patients with CHF, gradual β-blockade is likely to have less risk in asymptomatic dogs with MR due to CVD.

Pharmacokinetics and pharmacodynamics

There are currently limited data on the pharmacokinetics and pharmacodynamics of carvedilol in dogs. The pharmacodynamics of chronic oral carvedilol administration in normal conscious dogs has been reported in two studies. The combined data evaluated dose ranges between 0.05–1.5 mg/kg and demonstrated the ability of carvedilol to offer significant β-blockade based on an isoproterenol challenge with little effect on systemic blood pressure and heart rate even at the highest dose reported. Additionally, one study reported a statistically significant correlation between plasma carvedilol concentration and the percent attenuation of an isoproterenol-induced tachycardic response. The study suggested that a plasma carvedilol concentration between 60 and 100 ng/mL may be necessary for near maximum β-blockade in healthy, conscious hound dogs. The pharmacokinetic profile of oral and intravenous carvedilol in healthy, conscious hound dogs was also reported, suggesting a 6-h dosing interval and a low and variable oral bioavailability (approximately 1/10th of that reported in humans). Conversely, the available pharmacodynamic data suggest a 12–24 h dosing interval is adequate to ensure β-blockade.

Another study reported the cardiovascular and renal effects of oral carvedilol (0.2–0.8 mg/kg q.24 h) in dogs with experimental MR and control dogs. The authors demonstrated β-blockade with oral carvedilol and suggested that a dose of 0.4 mg/kg PO q.24 h may be a reasonable target dose based on their pharmacokinetic data, cautioning against overzealous β-blockade in dogs with heart failure. However, the majority of investigators who have worked with an experimental model of MR in large dogs and demonstrated beneficial effects associated with β-blockade, alone or on a background of ACE inhibitor, have used atenolol at an initial dose of 12.5 mg/d (0.5–0.8 mg/kg PO q.24 h) gradually increasing to a target dose of 50–100 mg/d (2–5 mg/kg PO q.24 h) over a few weeks. The target dose was designed and proven to offer essentially complete, and likely nonselective (due to the size of the dose), β-blockade.

These data combined with the reported rise in norepinephrine in dogs with spontaneous CVD and the systolic dysfunction that is now recognized to occur in spontaneous primary human MR beg the question of whether or not β-blockade alone or on a background of neurohormonal modulation such as that offered by an ACE inhibitor, spironolactone, and/or digoxin can delay the progression of CVD in dogs. Although carve-

dilol is currently used by some clinicians for the treatment of CVD and other cardiac diseases, dosing until recently was empirical. The availability of pharmacokinetic and pharmacodynamic data in normal dogs and those with experimental MR greatly aids in the determination of an evidence based dose and dosing interval for carvedilol. However, based on evaluation of plasma carvedilol concentrations in normal conscious dogs, a reported target plasma carvedilol concentration of 50–100 ng/mL is recommended.

Clinically significant β-blockade is reported to occur at a plasma concentration >10 ng/mL. In this small number of dogs, those dosed above 0.5 mg/kg twice per day achieved a plasma concentration that should result in clinically significant β-blockade (>10 ng/mL) while those dosed at 0.3 mg/kg or below failed to achieve this level. However, to achieve close to maximum β-blockade doses >0.7–0.9 mg/kg or higher may be required.

One small prospective nonplacebo-controlled study in cavalier King Charles spaniels (n = 5) with preclinical compensated CVD reported that chronic oral carvedilol at approximately 1 mg/kg PO is safe and well tolerated when gradually uptitrated. There was no evidence of disease progression over the duration of this study (approximately 5 months). Some echocardiographic and gated radionuclide ventriculography parameters suggested a reduction in left atrial size, improvement in LV function and reduced filling pressures. However, there was no control group for comparison. In this study the plasma carvedilol concentration was >10 ng/mL. The true utility of carvedilol in dogs with CVD awaits prospective placebo-controlled studies.

There are no data to evaluate regarding the use of β-blockade in heart failure due to CVD (the clinical stage). The same precautions as those outlined for heart failure in general would be expected to apply. That is, β-blockers should not be initiated in dogs with decompensated heart failure due to CVD and initial dose and target doses may need to be lower in heart failure versus preclinical disease. In addition uptitration may need to be more gradual.

Formulations and dose rates

GENERAL COMMENTS

- β-Blocker therapy in patients with overt heart failure should not be attempted by anyone other than an individual who has experience with this form of therapy.
- Pre-existing bradycardia is a contraindication.
- The initial dose should be low and gradually increased over biweekly intervals.
- Adverse effects usually occur following a dose increase and may include development of signs of progressive heart disease.
- Acutely, all β-blockers are dose dependent negative inotropes and can therefore result in the occurrence of adverse signs suggestive of progressive heart disease following initiation or during uptitration. The dose should be reduced to the last tolerated dose (not abruptly discontinued) and therapy for heart failure should be initiated as required based on clinical signs.
- Any beneficial effect of β-blockade is not immediate but rather takes approximately 3 months. Maximum desirable effects may be achieved with the highest tolerated dose.
- β-Blockers should never be discontinued abruptly but rather weaned off should discontinuation be necessary.
- The authors' preferred β-blocker in patients with acquired heart disease is carvedilol.
- Plasma samples can be submitted to Auburn University Clinical Pharmacology Lab for determination of a plasma carvedilol concentration. Take the sample about 2 h after dosing. Target concentration is 50–100 ng/mL.
- In patients with preclinical CVD or DCM who have been receiving chronic β-blockers and then go on to develop heart failure, the following recommendations may prove useful.
  - If the heart failure is mild (outpatient treatment is possible) then the β-blocker should be continued at the same dose and heart failure therapy should be initiated including an ACE inhibitor, pimobendan and furosemide as needed to control signs of congestion.
  - If the heart failure is severe (hospitalization and IV furosemide are indicated) then the β-blocker dose should be reduced by 50% (β-blockers should not be discontinued abruptly) and heart failure therapy should be initiated including pimobendan and parenteral furosemide as needed to control signs of congestion and stabilize the patient. Once stable an ACE inhibitor can be added and eventually the β-blocker dose can be uptitrated to the previous dose if tolerated.
- Do not combine with other β-blockers, calcium channel blockers or sotalol (a class III antiarrhythmic with β-blocking properties).

CARVEDILOL FORMULATION AND DOSE RATES

Carvedilol is available as 3.125, 6.25, 12.5 and 25 mg tablets. A stability study has been reported and the drug can be reformulated into a suspension with simple corn syrup. The suspension has an expiration time of 90 d. Formulation of the suspension using the 25 mg tablets facilitates accurate dosing and uptitration and is cost effective, particularly for small dogs.

CARVEDILOL IN PRECLINICAL DCM

- The starting dose is 0.1 mg/kg (lower than that in dogs with preclinical CVD)
- Start at 0.1 mg/kg and increase by 50–100% every 2–3 weeks to a target dose of approximately 1 mg/kg (if possible)

CARVEDILOL IN CLINICAL DCM (HEART FAILURE)

- β-Blockers should not be routinely initiated in clinical DCM unless there is a specific indication such as a supraventricular arrhythmia (atrial fibrillation)

CARVEDILOL IN PRECLINICAL CVD

- The starting dose is 0.25 mg/kg
- Start at 0.25 mg/kg and increase by 50–100% every 2–3 weeks to a target dose of approximately 1 mg/kg (if possible)

Formulations and dose rates—cont'd

CARVEDILOL IN CLINICAL CVD (HEART FAILURE)

- β-Blockers should not be routinely initiated in clinical CVD unless there is a specific indication such as a supraventricular arrhythmia (atrial fibrillation)

Conclusions regarding β-blockade in heart disease/failure

There is an ongoing interest in β-blocker therapy for the treatment of canine heart disease (preclinical stage) and heart failure (clinical stage) due to both DCM and CVD. However, there is currently no evidence of efficacy in either disease. In general, β-blockers should not be initiated in dogs or cats with decompensated heart failure. That is, if the patient has severe clinical signs of backward (pulmonary edema) or forward (systemic hypotension) heart failure β-blockers should not be initiated. β-Blockers may be easier to initiate in the setting of stable canine heart failure if the patient is receiving pimobendan concurrently. There is one recent report of the advantage of this approach in the human literature. Any definitive recommendations regarding β-blockade for the treatment of canine clinical and preclinical disease await adequately powered prospective clinical trials.

Digoxin

The digitalis glycosides have effects on vascular baroreceptors. Baroreceptor function is abnormally reduced in human patients and experimental dogs with heart failure. This results in attenuated cardiac vagal tone and increased sympathetic activity. This maladaptive compensatory mechanism can be detrimental in patients with heart failure. The digitalis glycosides increase baroreceptor function in normal cats, dogs and humans. They decrease plasma catecholamine concentrations, directly recorded sympathetic nerve activity and plasma renin activity, which may all be related to increased baroreceptor activity and are thus considered neuroendocrine modulators.

However, clinical significance of this effect on morbidity and mortality in heart failure has not been demonstrated. This may be related to the relatively high rate of adverse or side effects associated with digoxin use and narrow therapeutic window. For additional information on other properties of digoxin see the antiarrhythmic section of this chapter.

Angiotensin receptor blockers

EXAMPLES

Irbesartan, losartan

Angiotensin II receptor blockers were developed for the treatment of systemic hypertension and heart failure in humans. They block only one type of angiotensin II receptor (AT_1) and do not potentiate bradykinin activity in contrast to the ACE inhibitors. Despite this, hemodynamic and clinical benefits in humans with heart failure appear to be similar to the ACE inhibitors. The drugs were primarily developed to avoid ACE inhibitor-induced coughing that occurs in humans; this is not a problem in dogs. Clinical use of these drugs will probably be limited to those patients that cannot tolerate ACE inhibitors. More recently these agents are being evaluated alone or in combination with an ACE inhibitor for the treatment renal disease.

Irbesartan is investigational in veterinary medicine. One reported canine dose is 30–60 mg/kg.

POSITIVE AGENTS (MEDICATIONS THAT IMPROVE VENTRICULAR RELAXATION)

This class of agents is used primarily in the treatment of diseases that are characterized by concentric ventricular hypertrophy such as feline hypertrophic cardiomyopathy, congenital canine subaortic stenosis and pulmonic stenosis.

EXAMPLES

Calcium channel blockers (diltiazem), β-blockers (atenolol)

Calcium channel blockers

EXAMPLE

Oral: diltiazem (preferred for this indication)

Diltiazem

Calcium channel blockers as a class are considered vasodilators but individual agents have different relative potencies and additional effects. Diltiazem is a calcium channel blocker that affects the calcium channels in cardiomyocytes and to a lesser extent vascular smooth muscle. Thus it is not used as a primary vasodilator. Calcium channel blockers including diltiazem are class IV antiarrhythmics and positive agents. For further discussion of the antiarrhythmic properties please refer to the antiarrhythmic section of this chapter (p. 424).

Clinical applications

Diltiazem is primarily used as an adjunctive agent to treat heart failure in cats with HCM. Its use for this purpose has decreased markedly over the past decade. It improves myocardial relaxation, reduces myocardial contractility and may reduce heart rate in these patients.

The improvement in myocardial relaxation may help decrease left ventricular diastolic pressure and so reduce pulmonary edema formation. Decreased myocardial contractility may reduce systolic anterior motion of the mitral valve. However, it usually does not do this as effectively as β-blocking drugs. Heart rate reduction may be beneficial in cats with sinus tachycardia or atrial fibrillation. Net beneficial effects include lessened edema formation. Rarely, left ventricular wall thickness decreases.

Diltiazem is also commonly used to decrease the ventricular rate in patients with atrial fibrillation, a common sequela of severe heart disease. A rapid heart rate induce myocardial failure in dogs. Consequently, rate reduction with diltiazem may be viewed as producing myocardial protection. Digoxin and β-blockers are used for this same purpose.

Mechanism of action

Diltiazem improves early diastolic left ventricular relaxation in hypertrophic cardiomyopathy. It may also decrease heart rate and reduce the degree of systolic anterior motion in cats with this disease. It does this by binding to L-type calcium channels in the heart and reducing systolic calcium entry into myocardial and automatic cells.

Formulations and dose rates

Diltiazem is a calcium channel blocker supplied as a tablet. There are also several extended-release formulations. Cardizem CD® is a dual release capsule that contains two types of bead of diltiazem hydrochloride. The beads differ in the thickness of the membranes that surround them. The manufacturer states that 40% of the beads are meant to dissolve within the first 12 h after oral administration and the other 60% (which are surrounded by a thicker membrane) are formulated to dissolve throughout the next 12 h. The net effect is a drug that lasts for 24 h in humans and in cats. Dilacor XR® is an extended-release capsule that consists of multiple 60 mg tablets contained in a swellable matrix core that slowly releases the drug over 24 h in humans and 12 h in cats. The total capsule contains either 120, 180 or 240 mg of diltiazem. The 60 mg tablets can be removed. The tablet can be cut in half or administered whole.

CATS

- The usual dose is 7.5 mg q.8 h. This may be increased to 15 mg q.8 h in refractory cases
- The extended-release formulation Dilacor XR® is dosed at 30–60 mg q.12 h
- The dose for Cardizem CD® is 45 mg (one-quarter of a 180 mg capsule) q.24 h

Pharmacokinetics

Diltiazem, when administered PO at a dose of 1 mg/kg to cats, has a bioavailability of 94%, a terminal half-life of 2 h and a volume of distribution of 1.9 L/kg. Peak serum concentration occurs 30 min after dosing and the serum concentration remains in the therapeutic range (50–300 μg/mL) for 8 h.

The bioavailability of Cardizem CD® is only 38%, necessitating a much higher dose for this product (10 mg/kg). The half-life is much longer, at 6.5 h, than that of the nonextended-release preparation and peak serum concentration does not occur until 6 h after drug administration. Serum concentration remains within therapeutic range for 24 h. Dilacor XR® (30 mg) produces significant decreases in heart rate and blood pressure in cats with HCM for 12–14 h.

Adverse effects

The primary adverse effects of diltiazem are seen with diltiazem overdose. Overdose results in decreased contractility, systemic vasodilation and bradycardia, which, if severe enough, results in cardiovascular collapse. Patients with myocardial failure and conduction system disease are more sensitive to the calcium channel-blocking properties of diltiazem and so are more prone to adverse effects than normal dogs or cats.

Known drug interactions

In general, diltiazem should not be administered in conjunction with a α-adrenergic blocking agent. However, this can be done safely in most cats with severe HCM. Still, if this is done, low doses of both agents should be administered initially and the doses titrated up to an effective endpoint.

β-Blockers

EXAMPLE

Atenolol

In addition to their neuroendocrine modulatory effects and antiarrhythmic effects (Class 2) all β-blockers have the potential to improve relaxation indirectly by slowing heart rate. However, unlike diltiazem they have no direct effects that improve relaxation and indirectly they slow the rate of relaxation. The heart rate-mediated beneficial effects on relaxation may, however, be clinically useful in stable heart failure characterized by systolic dysfunction. For further discussion on effects and dosing of β-blockers see the sections on neuroendocrine modulators (p. 412) and antiarrhythmics (p. 444) in this chapter.

NEW OR EXPERIMENTAL HEART FAILURE DRUGS

Because there is no cure for most cardiovascular diseases that result in heart failure, there are always new drugs being developed to treat cardiac disease and heart failure.

Some drugs eventually make it to the marketplace while others fall by the wayside during any phase of drug development. This section presents a few drugs that may become useful for treating heart failure in the future.

Aquaretics

Aquaretics are vasopressin receptor anatagonists, e.g. tolvaptan (OPC-41061). Tolvaptan is selective V_2 receptor antagonist, which is showing promise in the acute and chronic treatment of human CHF. In contrast to loop diuretics like furosemide, V_2 receptor antagonism has demonstrated free water excretion with little to no sodium loss. In addition, the water loss associated with V_2 antagonism has not been associated with activation of the RAAS in contrast to the loop diuretics. This novel class of agents may prove to be an addition to our pharmacological arsenal against CHF but recent evidence in human medicine suggests this agent is not useful above and beyond available diuretics.

Prostacyclin analogs

Prostacyclin analogs have been shown to improve symptoms and short-term survival in human patients with pulmonary hypertension. Epoprostenol (Flolan®) was the first available prostacyclin used to treat pulmonary hypertension in humans. It is administered via continuous rate intravenous infusion. Due to a very short half-life abrupt withdrawal is associated with increased morbidity and mortality. Adverse effects related to the drug are mild and dose related while sepsis and thrombosis are important adverse effects related to chronic central venous access.

Treprostinil (Remodulin®) has similar hemodynamic effects as epoprostenol but is administered as a constant rate subcutaneous infusion which lowers the risk of sepsis associated with direct venous access.

Intravenous iloprost has similar hemodynamic effects as epoprostenol with a longer half-life diminishing the adverse effects associated with abrupt withdrawal. Inhaled iloprost is also available and has a short half-life of 20–25 min requiring administration every 2–3 h.

Beraprost, the first orally stable prostacyclin analog, requires administration four times a day to maintain adequate blood levels.

Endothelin receptor antagonists

The pro-molecule big endothelin (ET)-1 is converted to functional ET by endothelin converting enzyme. ET is a potent vasoconstrictor and smooth muscle mitogen resulting in vascular hypertrophy. ET levels are elevated in humans with pulmonary hypertension and dogs with experimentally induced dirofilariasis.

Two types of ET receptors have been identified, ET_A and ET_B. ET_A receptors are located on vascular smooth muscle cells and mediate vasoconstriction and vascular smooth muscle proliferation while ET_B receptors are located on both endothelial and vascular smooth muscle cells and mediate vasodilation and vasoconstriction. ET_B receptors are upregulated in pulmonary hypertension.

The ET receptor antagonist bosentan (Tracleer®) competitively antagonizes the ET receptor types ET_A and ET_B, with slightly more affinity for ET_A receptors. Optimal dosage in humans is 125 mg every 12 h. In human studies, bosentan resulted in significant increases in exercise capacity. A potentially important adverse effect of bosentan therapy is elevations in hepatic enzyme activity that typically resolve with discontinuation of the drug but require monthly monitoring of serum biochemistries. Bosentan was developed initially for the treatment of heart failure but in clinical trials did not prove useful for this indication. The selective ET_A receptor antagonists, sitaxsentan and ambrisentan, are currently being evaluated in human clinical trials.

DRUGS USED FOR THE TREATMENT OF CARDIAC ARRHYTHMIAS

Relevant physiology and pathophysiology

Antiarrhythmic drugs are used to manage cardiac arrhythmias that arise as a result of an intrinsic cardiac defect (myocardial or electrical) or because of the effect of toxins such as drugs (e.g. digoxin toxicity) or endogenous factors (e.g. secondary to gastric dilation and volvulus). Different antiarrhythmic drugs have different mechanisms of action and will have varying efficacy depending on the type of arrhythmia present.

An understanding of the mechanisms by which action potentials are generated in the normal heart and in cardiac disease is essential to an understanding of the mechanism of action of antiarrhythmic drugs.

Cardiac muscle action potentials

Myocardium (Fig. 17.1A)

- Excitation of the myocardium results in:
  - influx of sodium through fast sodium channels
  - influx of calcium through slow calcium channels.
- This slow influx of calcium results in the long duration of cardiac action potentials relative to other excitable tissues. It also results in a long refractory period, as the fast sodium channels cannot be reactivated until the cell has been repolarized. Calcium influx also causes release of calcium from intracellular stores and activates the contractile mechanism.
- Repolarization is predominantly due to an outward potassium current.

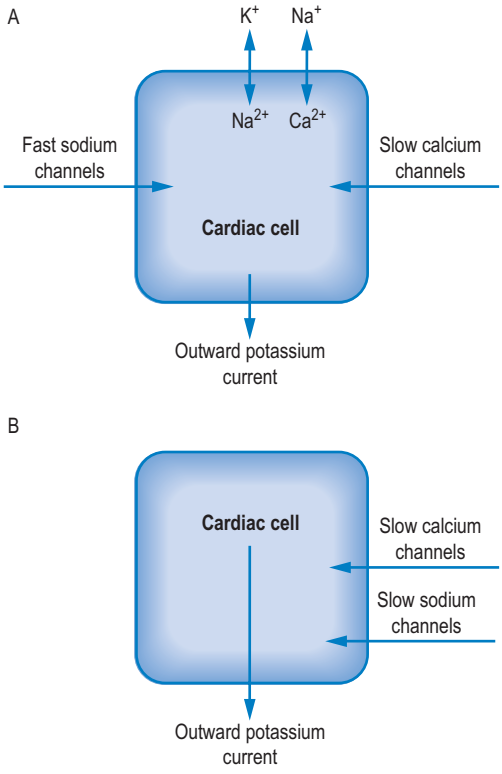

Fig. 17.1 Generation of action potentials in (A) normal myocardial cells and (B) normal pacemaker cells.

- During electrical diastole ionic balances are restored by membrane pumps that exchange sodium for potassium and calcium for sodium.

Pacemaker cells (SA and AV nodes), ischemic myocardial cells (Fig. 17.1B)

- The initial part of the action potential in these cells is due to a slow inward calcium current. This results in the initial part of the action potential being very slow, thus slowing conduction through the SA and AV nodes. This results in a delay between atrial and ventricular contraction, allowing time for adequate ventricular filling.
- Diastolic depolarization occurs because of a steadily declining outward potassium current and an increasing slow diastolic inward, predominantly sodium, current. The inward sodium current eventually reaches a threshold so that calcium ions start to flow in, hence initiating another action potential – automaticity.

Arrhythmias

Arrhythmias originate in either the atria (supraventricular arrhythmias) or the ventricles (ventricular arrhythmias). They can arise as a result of either the abnormal formation of impulses that arise from ectopic foci and have spontaneous activity or the abnormal propagation of impulses, where an extra anatomical or functional circuit exists so that the electrical impulse may take two possible pathways with different conduction velocities and refractory periods. The latter mechanism is termed re-entry.

Abnormal automaticity is a common form of abnormal impulse formation in small animals. In this abnormality, partly damaged cells become partially depolarized, attaining a resting membrane potential similar to automatic cells in the heart, such as the sinus node. When this occurs these cells attain the property of automaticity. When they depolarize at a rate faster than the normal pacemaker (i.e. automatic) cells, they take over control of the heart rate, sometimes for only one beat and at other times for long periods. All forms of abnormal impulse arrhythmia tend to be exacerbated by ischemia, high catecholamine concentrations and electrolyte imbalances, particularly decreased potassium and magnesium concentrations. Other forms of abnormal impulse formation are early and delayed or late afterdepolarizations and triggered activity.

DRUGS USED TO TREAT TACHYARRHYTHMIAS

The effective treatment of tachyarrhythmias is predicated on an accurate rhythm diagnosis and a working knowledge of the available antiarrhythmic drugs. The reader is referred elsewhere to learn rhythm diagnosis.

Classes of antiarrhythmic agents

The drugs used to treat supraventricular and ventricular tachyarrhythmias can be divided into separate classes based on their generalized mechanisms of action. Antiarrhythmic drugs exert their effects primarily by blocking sodium, potassium or calcium channels, or β-receptors. This classification scheme is somewhat helpful clinically when deciding to use particular drugs for specific arrhythmias. However, clinical experience with these drugs is the more important means of determining efficacy of various drugs to suppress different tachyarrhythmias. The common arrhythmias, the mechanisms responsible for their generation and the drugs most commonly effective clinically are listed in Table 17.6. The doses of the common antiarrhythmic agents are listed in Table 17.7.

Class I

Class I drugs are most frequently used to treat ventricular tachyarrhythmias, although they may also be used to treat supraventricular tachyarrhythmias. They are the

Table 17.6 Common arrhythmias and drugs used in their treatment

	Acute (intravenous)	Chronic (oral)
Ventricular arrhythmias–hemodynamically important VPCs or Vtach	1. Lidocaine (Class I) [5+] 2. Procainamide (Class I)[1+] 3. β-blockers (Class II) [1+]	1. Sotalol (Class III and II) [3+] 2. Amiodarone (Class III, II and IV) [2+] 3. Procainamide (Class I) [1+] 4. Mexiletine (Class I) [1+] 5. β-blockers (Class II) [1+] – not generally used as monotherapy but rather combined with a Class I
Supraventricular arrhythmias: hemodynamically importanty SVPBs or atrial fibrillation	1. Procainamide (Class I) [1+] 2. CCB: Diltiazem (Class IV) [2+] 3. β-blockers (Class II) [1+] 4. Quinidine (Class I, only horses) [1+]	1. Amiodarone (Class III, II and IV) [2+] 2. CCB: Diltiazem (Class IV) [2+] 3. β-blockers (Class II) [2+] 4. Digoxin (Class V) [2+] 5. Quinidine (Class I, only horses) [1+]
Both ventricular and supraventricular arrhythmias	1. Procainamide (Class I) [1+] 2. β-blockers (Class II) [1+]	1. Amiodarone (Class III, II and IV) [2+] 2. β-blockers (Class II) [1+]

Note: Class I antiarrhythmics work on Na^+ channels, Class II are beta-blockers, Class III work on K^+ channels (prolong action potential), Class IV are calcium channel blockers, Class V is digoxin and some agents have properties from more than one class. All agents are scored relative to how often they are used clinically to manage heart disease 1+ to 5+ where 5+ is the most common.

so-called 'membrane stabilizers'. Their common mechanism of action is the blockade of a certain percentage of the fast sodium channels in the myocardial cell membrane. Sodium channel blockade results in a decrease in the upstroke (phase 0) velocity of the action potential in atrial and/or ventricular myocardium and Purkinje cells. The upstroke velocity is a major determinant of conduction velocity. Consequently, class I drugs slow conduction velocity in normal cardiac tissue, abnormal cardiac tissue, or both.

Class I agents have variable effects on repolarization. Some of them prolong repolarization while others shorten it or have no effect. Primarily on the basis of differences in repolarization characteristics, class I agents are subdivided into classes Ia, Ib and Ic.

- Class Ia agents include quinidine, procainamide and disopyramide. These agents depress conduction in normal and abnormal cardiac tissue and prolong repolarization.
- Class Ib agents include lidocaine (lignocaine) and its derivatives, tocainide and mexiletine, along with phenytoin. Class Ib agents do not prolong conduction velocity in normal cardiac tissue nearly as much as class Ia drugs. They do, however, have profound effects on conduction velocity in abnormal cardiac tissue. They also shorten the action potential duration by accelerating repolarization. A greater degree of shortening occurs in fibers that have a longer action potential duration. Consequently, this effect is most profound in Purkinje fibers and does not significantly alter the effective refractory period of normal atrial and ventricular muscle. In contrast, class Ib agents may prolong the effective refractory period of damaged myocardium.
- Class Ic antiarrhythmic drugs include encainide and flecainide. These drugs slow conduction and have little effect on action potential duration.

Class II

Class II drugs are the β-adrenergic blocking drugs and are useful for treating both supraventricular and ventricular tachyarrhythmias. Although few tachyarrhythmias are the direct result of catecholamine stimulation, β-adrenergic receptor stimulation by catecholamines commonly exacerbates abnormal cellular electrophysiology. This can result in initiation or enhancement of a tachyarrhythmia. β-Blockers have additional properties including positive lusiotropy and neuroendocrine modulation in heart failure and further discussion of these uses can be found in the positive lusiotropy (p. 422) and neuroendocrine modulation (p. 412) sections of this chapter respectively.

Drugs that block β-adrenergic receptors do not have direct membrane effects at clinically relevant concentrations. Consequently, their action is indirect and related to blocking catecholamine enhancement of abnormal electrophysiology or related to other effects of the drug. An example of the latter is β-adrenergic receptor blockade resulting in a decrease in myocardial contractility and so in myocardial oxygen consumption. The resultant improvement in myocardial oxygenation might improve cellular electrophysiology and reduce arrhythmia formation.

Class II drugs are most commonly used to alter the electrophysiological properties of the AV junction in patients with supraventricular tachyarrhythmias. β-Receptor blockade at the AV junction results in an increase in conduction time through the AV junction

Table 17.7 Doses of common antiarrhythmic agents

Drug	Species	Route	Dose
β-blockers (Class II)			
Atenolol	Dog	PO	6.25 mg (0.25 mg/kg)–50 mg (1 mg/kg) q.12 h (total dose; start low; titrate)
	Cat	PO	6.25–12.5 mg q.12–24 h (total dose; start low; titrate)
Esmolol	Both	IV	0.25–0.5 mg/kg (single dose; maximum effect in 1–4 min); 10–200 μg/kg/min constant rate infusion
Propranolol	Dog	PO	0.1–2.0 mg/kg q.8 h (start low and titrate to effect in atrial fibrillation; higher doses used for other arrhythmias)
	Cat	PO	
	Both	IV	2.5–10 mg (total dose; start low; titrate)
			0.01–0.1 mg/kg (start low; titrate to effect for supraventricular arrhythmias)
Carvedilol*	Dog	PO	0.25-1.25 mg/kg q.12 h (total dose; start low and titrate, larger dogs and dogs with systolic dysfunction will not get to the highest dose)
Calcium channel blockers (Class IV)			
Diltiazem*	Dog	PO	0.5–1.5 mg/kg q.8 h (start low; titrate to effect for atrial fibrillation)
	Cat	IV	0.5–3 mg/kg (start low; titrate to effect for supraventricular tachycardia)
		PO	0.05–0.25 mg/kg (administer initial 0.05 mg/kg dose over 2–3 min; repeat every 5–10 min up to cumulative dose of 0.25 mg/kg)
			7.5–15 mg q.8 h (total dose)
Verapamil	Dog	IV	0.05–0.15 mg/kg (administer initial 0.05 mg/kg dose over 2–3 min; repeat every 5–10 min up to cumulative dose of 0.15 mg/kg)
Positive chronotropes			
Atropine*	Both	IV, SC	0.02–0.04 mg/kg
Glycopyrrolate*	Both	IV, SC	0.005–0.01 mg/kg
Isoproterenol	Both	IV	0.01–0.1 μg/kg/min (constant rate infusion; alternatively, dilute 1 mg in 500 mL of 5% dextrose or lactated Ringer's solution and infuse to effect)
Terbutaline	Dog	PO	2.5–10 mg (total dose; start low; titrate)
Other			
Digoxin	Dog	PO	0.22 mg/m^2 of body surface area q.12 h for dogs >20 kg
	Cat	PO	0.005–0.01 mg/kg q.12 h for dogs <20 kg
			0.03 mg/cat q.24 h for cats <3 kg
			0.03 mg/cat q.12–24 h for cats >3 kg
Ventricular antiarrhythmics			
Sotalol*	Dog	PO	1–3 mg/kg q.12 h
	Cat	PO	10 mg/cat q.12 h
Amiodarone* (supraventricular also)	Dog	PO	Loading dose: 10–20 mg/kg q.24 h × 7–10 days; maintenance dose: 5–15 mg/kg q.24 h
Lidocaine*	Dog	IV	Loading dose: 2–6 mg/kg (slow bolus); maintenance dose: 40–100 μg/kg/min
Mexiletine*	Dog	PO	5–10 mg/kg q.8 h
Phenytoin	Dog	PO	20–35 mg/kg q.8 h
Procainamide (supraventricular also)	Dog	PO	20–30 mg/kg q.6–8 h
		IV, IM	5–20 mg/kg (administer slowly; start low; titrate)
Quinidine (supraventricular also)	Dog	PO, IM	6–16 mg/kg q.6–8 h
Tocainide	Dog	PO	10–15 mg/kg q.8 h

* Agents commonly used by the authors for treatment of arrhythmias.

and an increase in the time that the AV junction is refractory to depolarization. Both changes effectively disrupt re-entrant circuits that use the AV node as part of the circuit. An increase in AV junctional refractoriness decreases the number of depolarizations reaching the ventricles from the atria in atrial fibrillation and flutter. Class II drugs are also used in combination with other agents to suppress ventricular arrhythmias.

Class III

Class III drugs act primarily by prolonging the action potential duration and refractory period. As such, they increase the fibrillation threshold and are used primarily to prevent sudden death due to ventricular tachyarrhythmias. They may, however, also have the ability to suppress ventricular arrhythmias. Examples of class III drugs are amiodarone, bretylium and sotalol. The use of these drugs is evolving in veterinary medicine.

Class IV

Class IV drugs are the calcium channel-blocking drugs. They are also known as calcium-entry blockers, calcium channel antagonists and slow-channel inhibitory blockers. They act by inhibiting the function of the slow

L-type calcium channels on cardiac cell membranes. Slow calcium channels are responsible for depolarization of sinus node and AV junctional tissues and for initiation of excitation–contraction coupling in myocardial cells. Calcium channel blockers have additional properties including positive lusiotropy and vasodilation and discussions of their utility in these settings can be found in the positive lusiotropy (p. 422) and vasodilator (p. 404) sections of this chapter respectively.

Calcium channel-blocking drugs slow the upstroke velocity of sinus node and AV junctional cell action potentials, resulting in slowing of sinoatrial and AV junctional conduction times. They may also slow the depolarization rate of the sinus node. Calcium channel-blocking drugs prolong the time for recovery from inactivation of the slow calcium channel and, as a result, markedly prolong the refractory period of the AV junctional tissue. Calcium channel-blocking drugs are also negative inotropic agents because of their effects on L-type slow calcium channels during phase 2 of the action potential in myocardial cells.

Because the primary effects of the calcium channel-blocking drugs are on the sinus node and the AV junction, these drugs are most effective for treating supraventricular tachyarrhythmias. Although they have been shown to suppress delayed afterdepolarizations (DADs) that occur secondary to digitalis intoxication and to depress automaticity in abnormally automatic cells, clinically they are generally considered not to be efficacious for treating ventricular tachyarrhythmias.

CLASS I ANTIARRHYTHMIC DRUGS

Lidocaine (lignocaine)

Clinical applications

Lidocaine (lignocaine) is used clinically to treat acute life-threatening ventricular arrhythmias in many different clinical settings. Its rapid onset of action, effectiveness, safety and short half-life make it ideal for acute interventions. Its short half-life also allows rapid changes in serum concentration so that lidocaine's effects can be titrated quickly. It is usually the most effective antiarrhythmic drug one can use to treat a ventricular arrhythmia. It does not affect supraventricular tachyarrhythmias.

Mechanism of action

Lidocaine is a class Ib antiarrhythmic agent that is also used for local anesthesia. It has little effect on atrial conduction or refractoriness and is not used for atrial tachyarrhythmias. Lidocaine can abolish both automatic and re-entrant ventricular arrhythmias. Lidocaine can abolish ventricular re-entrant arrhythmias either by increasing or decreasing conduction velocity within the circuit or by prolonging the refractory period.

The cellular actions of lidocaine are dependent on the extracellular potassium concentration. When the resting membrane potential is decreased, as when potassium concentration is high, lidocaine acts by suppressing the activity of fast sodium channels in a similar way to quinidine and procainamide. Lidocaine has more marked effects on automaticity, conduction velocity and refractoriness in damaged cells (where resting membrane potential is also often decreased) than in normal cells.

Lidocaine can also hyperpolarize partially depolarized cells and so can improve conduction in a region of damaged myocardium. Lidocaine's many potential effects on variables that cause re-entrant arrhythmias make it an especially effective drug for abolishing re-entrant arrhythmias. Lidocaine's ability to hyperpolarize partially depolarized cells gives it the ability to suppress arrhythmias due to abnormal automaticity in ventricular myocardium (e.g. accelerated idioventricular rhythm).

Although lidocaine has no direct effect on early afterdepolarizations (EADs), it may hyperpolarize or accelerate repolarization in cells with EADs, indirectly terminating the arrhythmia. However, in German shepherds with inherited ventricular arrhythmias due to EADs, lidocaine is not very effective. Lidocaine is effective at suppressing DADs due to digitalis intoxication. Because of this and because it is easy to use, lidocaine is the preferred drug for the acute termination of digitalis-induced ventricular tachyarrhythmias.

Formulations and dose rates

Lidocaine is supplied for intravenous administration in concentrations ranging from 10 mg/mL to 200 mg/mL. Concentrations above 20 mg/mL are used for infusion rather than bolus administration.

Lidocaine is administered parenterally because it has a short half-life and is extensively metabolized by the liver to toxic metabolites after oral administration. Although intramuscular lidocaine administration is feasible in the dog, clinical experience is limited at this time.

Lidocaine is generally administered as an initial intravenous loading dose followed by a constant intravenous infusion. If a loading dose is not administered, maximum infusion rates will take 1–2 h to achieve a therapeutic concentration. The initial loading dose in dogs is 2–4 mg/kg IV administered over 1–3 min, followed by an infusion of 25–100 μg/kg/min. The dose is titrated while observing the electrocardiogram. When the arrhythmia is suppressed, drug administration is discontinued. Half the initial loading dose may need to be repeated in 20–40 min if the arrhythmia recurs.

In cats the initial dose is 0.25–0.75 mg/kg IV, followed by an infusion administered at 10–40 μg/kg/min. Cats more commonly develop seizures with lidocaine. It must be used cautiously in this species.

Pharmacokinetics

Lidocaine's half-life in dogs is 90–100 min. Total body clearance is approximately 60 mL/min/kg. The liver primarily metabolizes lidocaine, with less than 5% of the clearance occurring through the kidneys. Clearance and half-life are prolonged by liver disease or poor hepatic perfusion (e.g. in heart failure, in shock and with propranolol administration). The volume of distribution is approximately 6 L/kg. Heart failure may also reduce the volume of distribution, resulting in a higher serum concentration. The therapeutic serum concentration is thought to be between 2 and 6 μg/mL.

Adverse effects

- Lidocaine exerts effects on the central nervous system when the serum concentration achieves a toxic concentration, producing signs of drowsiness, emesis, nystagmus, muscle twitching and seizures. Toxic effects can be particularly severe in the cat. Dogs administered infusion rates at the upper end of the dosage range are commonly sedated.
- Lidocaine can depress ventricular function in severe myocardial failure, produce atrioventricular block in conduction system disease and exacerbate sinus bradycardia and arrest in patients with sick sinus syndrome. It must be used with care in dogs with atrioventricular or ventricular conduction disorders, if at all.
- Lidocaine produces very few electrocardiographic changes except for a possible shortening of the Q-T interval. Unless the sinoatrial node is diseased, lidocaine does not affect its automaticity. It should be avoided in dogs with sick sinus syndrome. It does slow the rate of phase 4 depolarization in Purkinje fibers, resulting in a slowing of the rate of escape beats. For this reason, lidocaine (or for that matter any other antiarrhythmic drug) should never be administered to a patient dependent on an escape focus, such as a patient with a third-degree AV block. Lidocaine has fewer proarrhythmic effects than other antiarrhythmic agents.
- Treatment for toxicity is lidocaine withdrawal and, when necessary, intravenous diazepam administration (0.25–0.5 mg/kg IV) for seizure control.

Known drug interactions

Prolonged lidocaine infusions during concurrent propranolol administration prolong lidocaine's half-life.

Special considerations

Preparations containing adrenaline (epinephrine) used for local anesthesia should never be used intravenously. Lidocaine is absorbed by the PVC in the plastic bags used to store intravenous solutions.

Phenytoin

Clinical applications

Phenytoin may be effective in treating ventricular arrhythmias due to many causes but, because of dosing difficulties when administered intravenously, lidocaine is generally preferred for acute termination of ventricular arrhythmias. Phenytoin, however, may be useful for treating digitalis intoxication although generally lidocaine remains the preferred option. Because it can be administered orally, phenytoin can theoretically be administered prophylactically to patients that may be easily intoxicated with digitalis (e.g. severe myocardial failure patients).

Mechanism of action

Phenytoin, when used as an antiarrhythmic, shares many properties with lidocaine. It reduces normal automaticity in Purkinje fibers, abolishes abnormal automaticity due to digitalis intoxication and has effects identical to those of lidocaine on re-entrant arrhythmias. It can repolarize abnormal, depolarized cells, reduces sympathetic nerve effects and may modify parasympathetic nerve activity in digitalis toxicity.

Formulations and dose rates

Phenytoin is supplied as capsules. For parenteral administration, phenytoin sodium is supplied as injectable solutions of 50 mg/mL in 2 mL and 5 mL ampoules or vials.

The oral phenytoin dosage is 30–50 mg/kg q.8 h. Serious arrhythmias require intravenous treatment in intermittent doses of 2 mg/kg administered over 3–5 min to prevent hypotension and cardiac arrest from the propylene glycol vehicle. The total dose should not exceed 10 mg/kg. Because phenytoin in solution has a pH of 11.0, phlebitis will occur unless it is administered via a large vein and flushed immediately with normal saline.

Pharmacokinetics

Phenytoin absorption is erratic, slow and incomplete from both the gastrointestinal tract and intramuscular injection sites. The half-life is 3–4 h.

Adverse effects

Long-term phenytoin administration at 50 mg/kg q.8 h results in an increase in serum alkaline phosphatase concentration. Histological changes consist of increased hepatic cell size. This appears to be due to increased glycogen storage.

Known drug interactions

- The liver metabolizes phenytoin. Any drugs affecting microsomal enzymes will, therefore, also affect phenytoin metabolism.
- Chloramphenicol administration increases serum phenytoin concentration and in one study increased the half-life from 3 h to 15 h.

- Phenytoin may also decrease serum quinidine concentration.
- Phenytoin should not be added to intravenous fluids because of lack of solubility and resultant precipitation.

Quinidine

Quinidine is an optical isomer of quinine. It was originally prepared by Pasteur to treat malaria in 1853. It was not until 1918 that quinidine was recognized as an effective agent for treating atrial fibrillation in humans.

Clinical applications

Quinidine has been used most commonly for the long-term suppression of ventricular premature depolarizations and ventricular tachyarrhythmias. Chronic oral therapy of ventricular arrhythmias is most commonly aimed at preventing sudden death. Because quinidine does not appear to be very effective at preventing sudden death in dogs and, in humans, may increase the incidence of sudden death, use of this drug as a chronic agent has plummeted in the past 10 years.

Quinidine can also be used acutely to abolish ventricular arrhythmias and is occasionally effective in the control of atrial premature depolarizations and paroxysmal supraventricular tachycardia. However, other drugs (e.g. digitalis, β-blockers, calcium channel blockers) are generally more effective in the dog for supraventricular arrhythmias. Quinidine is ineffective in dogs with atrial fibrillation secondary to cardiac disease. However, it can be effective at converting atrial fibrillation to sinus rhythm in dogs without underlying cardiac disease (primary atrial fibrillation).

Mechanism of action

Quinidine is a class Ia antiarrhythmic agent that can be effective against automatic and re-entrant supraventricular and ventricular tachyarrhythmias in dogs. Its primary action is to decrease the movement of sodium through the fast sodium channel during phase 0. This results in a decrease in the upstroke velocity of the action potential and a consequent decrease in cardiac electrical impulse conduction velocity. This effect is enhanced by increasing extracellular potassium concentration because of the decreased resting membrane potential.

Quinidine prolongs the refractory period in atrial, ventricular and Purkinje cells, which can effectively interrupt re-entrant pathways. It also acts to decrease the slope of phase 4 and increase the threshold potential toward 0 in automatic cells. In so doing it suppresses normal automaticity in Purkinje fibers and suppresses cardiac excitability. Sinus node automaticity is unchanged or may even be increased owing to decreased vagal tone in normal patients (vagolytic effect).

There is a paucity of literature on the effects of quinidine on abnormal automaticity. Quinidine can suppress DADs in the Purkinje system but it can also increase the amplitude of DADs in atrial myocardium. Quinidine is used experimentally to produce EADs and so is unlikely to have beneficial effects with rhythms generated by this mechanism.

Formulations and dose rates

Quinidine is available as quinidine gluconate, quinidine sulfate and quinidine polygalacturonate. Quinidine sulfate and quinidine polygalacturonate are available as tablets. Quinidine gluconate comes as a solution for parenteral use.

DOGS

- Chronic oral dose for treating ventricular tachyarrhythmias: 6–16 mg/kg q.8 h. Quinidine sulfate is more rapidly absorbed than quinidine gluconate
- To convert atrial fibrillation to sinus rhythm in primary atrial fibrillation, doses ranging from 12.5 mg/kg q.6 h to 20 mg/kg q.2 h can be used. These doses are continued until conversion of the rhythm or until mild signs of toxicity are present
- Quinidine gluconate may be administered parenterally but rapid intravenous injections may cause dangerous hypotension. Lidocaine (lignocaine) and procainamide are preferred over quinidine for parenteral administration. The parenteral dose is 5–10 mg/kg IM or IV

Pharmacokinetics

Quinidine is about 85% protein bound and has a half-life of 5–6 h in the dog. A steady-state serum concentration is achieved approximately 24 h after initiating therapy but the serum concentration is commonly within the therapeutic range following the first dose. Pharmacokinetics have not been studied in cats.

Quinidine is metabolized in the liver to some cardioactive and some inactive metabolites and is also excreted by the kidneys. Renal disease and heart failure may increase the serum concentration. Microsomal enzyme-inducing drugs, such as anticonvulsants, may shorten the half-life of quinidine. Concomitant administration of the antacids aluminum hydroxide or magnesium oxide with quinidine decreases the maximum plasma quinidine concentration in dogs.

Adverse effects

- Gastrointestinal side effects have been reported to occur in approximately 25% of dogs administered quinidine. These appear to be direct effects of the drug on the gastrointestinal tract.
- Cardiovascular toxicity is frequently reported in human medicine and these findings have often been extrapolated to the veterinary literature. Quinidine toxicity is manifested as QRS and Q-T interval prolongation. However, clinically significant prolongation in the Q-T interval or QRS complex duration does not occur even in dogs that are seizuring due to toxicity.

- There is one report in the literature of a case of aplastic anemia in a dog treated with quinidine.
- The most important clinical problem is exacerbation of heart failure after quinidine administration. Presumably this is due to its negative inotropic effects. In general, quinidine use should be avoided in dogs with severe myocardial failure or in dogs that have, or have had, heart failure.
- Quinidine should not be used in cats.

Known drug interactions

Quinidine displaces digoxin from binding sites throughout the body and reduces digoxin renal clearance, resulting in a higher serum digoxin concentration. This is an important drug interaction and can lead to clinical signs of digitalis intoxication. Most of the digitalis toxicity in this situation is due to central nervous system stimulation (e.g. vomiting due to stimulation of the chemoreceptor trigger zone), since brain concentration of digoxin increases by 50% when quinidine is administered while digoxin concentration decreases in all other tissues, including myocardium.

Procainamide

Clinical applications

Procainamide is effective against ventricular tachyarrhythmias and may be effective against some supraventricular tachyarrhythmias in dogs. The authors have no experience using this drug in cats.

Although it is often effective at decreasing the frequency and rate of ventricular tachyarrhythmias, procainamide does not appear to be very effective at preventing sudden death in patients with severe underlying cardiac disease. It may have proarrhythmic effects in certain patients. Consequently, we do not recommend its use in Doberman pinschers and boxers with cardiomyopathy or dogs with subaortic stenosis that are prone to sudden death due to ventricular tachyarrhythmias.

Procainamide is more rationally used in dogs in the intensive care unit with malignant ventricular tachycardia that is unresponsive to lidocaine administration or in anesthetized dogs that have a serious ventricular tachyarrhythmia that is unresponsive to lidocaine.

Procainamide can also be used to treat a variety of supraventricular arrhythmias, including atrial fibrillation and supraventricular tachycardia due to pre-excitation syndrome. However, it is almost never the drug of choice for these arrhythmias.

Mechanism of action

Procainamide is a class Ia antiarrhythmic agent with properties very similar to those of quinidine. Procainamide decreases the upstroke velocity of phase 0 depolarization in normal action potentials and in action potentials produced by abnormal automaticity. This slows conduction in these tissues.

Re-entrant tachyarrhythmias may be terminated by procainamide either slowing conduction or producing a bidirectional block in the abnormal segment of the re-entrant pathway. This effect is enhanced as extracellular potassium concentration is increased. Therefore procainamide may be more effective in a patient with hypokalemia if the serum potassium concentration is normalized.

Procainamide shifts the threshold potential to more positive values. This reduces the excitability of cardiac tissue. It also increases the duration of repolarization and the effective refractory period. The increase in effective refractory period is greater than the increase in action potential duration. Theoretically, this function should increase fibrillation threshold and make procainamide an effective drug for preventing sudden death due to ventricular fibrillation. However, clinically this does not appear to be the case in human or veterinary medicine.

Procainamide can suppress digitalis-induced DADs. This should theoretically make it effective for treating digitalis intoxication-induced tachyarrhythmias. Although it does suppress these arrhythmias in dogs, a very high serum concentration is required. Procainamide was not effective against DADs produced by mechanisms other than digitalis intoxication in one in vitro study. The drug does not appear to suppress automatic atrial arrhythmias. Procainamide has vagolytic properties but these are less than those observed with quinidine and are rarely clinically significant.

Formulations and dose rates

Procainamide hydrochloride is available for oral administration in tablets or capsules and for parenteral administration. A sustained-release oral preparation is available.

Clinically, a dose of 20–30 mg/kg q.6 h PO for procainamide hydrochloride and q.8 h for the sustained-release preparation is generally used. We rarely observe any clinically significant toxicity at these doses and can usually document efficacy. There is a report of a young adult male Labrador retriever that required a dose of procainamide in the 30–40 mg/kg q.8 h PO range to control an arrhythmia associated with pre-excitation. No untoward effects were reported in this dog. Consequently, higher doses can be tried if the recommended dose is not effective.

When administered intravenously, intermittent boluses of 2–4 mg/kg should be injected slowly (over 2 min) up to a total dose of 12–20 mg/kg until the arrhythmia is controlled. This can be followed by a CRI of 10–40 μg/kg/min.

The sustained-release preparation has the same half-life as procainamide but has a longer time to peak concentration (longer absorption half-life). This enables 8-hourly administration. However, the peak serum concentration achieved with the sustained-release preparation is lower than the regular preparation when given at the same dose. Consequently, it has been recommended that the dose of the sustained-release preparation be higher.

Pharmacokinetics

Procainamide has a short half-life of approximately 3 h in the dog. The short half-life is problematic when administering procainamide orally to a dog. To maintain a serum concentration within the therapeutic range generally requires administering the drug at least q.6 h PO. The volume of distribution is approximately 2 L/kg. The vast majority of the drug is metabolized in the liver. Parenteral and oral routes of administration are used but intravenous injections must be administered slowly to prevent circulatory collapse from peripheral vasodilation and decreased cardiac contractility.

Humans commonly have beneficial effects from procainamide at lower doses and at a lower serum concentration than commonly seen in dogs. One reason for this may be because they metabolize procainamide to a metabolite, *N*-acetyl procainamide (NAPA), which has antiarrhythmic properties. Dogs cannot acetylate aromatic and hydrazine amino groups and so are incapable of producing NAPA.

Procainamide pharmacokinetics have not been studied in the cat.

Adverse effects

- Theoretically, procainamide can produce cardiotoxicity manifested as QRS and Q-T interval prolongation. However, this is almost never observed clinically.
- In humans, procainamide can have a proarrhythmic effect in some patients. This has never been documented in dogs, although it is suspected to occur.
- Toxic concentrations can depress myocardial contractility and produce hypotension. This only occurs with rapid intravenous administration.
- In humans, procainamide can cause systemic autoimmune reactions. Experimental dogs (beagles) given procainamide at 25–50 mg/kg q.6 h for 1–5 months developed antinuclear antibodies (ANA). This has not been reported in clinical patients, although the authors have observed two possible immune-mediated abnormalities in dogs receiving procainamide. One dog developed granulocytopenia that resolved when procainamide administration was discontinued. Another dog developed lymphadenopathy and a positive ANA test that resolved after procainamide administration was discontinued. Both dogs had been on procainamide for several years prior to these abnormalities occurring.

Special considerations

The intravenous preparation may become a light yellow color; it can still be used. If the solution becomes amber, however, the drug has deteriorated and the solution should not be used.

Disopyramide

Clinical applications

Because procainamide is as effective as disopyramide and is safer, disopyramide is almost never used in canine or feline patients.

Mechanism of action

Disopyramide is an oral antiarrhythmic agent with properties almost identical to those of quinidine and procainamide.

Formulations and dose rates

Disopyramide phosphate is supplied in capsules. When used as an antiarrhythmic in dogs, 7–30 mg/kg is administered q.4 h PO.

Pharmacokinetics

In the dog, disopyramide has a half-life of approximately 3 h, which makes effective dosing difficult. It is rapidly absorbed and its bioavailability is 70%.

Adverse effects

- In experimental dogs, all doses of disopyramide prolong the P-R interval. Doses of 15 and 30 mg/kg q.8 h prolong the Q-T interval while the 30 mg/kg q.8 h dose also prolongs the duration of the QRS complex.
- Doses of 15 and 30 mg/kg q.8 h significantly decrease the echocardiographic shortening fraction.
- Disopyramide is contraindicated in heart failure patients because it decreases myocardial contractility and increases peripheral vascular resistance, a potentially lethal combination.
- Disopyramide is such a potent negative inotropic agent that it is used in humans with HCM to reduce systolic anterior motion of the mitral valve.
- Disopyramide possesses significant anticholinergic properties that may produce toxic effects.
- It also decreases the serum glucose concentration in a dose-dependent manner (approximately 15% decrease at a dose of 30 mg/kg).

Mexiletine

Mexiletine is an analog of lidocaine that is not extensively metabolized on its first pass through the liver. It was first used as an antiarrhythmic agent in Europe in 1969.

Clinical applications

Mexiletine is indicated for chronic treatment of ventricular tachyarrhythmias in dogs but reports of clinical efficacy vary. One group of investigators reported limited success in suppressing ventricular arrhythmias with mexiletine in canine patients. In contrast, another

group reported good efficacy. However, in the latter report, many dogs had what appeared to be benign and self-limiting ventricular tachyarrhythmias, so determining whether or not the drug was effective is difficult.

One investigator has reported that mexiletine appears to be effective at controlling ventricular tachyarrhythmias and preventing sudden death in Doberman pinschers with dilated cardiomyopathy. Although this has not been tested in any clinical trials, this report is encouraging and is consistent with the reported increase in the fibrillation threshold.

Mechanism of action

Mexiletine can interrupt re-entry circuits by slowing conduction and depressing membrane responsiveness, as for other class I drugs. Abnormal automaticity is suppressed by mexiletine. It can also suppress digitalis-induced DADs. Most important, mexiletine can increase the fibrillation threshold in the dog ventricle. In one study of experimental dogs with myocardial infarction, ventricular fibrillation or a rapid ventricular tachycardia could be induced in six of 10 dogs at baseline by stimulating the heart with two premature beats. These arrhythmias could not be induced after mexiletine administration.

Combination therapy is sometimes more effective than administration of one drug alone. A combination of mexiletine and quinidine was more effective at preventing induced ventricular arrhythmias in experimental dogs with myocardial infarction than was either drug alone in one study.

Formulations and dose rates

Mexiletine is supplied as capsules. The dose in dogs is 5–10 mg/kg q.8 h PO. An effective serum concentration may be achieved after three doses.

Pharmacokinetics

Mexiletine is well absorbed from the gastrointestinal tract in dogs, with a bioavailability of approximately 85%. Approximately 80% is excreted in the urine in dogs and 10% is metabolized by the liver and excreted in the feces. It has a plasma half-life of 3–4 h in the dog. Therapeutic serum concentration is thought to be between 0.5 and 2 fg/mL.

Adverse effects

Toxic effects can include vomiting and disorientation or ataxia but are uncommon at the suggested dosage range.

- A dose of 25 mg/kg PO to dogs can induce seizure activity.
- A dose of 40 mg/kg PO consistently produces ataxia, tremor and salivation within 10 min after administration. These signs last for up to 2.5 h. Tonic-clonic spasms often begin within 15–40 min after administration and last for up to 1 h.
- Vomiting and diarrhea can be seen at doses of 15–30 mg/kg.
- In humans, mexiletine has no effect on sinus rate, P-R interval and QRS duration in patients without pre-existing conduction system disease. In human patients with sinus node or conduction system disease, bradycardia and AV block can be produced. Mexiletine has been studied in normal dogs at doses ranging from 3 mg/kg to 15 mg/kg for 13 weeks. No effects on heart rate, P-R interval, QRS complex duration or Q-T interval were noted. No clinical signs of toxicity were seen.

Tocainide

Clinical applications

At present there are no indications for the use of tocainide in dogs or cats. Doses that are adequate to suppress arrhythmias result in unacceptable toxicity.

Mechanism of action

Tocainide is structurally similar to lidocaine. The major difference is that it is not metabolized extensively on first pass through the liver after absorption. Its actions on the normal action potential are almost identical to lidocaine. Although its effects on abnormal action potentials have not been well studied, they are likely to be similar to lidocaine's effects. Depression of the sodium current is more pronounced in abnormal than in normal myocardial tissue. Tocainide does increase the fibrillation threshold.

Formulations and dose rates

Tocainide is supplied as tablets. Clinical experience with the use of tocainide in small animal veterinary medicine is limited. Doses required to adequately suppress ventricular arrhythmias in Doberman pinschers range between 15 and 25 mg/kg q.8 h PO. These doses produce a serum tocainide concentration between 6.2 and 19.1 μg/mL 2 h after dosing and between 2.3 and 11.1 μg/mL 8 h after dosing. Apparently, smaller doses are not effective.

Pharmacokinetics

The half-life of the drug after oral administration is dose dependent. After oral doses of 50 and 100 mg/kg the half-life is 8.5 and 12 h respectively. These doses are much higher than those used clinically, so the half-life of the drug at clinical doses is unknown but probably shorter. Tocainide is metabolized by the liver and excreted in the urine. About 30% of an intravenous dose is excreted unchanged in the urine. Therapeutic plasma concentration is thought to be in the range 4–10 μg/mL.

Adverse effects

- At doses adequate to suppress arrhythmias:
  - about 25% of dogs acutely develop anorexia
  - about 10–15% develop central nervous signs of ataxia or head tremor.
- Chronically, these doses produce the intolerable side effects of:
  - corneal dystrophy in 10–15% of dogs
  - renal failure in about 25% of dogs within 4 months.
- Consequently, it does not appear that tocainide should be used in dogs for the suppression of ventricular arrhythmias and the prevention of sudden death.
- In humans, tocainide produces little effect on the electrocardiogram in patients without conduction system disease. It has been documented to produce asystole when administered concurrently with a β-adrenergic blocking agent in human patients with sinus node dysfunction. It produces no adverse effects in human patients with pre-existing conduction abnormalities.

CLASS II ANTIARRHYTHMIC DRUGS (β-ADRENERGIC BLOCKERS)

Class II antiarrhythmic drugs competitively bind with β-adrenergic receptors and so are termed β-blockers. All β-blockers exert their antiarrhythmic effects by inhibiting the effects of the adrenergic system on the heart. Cardiac adrenergic stimulation increases the heart rate, increases the conduction velocity through all regions of the conduction system and myocardium and decreases the refractoriness of cardiac tissues. In addition, it enhances normal automaticity of subsidiary pacemaker tissue.

Three types of β-receptor, termed β_1-, β_2- and β_3-receptors, are present in the body. The β_1- receptors are primarily located within the heart and adipose tissue. Stimulation of these receptors results in increases in heart rate, myocardial contractility, atrioventricular conduction velocity and automaticity of subsidiary pacemakers.

The β_2-receptors are primarily located in bronchial and vascular smooth muscle, where they produce relaxation. However, β_2-receptors also occur in the sinus and AV nodes, where they contribute to the increase in heart rate and increased conduction velocity. They are also present in myocardium, where stimulation results in increased contractility. In addition, they are present in kidney and pancreas, where they mediate renin and insulin release.

The β_3-receptors have only been recently discovered and appear to depress myocardial contractility. See Chapter 4 for further detail.

Classes

Numerous β-blockers are marketed for pharmacological use. They differ in their abilities to block β-receptor types. Some, in addition to their ability to block β-receptors, can also stimulate β-receptors mildly. Some are said to have membrane-stabilizing effects but these effects occur only at very high doses. Consequently, this is of no clinical significance. Some β-blockers also weakly inhibit α-receptors and so have mild vasodilating properties.

Many β-blockers have been developed to selectively block β_1-adrenergic receptors. This is primarily because bronchospasm develops in humans with asthma who receive a β_2-adrenergic blocking drug. Dogs do not develop asthma so there is no advantage in using a specific β_1-blocking drug in this species. However, it is a reason to use a specific β_1-blocking drug in cats with asthma. Drugs that block β_2-receptors also limit the ability of patients with diabetes mellitus to respond to hypoglycemia with glycogenolysis. Consequently, drugs that block β_2-receptors should be avoided in diabetic patients. Drugs that block β_2-receptors also have the potential of blocking the peripheral vasodilating response to β-agonists. As a result, peripheral vascular resistance may increase.

In veterinary medicine, very few individuals have any clinical experience with the vast majority of β-blockers. The three primary drugs in veterinary use today are propranolol, atenolol and carvedilol (see β blocker section of this chapter p. 419). The drugs are equipotent but their pharmacokinetics differ. Esmolol, a β-blocker with a very short half-life, is also used on occasion as an intravenous agent for short-term management of arrhythmias.

Clinical applications

In veterinary medicine, β-blockers are used to treat both supraventricular and ventricular tachyarrhythmias and prevent sudden death due to ventricular tachyarrhythmias. They are also used to treat HCM in cats. They are occasionally used to treat systemic arterial hypertension and more recently preclinical and clinical heart disease. They may be more effective in cats than dogs for controlling blood pressure. However, amlodipine is more effective than propranolol for this purpose in cats. β-Blockers are usually ineffective for treating systemic hypertension secondary to renal disease in dogs.

As antiarrhythmic drugs, β-blockers are most commonly used to slow the ventricular rate in patients with atrial fibrillation, to abolish supraventricular tachycardia and HCM, to slow the sinus rate in cats with hyperthyroidism, to prevent sudden death in dogs with severe subaortic stenosis and to chronically treat ventricular

tachyarrhythmias. They are used either as sole agents or in combination with other antiarrhythmic drugs. They are also used to treat the cardiac effects of pheochromocytoma in combination with prazosin.

Mechanism of action

Drugs that block β-adrenergic receptors do not produce many of the specific cellular membrane changes observed with other antiarrhythmic drugs. At doses that induce β-adrenergic blockade, there is no change in resting membrane potential, amplitude of the action potential or velocity of depolarization. In the dog, however, atenolol does prolong the refractory period. This change, along with the inhibition of sympathetic input, reduces the ability of induced premature beats to produce ventricular tachycardia and fibrillation in experimental dogs 7–30 days following induced myocardial infarction, at a time when ventricular arrhythmias are caused by re-entry.

With all β-blockers, no simple correlation between dose or serum concentration and therapeutic effect exists. The serum concentration required to produce a beneficial effect depends on the prevailing sympathetic tone and on β-adrenergic receptor density and sensitivity. These variables vary widely from patient to patient.

In addition, the pharmacokinetics of β-blockers can differ substantially between patients. In humans, there can be a 20-fold difference in plasma concentration between patients receiving the same oral dose. In one study in normal dogs, a five-fold difference between dogs administered the same dose was reported. Because hepatic blood flow is a major determinant of propranolol clearance and half-life, this variability can be expected to be even greater in cardiac patients where hepatic blood flow is compromised. Consequently, the dose required to produce a therapeutic effect varies substantially. Because of this, the dosage must be titrated to an effective endpoint in each patient.

Adverse effects

In patients subjected to chronic increases in circulating catecholamine concentrations and increased sympathetic nervous system activity (e.g. patients with heart failure), β-adrenergic receptors decrease in number, internalize into the cell membrane and become less efficient at producing cAMP. These changes are commonly lumped together and termed receptor downregulation. In these patients, fewer receptors are available for drug binding. However, many of these patients are very dependent on stimulated β-receptors to maintain myocardial contractility. Acute administration of medium-to-high doses of a β-blocker to patients with compromised myocardial function (e.g. patients with dilated cardiomyopathy) dependent on β-receptor stimulation can result in lethal decreases in contractility and heart rate.

Propranolol

Clinical applications

Propranolol is indicated in canine and feline patients with ventricular and supraventricular tachyarrhythmias. It is commonly used with digoxin to slow the ventricular rate in patients with atrial fibrillation. It is effective for terminating and preventing the recurrence of supraventricular tachycardia.

Propranolol can be effective as the sole agent for terminating ventricular tachyarrhythmias but is generally more effective when used in combination with other antiarrhythmic agents. Propranolol is effective for decreasing the sinus rate in patients with hyperthyroidism, pheochromocytoma and heart failure. Few antiarrhythmic drugs can be used in cats. Propranolol has been used to treat both supraventricular and ventricular tachyarrhythmias in cats with moderate success.

Mechanism of action

Propranolol is the prototype β-receptor blocking agent. It reduces catecholamine-dependent automatic (normal and abnormal) rhythms and slows conduction in abnormal ventricular myocardium. Propranolol also increases the refractory period and slows conduction velocity in AV nodal tissues. This slows the ventricular response to atrial fibrillation and flutter and effectively abolishes supraventricular arrhythmias due to AV nodal re-entry.

By reducing contractility, propranolol reduces myocardial oxygen consumption, which may reduce myocardial hypoxia and arrhythmia formation in patients with subaortic stenosis. Propranolol also abolishes supraventricular and ventricular tachyarrhythmias due to pheochromocytoma and thyrotoxicosis.

Propranolol, like any β-blocker, produces dose-dependent decreases in myocardial contractility. This does not occur after an intravenous dose of 0.02 mg/kg in normal dogs (this would be comparable to an oral dose of 0.2 mg/kg). An intravenous dose of 0.08 mg/kg (comparable oral dose = 0.8 mg/kg) decreases dP/dt, an index of myocardial contractility, by approximately 30%.

Propranolol has a profound effect on peripheral vascular resistance in normal, conscious experimental dogs. At an intravenous dose of 0.02 mg/kg, peripheral vascular resistance increases to almost twice the baseline. There is no further increase with a dose of 0.08 mg/kg. These effects have not been studied in dogs with heart failure but it is apparent that larger doses of propranolol must be avoided in these patients. Propranolol appears to have a greater effect on the sinus rate in normal dogs

than drugs that specifically block β_1-receptors. This is probably because β_2-receptors are also present in the sinus node and help modulate the sinus rate.

Formulations and dose rates

Propranolol hydrochloride is available as tablets for oral administration and ampoules for intravenous administration.

The dose of propranolol depends on the situation for which it is used. In dogs with atrial fibrillation due to severe underlying cardiac disease, the oral dose is 0.1–0.5 mg/kg q.8 h. At this dose range, the negative inotropic effects of propranolol appear to be negligible. We have never witnessed exacerbation of heart failure at this dose range in dogs with dilated cardiomyopathy or severe mitral regurgitation, even when the patient was not being administered a concomitant positive inotropic agent, like digoxin.

In canine patients with supraventricular or ventricular tachyarrhythmias and normal myocardial function, doses as high as 2 mg/kg q.8 h are well tolerated and often required. Doses in this range are contraindicated in patients with severe myocardial failure. Duration of drug effect is longer than the drug's half-life because of active propranolol metabolites and receptor binding of the drug. Consequently, administering the drug q.8 h appears to be effective. The feline oral dose is 2.5–10 mg q.8 h for control of tachyarrhythmias.

The intravenous dose in dogs is administered as intermittent boluses to effect. The initial IV dose is 0.02 mg/kg and the total dose should not exceed 0.1 mg/kg. Intravenous doses of propranolol must be administered cautiously to heart failure patients because a decrease in contractility may acutely worsen hemodynamics. The therapeutic endpoint is abolition or improvement of a tachyarrhythmia, slowing of the sinus rate or slowing of the ventricular response to atrial fibrillation.

Pharmacokinetics

Propranolol is lipid soluble and so is almost completely absorbed by the small intestine. It is largely metabolized by the liver. Oral propranolol undergoes a variable but extensive first-pass hepatic metabolism. As a result, its bioavailability for the first dose ranges from only 2% to 17% for oral administration in the dog. Serum half-life after the first dose is about 1.5 h in the dog. Chronic oral dosing increases half-life to about 2 h and results in serum concentrations 1.25–10 times greater than after initial doses due to an increase in bioavailability. This increase is probably due to saturation of first-pass metabolism.

Adverse effects

- Patients with myocardial failure or heart failure due to severe volume overload may have their heart failure exacerbated by propranolol, especially if it is administered intravenously. These patients usually receive propranolol for control of heart rate and only low oral doses are generally needed. If acute heart failure is precipitated it cannot be reversed by catecholamines, so calcium, glucagon or digitalis must be used.
- Propranolol should not be administered to patients with conduction disturbances or abnormal inherent pacemaker function. Propranolol will exacerbate sinus node dysfunction in patients with sick sinus syndrome. It will also exacerbate AV nodal dysfunction in patients with first- and second-degree AV block, potentially creating third-degree AV block. In patients with third-degree AV block, it will decrease the rate of the subsidiary pacemaker, a potentially lethal effect.
- Propranolol should not be used in patients with asthma or chronic lower airway disease, as increases in lower airway resistance may occur with β-blockade.
- Propranolol should also be used with caution in diabetic patients receiving insulin because propranolol reduces sympathetic compensation for hypoglycemia.
- Acute propranolol withdrawal may exacerbate the original problem for which the drug was being administered, so gradual withdrawal should be performed. As an example, the authors have witnessed sudden death in one boxer dog with ventricular arrhythmia following the acute cessation of propranolol administration.
- β-Blockers should not be administered to patients with hyperkalemia because the β-blockade reduces the potassium flux from intravascular to extravascular spaces.

Known drug interactions

Digitalis plus propranolol can cause varying degrees of AV block.

Special considerations

The intravenous preparation of the drug rapidly decomposes in alkaline solutions.

Atenolol

Clinical applications

Atenolol has clinical indications in both dogs and cats. In dogs, it is most commonly used in conjunction with digoxin to slow the heart rate in patients with atrial fibrillation. It is also used in dogs to treat supraventricular tachycardia and ventricular tachyarrhythmias and in an attempt to prevent sudden death in dogs with severe subaortic stenosis. Its most common indication in cats is to decrease systolic anterior motion of the mitral valve in feline HCM and to treat ventricular tachyarrhythmias.

Mechanism of action

Atenolol is a specific β_1-adrenergic blocking drug. It has the same potency as propranolol but different pharmacokinetics.

Formulations and dose rates

Atenolol is supplied as tablets. It is also supplied as a solution for IV injection. The IV dosage for dogs and cats is not known.

DOGS

- 6.25–50 mg/dog q.12 h PO. In humans, q.24 h dosing is adequate to maintain efficacy. Because of its shorter half-life in the dog, it is recommended that atenolol be administered q.12 h to dogs
- In large dogs with atrial fibrillation, the starting dose is 12.5 mg q.12 h PO. The dose is titrated upward until the heart rate is above 160 beats/min. In small dogs, the starting dose is 6.25 mg q.12 h PO
- If used to treat ventricular arrhythmias in dogs without underlying myocardial failure or in an attempt to prevent sudden death in dogs with subaortic stenosis, the dose should be at the higher end of the dosage range

CATS

- In hypertrophic cardiomyopathy, atenolol can be used to decrease the subaortic pressure gradient that occurs secondary to systolic anterior motion of the mitral valve. The starting dose is 6.25 mg q.12 h PO. It is then titrated upwards to as high as 25 mg q.12 h PO

Pharmacokinetics

Atenolol is more water soluble than propranolol. In the dog, bioavailability appears to be approximately 80%. Atenolol is eliminated unchanged in the urine. There is very little hepatic metabolism. The half-life of atenolol is longer than the half-life of propranolol, being 5–6 h in the dog. This is somewhat shorter than the half-life in humans, which is 6–9 h. In the cat, atenolol has a half-life of 3.5 h. Its bioavailability is high at 90% and the pharmacokinetic variability from cat to cat is small. When administered to cats at a dose of 3 mg/kg, atenolol attenuates the increase in heart rate produced by isoprenaline for 12 but not for 24 h.

Esmolol

Clinical applications

Esmolol has several clinical indications. It can be used for the acute termination of supraventricular tachycardia. It can also be used, at low doses, to decrease acutely the heart rate of dogs with severe tachycardia (heart rate >250 beats/min) due to atrial fibrillation. It has been administered to cats with HCM to determine if β-blockade will reduce the dynamic left ventricular outflow tract obstruction due to systolic anterior motion of the mitral valve.

Mechanism of action

Esmolol is an ultra-short-acting (half-life <10 min) β_1-adrenergic blocking drug used for intravenous administration.

Steady-state β-blockade is produced within 10–20 min after starting intravenous administration of esmolol in dogs. After discontinuation of drug administration, no detectable β-blockade is apparent at 20 min post-infusion, regardless of the dose administered. Esmolol decreases the sinus node rate. At an infusion rate of 25 μg/kg/min, approximately 30% of the effect of isoprenaline-induced tachycardia is inhibited. This value increases to approximately 60% with a 50 μg/kg/min dose and to approximately 70% with a 100 μg/kg/min infusion rate.

Myocardial contractility is depressed with esmolol. In normal conscious dogs, an infusion rate of 10 μg/kg/min does not change dP/dt. An infusion rate of 40 μg/kg/min decreases dP/dt by approximately 30% and an infusion rate of 160 μg/kg/min decreases it by 50%. Because esmolol only blocks β_1-adrenergic receptors, it produces no increase in peripheral vascular resistance.

Formulations and dose rates

Esmolol hydrochloride is supplied as a solution for injection and a concentrated solution for dilution in solution for intravenous infusion.

DOGS

- Esmolol can be administered in two different ways. An initial loading dose of 0.25–0.5 mg/kg (250–500 μg/kg) can be administered intravenously as a slow bolus over 1–2 min followed by a constant rate infusion of 50–200 μg/kg/min. Alternatively, a CRI of 10–200 μg/kg/min can be started without a loading dose. In this manner, maximal effect should be apparent within 10–20 min. With the loading dose, an effect should be apparent more quickly
- An initial loading dose and the high end of the dosage range should only be used in dogs with normal cardiac function. In dogs with severe dilated cardiomyopathy or severe mitral regurgitation and atrial fibrillation with a very fast ventricular rate, esmolol should be infused only (no loading dose). The infusion should start at 10–20 μg/kg/min and be titrated upward every 10 min to an effective endpoint

Pharmacokinetics

Esmolol has the basic structure of a β-adrenergic blocking drug but it contains an ester on the phenoxypropanolamine nucleus that is rapidly hydrolyzed by RBC esterases. The major metabolite of esmolol is ASL-8123 which has a half-life in dogs of 2.1 h. This metabolite has one-1500th the β-blocking activity of esmolol, which is clinically insignificant.

Carvedilol

See Neuroendocrine modulator section (p. 412).

CLASS III ANTIARRHYTHMIC DRUGS

There is increasing evidence in human medicine that class I antiarrhythmic agents are ineffective for preventing sudden death. In some instances they may actually increase the incidence of sudden death in patients with organic heart disease and ventricular arrhythmias. Because of this, the use of these drugs in human medicine has plummeted within the past 10 years. At the same time, the efficacy of other drugs has been examined more vigorously. Class II antiarrhythmics (β-blockers) are effective agents for preventing sudden death in human patients with myocardial infarction. As class III drugs act primarily by prolonging the refractory period, they theoretically reduce the propensity for micro re-entrant circuits to develop and so make it more difficult for ventricular fibrillation to develop.

Amiodarone

Clinical applications

It has been suggested that amiodarone may be useful in dogs with DCM that are at risk of sudden death. There have been no controlled studies but anecdotal evidence suggests it is effective. More recently, amiodarone has been reported to be beneficial in atrial fibrillation and may result in conversion to sinus rhythm in as many as 25% of dogs. Amiodarone is potentially useful and may become more popular in small animal medicine as veterinarians gain more experience with the drug.

Mechanism of action

Amiodarone is a benzofurane derivative. It is structurally related to levothyroxine (thyroxine) and has a high iodine content. It is metabolized to desethylamiodarone in the dog. Desethylamiodarone has important antiarrhythmic effects because of its ability to block fast sodium channels. It is more effective than amiodarone at suppressing ventricular arrhythmias 24 h after myocardial infarction in experimental dogs.

Amiodarone was first introduced into human medicine in 1961 as an antianginal agent. Its antiarrhythmic properties were recognized in 1970. Since then, it has been used for this purpose extensively in human medicine in European countries. It is currently being used more frequently in human medicine in the USA to treat patients at risk of sudden death due to ventricular arrhythmia. This increased use is primarily a result of reports of proarrhythmia and increased mortality in patients with ventricular tachyarrhythmias receiving class I antiarrhythmic agents and of the recognition that antifibrillatory actions may be more important than antiarrhythmic action in preventing sudden death.

Electrophysiologically, amiodarone's primary effect is to prolong the refractory period of atrial and ventricular myocardium and the AV junction without changing resting membrane potential when administered chronically. This may result in an increase in the P-R interval and the Q-T interval on the ECG. Because of its effect on refractory period in myocardium, amiodarone has a marked antifibrillatory effect. Consequently, its primary clinical use is to prevent sudden death. In automatic cells, amiodarone reduces the slope of phase 4 of the action potential. This results in a decrease in the sinus rate. Amiodarone can also suppress tachyarrhythmias. Prolongation of the refractory period can interrupt re-entrant circuits. In addition, amiodarone has sodium channel-blocking properties (class I effects), which can slow conduction and interrupt re-entrant circuits. Amiodarone also noncompetitively blocks α- and β-receptors and appears to have some ability to block slow calcium channels.

Formulations and dose rates

Amiodarone is supplied as tablets. The effective dose in the dog is unknown. Because of its bizarre and variable pharmacokinetics, predicting the ultimate serum concentration is difficult and predicting the myocardial concentration impossible. For years, amiodarone was administered to humans at higher doses than are currently used. More recently, lower doses have proved to be efficacious. This was discovered through clinical use.

Because amiodarone has not been used extensively in clinical veterinary medicine, it is unknown whether or not lower doses than those used in experimental studies are effective. It is known that an oral dose of approximately 10 mg/kg/d to experimental dogs increases the defibrillation threshold after 9 d.

No established relationship between plasma concentration and efficacy in humans exists. However, a plasma concentration below 1 mg/L is often not effective and a plasma concentration above 2.5 mg/L is usually not needed. A plasma concentration above 2.5 mg/L is associated with a higher incidence of side effects in humans.

It is known that the plasma concentration was 1.9 ± 1.1 mg/L within 3 weeks in experimental dogs administered 40 mg/kg/d PO for 10 d followed by 30 mg/kg/d PO for 4 d followed by 20 mg/kg PO d for 6 weeks. It is also known that this dose was effective in preventing inducible ventricular tachycardia/fibrillation in these dogs with experimentally induced myocardial infarction. From these data, it would appear that this dose regimen might be effective in clinical canine patients. However, lower doses were not tested in this study so it is unknown if a lower dose might have been equally effective.

The dose regimen outlined above resulted in a plasma concentration above 2.5 mg/L in some dogs. This may suggest that a lower dose might be safer. One veterinary clinician has reported that a dose regimen of 10–15 mg/kg q.12 h (20–30 mg/kg/d) PO for 7 d followed by 5–7.5 mg/kg q.12 h (10–15 mg/kg/d) PO improved ventricular arrhythmias in a few dogs.

Pharmacokinetics

Amiodarone has unusual pharmacokinetics. After repeated administration, the drug has a long half-life of

3.2 days in the dog. It is very lipophilic and accumulates to up to 300 times the plasma concentration in adipose tissue. Once drug administration is discontinued, amiodarone is cleared rapidly from all tissues except adipose tissue.

Myocardial concentration of the drug is approximately 15 times that of plasma. The long half-life of the drug means that it takes a long time to produce a significant effect once administration starts. It also takes a long time for the drug effect to dissipate once administration is discontinued. For example, the time to reach one-half of the peak value ultimately achieved for the increase in left ventricular refractory period in dogs is 2.5 days. The time to come down to one-half the peak value after drug administration is discontinued is 21 days in dogs. Because of the long time to onset, loading doses of amiodarone are commonly administered in human medicine. In humans it may take 1–3 weeks to observe onset of action, even with loading doses. Antiarrhythmic effects are present for weeks to months after discontinuing the drug in humans.

Adverse effects

- Numerous side effects of amiodarone have been reported in the human literature. In humans who receive more than 400 mg/d of amiodarone (400 mg is approximately 6 mg/kg/d), 75% experience adverse reactions and 7–18% discontinue the drug because of side effects. Most of the adverse sequelae occur after 6 months of drug use.
- Adverse reactions in humans consist of neurological problems (20–40%), gastrointestinal disturbances (25%), visual disturbances including corneal microdeposits (4–9%), dermatological reactions including photosensitivity and blue discoloration of the skin (5%), cardiovascular reactions including congestive heart failure and bradycardia (3%), abnormal liver function tests (4–9%), pulmonary inflammation and fibrosis (4–9%) and hypothyroidism and hyperthyroidism.
- Pulmonary fibrosis is the most common severe sequela of amiodarone administration in humans. Pulmonary fibrosis, heart failure and elevation of liver enzymes necessitate discontinuing the drug in humans. Pulmonary toxicity appears to be multifaceted but inhibition of phospholipase A with resultant phospholipidosis is one mechanism responsible for producing pulmonary lesions.
- Amiodarone's side effect profile in dogs is poorly documented.
  - In two studies elevated liver enzymes and neutropenia were reported in some dogs. The liver enzymes returned to normal following discontinuation of the medication in most dogs.
  - Gastrointestinal disturbances have also been reported.
  - The authors can find no studies of chronic toxicity of amiodarone in dogs.
  - Comparable lung changes to those seen in humans are induced in rats and mice.
  - Dyslipidic lesions can be produced in the gastrointestinal tract of dogs by amiodarone administration but only at very high doses (>50 mg/kg/d for 30 d).
  - It is also known that amiodarone increases the phospholipid content of feline myocardium. Consequently, it is suspected that chronic amiodarone toxicity could occur in dogs and cats.
- Amiodarone can result in either hypothyroidism or hyperthyroidism in humans. Amiodarone inhibits T4 and T3 secretion from canine thyroid glands. Consequently, thyroid function should be monitored when amiodarone is chronically administered in veterinary patients.

Known drug interactions

- Amiodarone alters the pharmacokinetics and increases the serum concentrations or the effects of several drugs in humans, including digoxin, quinidine, procainamide, phenytoin and warfarin.
- Amiodarone administration increases the bioavailability of diltiazem and decreases total body clearance and volume of distribution of the drug in the dog. This results in an increased serum diltiazem concentration and could produce a toxic concentration. This combination should be used cautiously and the dose of diltiazem reduced.

Bretylium

Clinical applications

Bretylium was first developed as an antihypertensive agent. In 1966, it was noted that it increased the fibrillation threshold. Since then, it has found limited usefulness as an antiarrhythmic and antifibrillatory agent in human medicine.

Bretylium is used for the emergency treatment of life-threatening ventricular tachycardia or ventricular fibrillation that recurs despite direct current shock and lidocaine. It is generally ineffective against supraventricular arrhythmias. Bretylium appears to have no use as an agent to produce chemical defibrillation in dogs.

Mechanism of action

Bretylium's primary effect is prolongation of the action potential and refractory periods in myocardium. It also decreases the disparity in action potential duration between normal and diseased myocardium. Bretylium is

taken up by and concentrated in adrenergic nerve terminals. This initially results in noradrenaline (norepinephrine) release and a brief sympathomimetic effect. This is followed by an inhibition of noradrenaline release.

Bretylium's major effect on cardiac tissues is to prolong the action potential and refractory period of atrial and ventricular myocardium and Purkinje fibers. In so doing, it increases the fibrillation threshold. Bretylium produces a biphasic effect on impulse initiation and conduction and on hemodynamics. Sinus rate, myocardial contractility and blood pressure increase transiently for 10–15 min. These variables then tend to decrease as sympathetic tone decreases. These antiadrenergic effects prolong atrioventricular conduction time in dogs.

Formulations and dose rates

Bretylium tosylate is supplied as a solution for intravenous administration. Because the oral route results in erratic absorption, bretylium is only administered intravenously.

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- 2–6 mg/kg IV. This dose increases the fibrillation threshold to 5–18 times the baseline
- In experimental dogs, this dose is effective at preventing ventricular fibrillation and tachycardia when administered every 12 h chronically. This, however, is not a practical means of treating canine patients
- When bretylium is administered to dogs during cardiopulmonary resuscitation, the antifibrillatory effects are not immediate. Lidocaine produces a more rapid but less pronounced antifibrillatory effect. A combination of lidocaine (2 mg/kg) and bretylium (5 mg/kg) may have a more beneficial effect than either drug alone

Pharmacokinetics

In the dog, bretylium has a biological half-life of approximately 16 h. However, plasma concentration declines rapidly after intravenous administration of 15 mg/kg from approximately 20 μg/mL at 6 min to less than 2 μg/mL after 1 h. The drug is cleared from the body through renal elimination. The antifibrillatory action correlates with myocardial concentration, which increases slowly after intravenous administration to reach a peak 1.5–6 h after dosing.

Adverse effects

- Toxicity is rare, although hypotension can occur. Blood pressure should be monitored and dopamine or noradrenaline (norepinephrine) administered if systolic blood pressure falls below 75 mmHg.
- Transient hypertension and arrhythmia exacerbation may occur after the initial dose because of noradrenaline (norepinephrine) release from nerve terminals.

Sotalol

Sotalol is a class III antiarrhythmic with important β-blocking properties but should not be substituted for a pure β-blocker. The information provided on this drug in this chapter is based on studies in experimental animals, on reports of its use in human medicine, on limited clinical experience and on anecdotal reports from individuals who have used the drug. Sotalol is potentially a very useful drug in small animal veterinary medicine but this potential has not yet been fully explored.

Clinical applications

In human medicine, sotalol is effective for treating various arrhythmias. It is not as successful as quinidine at converting primary atrial fibrillation to sinus rhythm. It is, however, as effective as quinidine at preventing recurrence of atrial fibrillation after electrical cardioversion. Sotalol is effective at terminating supraventricular tachycardia due to AV nodal re-entry or pre-excitation in humans. In human patients with ventricular tachycardia, sotalol may be one of the more effective agents for terminating or slowing the tachycardia. It also appears to be efficacious for preventing sudden death. These effects, however, are not profound and have required large clinical trials to reach statistical significance.

A major indication in veterinary medicine is boxer dogs with severe ventricular tachyarrhythmias and syncope. Sotalol is very effective at suppressing the arrhythmias and stopping the syncopal events in this breed. The authors have limited experience with sotalol for the treatment of supraventricular arrhythmias and ventricular arrhythmias in other breeds.

Mechanism of action

Sotalol is a potent and nonselective β-adrenergic blocking drug that also prolongs the action potential duration and increases the refractory period of both atrial and ventricular myocardium (class III effect). In human medicine it is useful for treating a variety of arrhythmias and for increasing the fibrillation threshold.

Sotalol is marketed as the racemic mixture of its stereo isomers, D- and L-sotalol. The D-isomer has less than one-50th the β-blocking activity of the L-isomer. The L-isomer's potency is similar to that of propranolol. The D- and L-isomers both prolong action potential duration and refractoriness. The increase in action

potential duration is caused by blockade of potassium channels.

Sotalol, when administered intravenously or at high doses orally, increases the Q-T interval on the ECG in experimental dogs. As for any β-blocker, the heart rate is decreased with sotalol administration. It also prolongs the AV nodal refractory period and the P-R interval because of its β-blocking effect. Sotalol increases the atrial and the ventricular fibrillation threshold in experimental dogs. The effect on atrial refractoriness should make it a good drug for preventing atrial fibrillation in dogs, especially those with primary atrial fibrillation after cardioversion. The effect on the ventricular fibrillation threshold should make it an effective agent for preventing sudden death in dogs. Its effects on defibrillation are less well understood. In one study, sotalol decreased the success rate for defibrillation, while in another study, it decreased the energy required for defibrillation.

The hemodynamic effects of sotalol are mixed. Because it is a β-blocker, a decrease in myocardial contractility is expected and has been identified in anesthetized, experimental dogs with normal hearts and in experimental dogs after myocardial infarction. However, in isolated cardiac tissues, sotalol does not have any negative inotropic effect and may have a modest (20–40% increase) positive inotropic effect in catecholamine-depleted experimental cats. This effect may be caused by the prolongation of the action potential allowing more time for calcium influx in systole.

In experimental dogs, sotalol has less of a negative inotropic effect than propranolol. In humans with compromised myocardial function, sotalol can induce or exacerbate heart failure but the incidence is much lower than one might expect. In one study, heart failure was aggravated by sotalol in only 3% of human patients. The potential negative inotropic effects of sotalol could theoretically produce myocardial depression and produce or aggravate heart failure in small animal patients. As in human patients, if one uses this drug, the dose must be carefully titrated and canine or feline patients with moderate to severe cardiac disease must be monitored carefully.

Formulations and dose rates

Sotalol hydrochloride is supplied as tablets. Sotalol is marketed as D,L-sotalol. Both the D-and L-isomers prolong action potential duration, while the L-isomer is responsible for the β-blocking properties of the drug.

Doses used in experimental dogs

In one study in experimental dogs, sotalol successfully converted atrial flutter to sinus rhythm in 14 of 15 dogs at a dose of 2 mg/kg IV administered over 15 min. Quinidine only converted nine of the 15 dogs at a dose of 10 mg/kg IV over 15 min. In another study to examine sotalol's ability to terminate and to prevent atrial fibrillation, it was administered intravenously to dogs with induced atrial fibrillation. At a dose of 2 mg/kg IV, sotalol did not terminate or prevent atrial fibrillation. At a cumulative dose of 8 mg/kg, however, it terminated the arrhythmia in seven of eight dogs and prevented its reinduction in all eight dogs. This effect was due to a prolongation of atrial refractory period.

A high dose of D-sotalol is required to suppress the formation of ventricular arrhythmias in experimental dogs. This compound has no β-blocking activity and one would expect that a lower dose of the racemic mixture would be effective. In one study of conscious experimental dogs 3–5 d after myocardial infarction, four doses of 8 mg/kg D-sotalol administered intravenously successfully prevented the induction of ventricular tachycardia by programmed electrical stimulation in six of nine dogs and slowed the rate of the tachycardia in two of the three remaining dogs.

D-sotalol is also effective in increasing the ventricular fibrillation threshold in experimental dogs with myocardial infarction. Again, the dose required to produce this beneficial effect appears to be quite high, although the data are conflicting and lower doses were not used in most studies. In one study that examined conscious dogs, four doses of 8 mg/kg of D-sotalol PO were administered over 24 h. This dose prevented ventricular fibrillation secondary to ischemia produced distal to a previous myocardial infarction. The use of lower doses was not reported. In another study using conscious dogs subjected to distal myocardial ischemia and infarction, sotalol was administered at 2 mg/kg and at 8 mg/kg intravenously. Although the two groups were not reported separately, it appears that both doses prevented ventricular fibrillation and sudden death. In the group of dogs given sotalol, 13 of 20 dogs survived while only one of 15 dogs given a placebo lived.

Clinical experience with sotalol doses

Boxers with severe ventricular arrhythmias and syncope without severe myocardial failure often respond favorably to the administration of sotalol. Syncopal episodes cease and a marked reduction in ventricular arrhythmias occurs. The dose ranges from 40 mg to 120 mg q.12 h (approximately 1–4 mg/kg q.12 h) PO. This dose is comparable to the human pediatric dose of 50 mg/m^2 of body surface area q.12 h PO. The dose is generally titrated, starting at 40 mg q.12 h. If that dose is ineffective the dose is increased to 80 mg in the morning and 40 mg in the evening, followed by 80 mg q.12 h.

Sotalol may, in some circumstances, be used cautiously in dogs with moderate to severe myocardial failure. The authors recommend that **patients with moderate to severe myocardial failure be monitored very carefully during the initial stages of sotalol administration**. If this cannot be done, sotalol should not be used. In dogs with myocardial failure, the most common response to a relative overdose is weakness, presumably secondary to a low cardiac output. In patients in heart failure, exacerbation of edema can occur. In most cases, withdrawal of the drug should be the only action required if evidence of low cardiac output or exacerbation of the edema becomes apparent. If this does not suffice or if the clinical abnormalities are severe, the administration of a bipyridine compound, calcium or glucagon may be beneficial. Administration of a catecholamine, such as dobutamine or dopamine, will not produce the desired response, since β-receptors are blocked by sotalol.

Pharmacokinetics

In experimental dogs, sotalol is rapidly absorbed from the gastrointestinal tract and has a bioavailability in the 85–90% range. Less than 1% of the drug is metabolized. Elimination is via renal clearance and is linearly related to the glomerular filtration rate. Consequently, the drug dose must be reduced in patients with compromised renal function due to any cause. Sotalol is not protein bound in plasma of dogs. The elimination half-life is 4.8 ± l.0 h. The apparent volume of distribution is in the 1.5–2.5 L/kg range.

Following oral administration of sotalol at 5 mg/kg q.12 h for 3 d (when steady state is reached in experimental dogs), the plasma concentration is in the 1.1–1.6 mg/L range. In humans given the same dose, the plasma concentration is in the 2–3 mg/L range. This discrepancy probably occurs because the elimination half-life in humans is longer (7–18 h). This suggests that the dose in dogs should be roughly double that used in humans. The human dosage recommendation is to administer 40–80 mg q.12 h as an initial dose. This dose then can be increased as necessary every 3–4 d. The maximum dose is 320 mg q.12 h. Assuming an average weight of 70 kg for humans means the dose starts at approximately 0.5–1.0 mg/kg q.12 h and can achieve a maximum dose of approximately 5 mg/kg q.12 h.

A plasma concentration of 0.8 mg/L is needed to produce half-maximal β-adrenergic blockade in experimental dogs. This suggests that a dose of 5 mg/kg q.12 h PO to a dog should result in near-maximal blockade. The plasma concentration required to prolong cardiac refractoriness is higher. In humans, a plasma concentration of 2.6 mg/L is necessary to increase the Q-T interval. Doses between 2 and 5 mg/kg q.12 h PO in humans prolong the Q-T interval by 40–100 ms. In experimental dogs, a dose of 5 mg/kg q.12 h PO also prolongs the Q-T interval.

Adverse effects

- Adverse effects of sotalol in humans are related to the negative inotropic effects of sotalol and to its ability to prolong the Q-T interval. As stated earlier, the negative inotropic effects appear to be minor and very few human patients experience exacerbation of heart failure.
- The most dangerous adverse effect of sotalol in humans is aggravation of existing arrhythmias or provocation of new arrhythmias.
- Excessive Q-T interval prolongation can provoke torsades de pointes in humans. Torsades de pointes has also been produced in experimental dogs but appears to be more difficult to invoke in dogs. For example, one canine model requires that the dog be bradycardic from experimentally induced third-degree AV block and hypokalemic (serum potassium concentration in the 2.5 mEq/L range) before sotalol can cause this serious arrhythmia. The arrhythmia in this model can be terminated with intravenous magnesium administration (1–2 mg/kg/min for 20–30 min).
- Sotalol apparently can also induce other forms of ventricular tachyarrhythmia because of the prolongation of the Q-T interval.
- As for any other β-blocker, withdrawal of sotalol should be performed gradually over 1–2 weeks because of 'upregulation' of β-receptors. Sudden cessation of use can produce fatal ventricular arrhythmias. The drug should not be used in patients with conduction system disease such as sick sinus syndrome, AV block or bundle branch block.

CLASS IV ANTIARRHYTHMIC DRUGS

Description and discovery

Class IV antiarrhythmic drugs are the calcium channel-blocking drugs. These are also known as calcium entry blockers, slow channel blockers and calcium antagonists. Verapamil, the prototype calcium channel blocker, was discovered in 1963. It was being developed as a coronary vasodilator and was discovered to have negative inotropic properties. The negative inotropism could be neutralized by the addition of calcium, β-adrenergic agonists and digitalis glycosides – measures that increase calcium flux into myocardial cells. It was subsequently discovered in 1969 that verapamil and other drugs with similar effects selectively suppressed transmembrane calcium flow. Today, at least 29 different calcium channel blockers are used in clinical human medicine worldwide. In veterinary medicine, only verapamil and diltiazem have been used with enough frequency to make recommendations regarding therapy of arrhythmias.

Classification and mechanism of action

Calcium channel blockers have a variety of chemical structures. They can be classified into three groups: the phenylalkylamines, the benzothiazepines and the dihydropyridines. The phenylalkylamines include verapamil. Diltiazem is a benzothiazepine. The dihydropyridines include nifedipine and amlodipine.

The primary sites of action for calcium channel blockers in cardiovascular medicine are the L-type calcium channels in cardiac cells and in vascular smooth muscle cells. In the heart, calcium channel blockers directly decrease myocardial contractility and slow sinoatrial depolarization and atrioventricular conduction. In vascular smooth muscle, calcium channel blockers produce

relaxation of systemic arterioles, resulting in a decrease in peripheral vascular resistance.

The ability of calcium channel blockers to affect these sites varies tremendously. Verapamil binds equally well to cardiac and vascular smooth muscle sites, producing profound electrophysiological changes, depression in myocardial contractility and vasodilation. The dihydropyridines have very little effect on cardiac calcium channels but have profound effects on vascular smooth muscle. Diltiazem is somewhere between these two extremes, with profound electrophysiological changes, an intermediate effect on cardiac function and a mild effect on vascular smooth muscle. In conscious dogs, nifedipine and verapamil increase the heart rate. This is presumably due to reflex increase in sympathetic tone caused by vasodilation. Diltiazem has little effect.

Myocardial contractility is increased reflexly by nifedipine, decreased directly by verapamil and not changed by diltiazem in the normal cardiovascular system. When the autonomic nervous system is blocked with propranolol and atropine, all three drugs decrease contractility and heart rate. The variable effects are due to slight differences in L-type channel subunit structure between different sites that result in marked differences in channel pharmacology.

Calcium channel-blocking agents that affect myocardial channels block the slow inward calcium current during phase 2 of the cardiac cell action potential. This results in a decrease in myocardial contractility. This may be beneficial in certain circumstances, such as in feline patients with HCM and dynamic subaortic stenosis. In human patients with normal myocardial function, the negative inotropic effect is generally offset by reflex increase in sympathetic tone. However, in human patients with myocardial dysfunction the negative inotropic and negative chronotropic effects of a drug such as verapamil cannot be offset by a sympathetic nervous system that is already maximally stimulated. The resultant decrease in contractility and heart rate following calcium channel blockade can be clinically significant.

Slow calcium channel activity is responsible for depolarization in the sinus and AV nodes. Calcium channel blockers prolong AV conduction, slow the ventricular response to supraventricular tachyarrhythmias such as atrial fibrillation and abolish supraventricular arrhythmias when caused by re-entry through the AV node. The depolarizing currents of the sinus node and the atrioventricular junction are, at least in part, carried by calcium. Calcium channel blockers have the potential to decrease sinus rate in patients with tachycardia but reflex increases in sympathetic tone due to decreased vascular resistance commonly overcome this effect. This effect can be lethal in patients that are dependent on escape rhythms to maintain heart rate (e.g. canine patients with third-degree AV block).

Clinical applications

Calcium channel blockers are highly effective for treating paroxysmal supraventricular tachycardia. Diltiazem is particularly useful for slowing ventricular rate in patients with atrial fibrillation. Experimentally, calcium channel blockers are effective for suppressing accelerated idioventricular rhythms in dogs following shock-induced myocardial injury and myocardial infarction. They have also been effective at suppressing digitalis-induced ventricular arrhythmias in conscious experimental dogs. To our knowledge, however, no reports exist in the veterinary literature concerning the use of calcium channel blockers to suppress ventricular arrhythmias in canine patients.

The dihydropyridines are not useful for treating arrhythmias. Instead, they are used to treat heart failure secondary to mitral regurgitation as well as systemic hypertension in dogs and cats.

Verapamil

Clinical applications

Verapamil is indicated for the acute termination of supraventricular tachycardia in the dog. Although other indications may exist, the authors have not used this drug to treat any other arrhythmia and there are no reports of its use for other indications in the veterinary literature. The experimental literature suggests that verapamil may be effective for terminating accelerated idioventricular rhythm in intensive care patients and for treating digitalis-induced ventricular tachyarrhythmias.

Mechanism of action

The ability of verapamil to terminate supraventricular tachycardia is probably due to its effects on the AV junctional tissue. Most probably, most supraventricular tachycardias that respond to verapamil use the AV junction as part or all of a re-entrant loop. Verapamil has the ability to slow conduction through the AV junction and to prolong the refractory period of this tissue at clinically relevant doses and plasma concentrations. Prolongation of conduction and refractoriness are classic means of terminating re-entrant arrhythmias.

Formulations and dose rates

Verapamil hydrochloride is supplied for intravenous use in ampoules and tablets for oral administration.

For the acute termination of supraventricular tachycardia, the intravenous dose ranges from 0.05 to 0.15 mg/kg. The initial dose of 0.05 mg/kg should be administered over 1–2 min while the ECG is monitored. If this initial dose is not effective, the same dose should be repeated 5–10 min later. If the arrhythmia still is not terminated, a last dose of 0.05 mg/kg (total dose = 0.15 mg/kg) should be

Formulations and dose rates—cont'd

administered 5–10 min after the second dose. This dosage schedule is effective at terminating supraventricular tachycardia in approximately 85% of dogs. The effect following termination of administration is short-lived, often lasting less than 30 min. For longer control, the initial bolus injections can be followed by a constant infusion of verapamil at 2–10 μg/kg/min.

Pharmacokinetics

In dogs, verapamil is absorbed well (more than 90%) but undergoes extensive first-pass hepatic metabolism so that bioavailability is only 10–23%. Verapamil is metabolized to several active and inactive metabolites. Most of the metabolites are excreted in bile. The half-life of verapamil is 1.8–3.8 h in anesthetized experimental dogs and the volume of distribution 2.6 ± 1.0 L/kg. The effective plasma concentration is probably in the range 50–200 ng/mL. A plasma concentration of approximately 100 ng/mL increases the P-R interval in normal dogs and a plasma concentration of approximately 200 ng/mL will produce second-degree AV block. Myocardial concentration of the drug is linearly related to plasma concentration and is approximately nine times the plasma concentration. Left ventricular and AV nodal region concentrations are greater than the atrial concentration.

Adverse effects

- Verapamil can depress cardiac contractility and cause peripheral vasodilation. It should not be used in patients with severe myocardial failure or patients in heart failure unless hemodynamic monitoring can be done and calcium or catecholamines can be administered immediately.
- In mild to moderate myocardial failure patients, verapamil may increase cardiac output by dilating arterioles.
- Occasionally, severe hypotension and cardiovascular collapse can be induced in dogs with normal cardiac function, especially if the drug is administered too quickly.
- Verapamil should not be used in patients with sick sinus syndrome or AV block because of its ability to depress automaticity in these diseased tissues.
- Adverse effects can be reversed by calcium or catecholamine administration. Catecholamine administration is more effective than calcium for treating calcium channel blocker-induced AV blocks in experimental conscious dogs.

Known drug interactions

- Verapamil and β-blockers should not be used together for several reasons.
  - Coadministration of verapamil and β-blockers results in additive negative inotropic, chronotropic and dromotropic (conduction properties) effects on the heart. This produces profound myocardial depression, prolonged AV nodal conduction and depressed heart rate, resulting in severe cardiovascular depression.
  - Verapamil can increase the bioavailability of some β-blockers by decreasing first-pass hepatic metabolism.
  - Addition of β-blocker administration to dogs with a stable plasma concentration of verapamil results in an increase in the plasma verapamil concentration.
- Coadministration of verapamil and lidocaine to isoflurane-anesthetized experimental dogs produces profound cardiovascular depression and severe systemic hypotension.
- Cimetidine decreases total body clearance of verapamil. This increases the plasma concentration of intravenously and orally administered verapamil. This effect probably occurs because of cimetidine's ability to inhibit hepatic microsomal enzymes.
- Verapamil increases the serum digoxin concentration in humans and probably does the same in dogs. The increase is thought to be due to reduced renal and extrarenal clearances of digoxin.

Diltiazem

Clinical applications

The clinical pharmacology of diltiazem when used to treat heart failure in cats is described earlier in the chapter (p. 422).

Diltiazem is also popular for decreasing ventricular rate in dogs with atrial fibrillation. In most canine patients, digoxin is administered first and the heart-rate response determined once a therapeutic serum concentration is achieved. If an adequate response is not achieved, diltiazem can be added to treatment protocol. Diltiazem can also be used in dogs to treat supraventricular tachycardia.

Mechanism of action

Diltiazem slows AV conduction and prolongs the AV refractory period to a similar degree to verapamil. It has minimal effects on myocardial contractility at clinically relevant plasma concentrations in normal dogs. Diltiazem's effects on peripheral vascular smooth muscle are mild, although it is a potent coronary vasodilator.

In normal experimental dogs, one study found that diltiazem (0.8 mg/kg IV) did not alter left ventricular myocardial contractility but did decrease peripheral vascular resistance and increased the heart rate in response to a reflex increase in plasma catecholamine concentra-

tions. These effects resulted in increased cardiac output. In the same study in experimental dogs with pacing-induced myocardial failure, however, the effects were very different. In these dogs, diltiazem decreased myocardial contractility and did not change the heart rate. The net result was a decrease in cardiac output. Another study identified similar findings in dogs with left ventricular volume overload induced by creating an aortocaval fistula. Consequently, diltiazem must be administered cautiously to dogs with moderate to severe myocardial failure or heart failure.

Formulations and dose rates

The formulations of diltiazem available are discussed earlier in the chapter (p.423) as well as appropriate doses for cats.

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- To decrease ventricular rate in dogs with atrial fibrillation, an initial dose of 0.5 mg/kg q.8 h PO should be administered. If the heart rate does not decrease adequately, the dose can be increased to 1.0 mg/kg q.8 h PO and finally to 1.5 mg/kg q.8 h PO. In general, the heart rate should be decreased to less than 160 beats/min. At these doses, diltiazem appears to have no or negligible negative inotropic effects, since exacerbation of heart failure at this dose is rare
- For acute termination of supraventricular tachycardia, a dose of 0.1–0.25 mg/kg can be administered intravenously over 2–5 min
- Diltiazem can also be used for the chronic control of supraventricular tachycardia. Doses higher than those used for heart rate control in atrial fibrillation are commonly needed to suppress supraventricular tachycardia. Doses as high as 4 mg/kg q.8 h PO may be required for this purpose in dogs without significant ventricular dysfunction. In general, the dose should be titrated, starting at a dose of 1 mg/kg q.8 h PO
- Diltiazem at doses ranging from 2–4 mg/kg q.8 h should probably not be administered to dogs that have moderate to severe myocardial failure or dogs with significant cardiac compromise

Pharmacokinetics

In normal experimental dogs, diltiazem is rapidly absorbed from the gastrointestinal tract, reaching a maximum plasma concentration approximately 30 min after oral administration. Bioavailability of the tablets is approximately 24% in dogs. The volume of distribution is 7.6 ± 1.1 L/kg. Approximately 70% of the drug is protein bound. The elimination half-life has been estimated to be 2.3 h and 4.2 h in two different studies. The effective plasma concentration for terminating supraventricular tachycardia is probably in the 50–200 ng/mL range. For controlling the ventricular rate in atrial fibrillation, a lower plasma concentration may be efficacious.

An oral dose of approximately 4 mg/kg results in a plasma concentration of 162–176 ng/mL 1 h after administration in dogs. Administration of a sustained-release diltiazem preparation at approximately 4 mg/kg q.8 h results in steady plasma concentrations between 60 and 100 ng/mL. Intravenous administration of a dose of 0.2 mg/kg results in an average plasma concentration of 138 ng/mL 1 min after administration. An infusion rate of 7 μg/kg/min produces a plasma concentration of 140 ± 23 ng/mL.

Adverse effects

The primary adverse effects of diltiazem are seen with diltiazem overdose. Overdose results in decreased contractility, systemic vasodilation and bradycardia, which, if severe enough, result in cardiovascular collapse. Patients with myocardial failure and conduction system disease are more sensitive to the calcium channel-blocking properties of diltiazem and so are more prone to adverse effects than normal dogs or cats.

Known drug interactions

In general, a β-blocker should not be administered in conjunction with diltiazem because of the possibility of increasing plasma concentrations of both drugs and because of the potential for negative inotropic effects, exacerbation of heart failure and death. However, this can be done safely in most cats with severe HCM although low doses of both agents should be administered initially and the doses titrated up to an effective endpoint.

DIGITALIS GLYCOSIDES

Cardiac glycosides, digitalis glycosides and digitalis are terms used to identify a spectrum of compounds that are steroid derivatives with the ability to mildly increase myocardial contractility and elicit characteristic electrophysiological responses. The most frequently used compounds are digoxin, an extract from the leaf of the *Digitalis lanata* plant and digitoxin, which is extracted from the *Digitalis purpurea* plant. Both plants are from the foxglove family.

A cardiac glycoside consists of a steroid nucleus combined with a lactone ring and a series of sugars linked to the carbon 3 of the nucleus. The steroid nucleus and the lactone ring are termed an aglycone. The number of sugar moieties is a major determinant of drug half-life, although other factors also change half-life. The lactone ring is crucial for inotropic activity.

Clinical applications

Historically, the digitalis glycosides were indicated for the treatment of myocardial failure (i.e. decreased myo-

cardial contractility) and supraventricular tachyarrhythmias. In dogs with myocardial failure, digitalis does not routinely result in a clinically significant increase in myocardial contractility and there are now more potent oral positive inotropes available. Currently the primary clinical indication for digoxin is for the management of clinically significant supraventricular arrhythmias such as atrial fibrillation where it is often used in combination with other antiarrhythmics such as beta blockers or diltiazem.

The digitalis glycosides are moderately effective (usually in combination with other antiarrhythmics) for the treatment of supraventricular tachyarrhythmias, including control of ventricular response rates in atrial fibrillation. If the decrease in heart rate in patients with atrial fibrillation is inadequate (ventricular rate >160 beats/min) and or the initial documented heart rate is >200 bpm, an additional antiarrhythmic agent should be initiated such as a low dose of a β-adrenergic blocker or diltiazem, or amiodarone to produce the desired decrease in heart rate.

Digoxin is the only digitalis glycoside discussed in this chapter as it is virtually the only compound of this type used in veterinary medicine.

The ability of digoxin to improve quality and quantity of life is controversial in both human and veterinary medicine. A large clinical trial designed to answer the question of digoxin's efficacy in human patients was completed in 1997. The results lead to the following editorial comment: 'Digoxin's inability to substantially influence morbidity or mortality eliminates any ethical mandate for its use and effectively relegates it to be prescribed for the treatment of persistent symptoms after the administration of drugs that do reduce the risk of death and hospitalization'. This comment adequately reflects the current majority opinion on the use of digoxin for the treatment of heart failure in dogs and cats, particularly as other medications are demonstrated to have good efficacy in this setting (ACE inhibitors, pimobendan).

Mechanism of action

Antiarrhythmic effects

The current primary indication for digoxin in veterinary medicine is for the management (usually in combination with other antiarrhythmics) of supraventricular arrhythmias, including atrial fibrillation. Digitalis glycosides increase parasympathetic nerve activity to the sinus node, atria and AV node when the digitalis serum concentration is within the therapeutic range. By so doing, they decrease the sinus rate and are capable of abolishing supraventricular premature depolarizations and some supraventricular tachycardias. Cardiac glycosides also produce direct effects that help slow AV nodal conduction and prolong the AV nodal refractory period. The direct and indirect effects of the digitalis glycosides on the AV node are most commonly used to slow the ventricular response to atrial flutter and fibrillation.

Baroreceptor/neuroendocrine modulatory effects

The digitalis glycosides also have effects on vascular baroreceptors. Baroreceptor function is abnormally reduced in human patients and experimental dogs with heart failure. This results in attenuated cardiac vagal tone and increased sympathetic activity. This maladaptive compensatory mechanism can be detrimental in patients with heart failure. The digitalis glycosides increase baroreceptor function in normal cats, dogs and humans. They decrease plasma catecholamine concentrations, directly recorded sympathetic nerve activity and plasma renin activity, which may all be related to increased baroreceptor activity, and are thus considered neuroendocrine modulators. However, the clinical significance of this effect on morbitiy and mortality in heart failure has not been demonstrated. This may be related to the relatively high rate of adverse or side effects associated with digoxin use and narrow therapeutic window.

Positive inotropic effects

The digitalis glycosides are weak positive inotropic agents when compared to inodilators (e.g. pimobendan, milrinone) and β-agonists (e.g. dobutamine). The positive inotropic effect is caused by digitalis poisoning the Na^+,K^+-ATPase pumps on myocardial cell membranes. Digitalis competitively binds to the site on this pump to which potassium normally attaches and effectively stops pump activity. A therapeutic concentration of digoxin 'poisons' approximately 30% of the Na^+,K^+-ATPase pumps in the myocardium. Thus, the cell loses some of its ability to extrude sodium from the intracellular space during diastole, resulting in an increase in intracellular sodium concentration. The cell exchanges the excess intracellular sodium for extracellular calcium via the Na^+/Ca^{2+} cation exchanger or by reducing the exchange of intracellular calcium for extracellular sodium. The net result is an increase in the number of calcium ions within the cell. In a normal cell, these excess calcium ions are bound by the sarcoplasmic reticulum during diastole and are subsequently released on to the contractile proteins during systole, causing increased contractility. This effect is reduced by myocardial failure.

Diuretic effects

Investigators have examined the renal effects of a digitalis glycoside (ouabain) and found it to have diuretic properties. There are Na^+,K^+-ATPase pumps present on the basolateral aspect of renal tubular epithelial cells which promote renal tubular reabsorption of sodium.

In one study, digitalis increased sodium excretion 284% above baseline in experimental dogs with heart failure. This would translate into percentage of filtered sodium load increasing from 1% to approximately 4%, making digoxin a slightly better diuretic than spironolactone.

Formulations and dose rates

Digoxin is available as tablets (preferred), capsules, suspension, elixir and as an injectable formulation. Tablets are better tolerated than the alcohol-based elixir. In the authors' opinion use of the injectable formulation has no place in clinical veterinary medicine.

The therapeutic range for digoxin is based on evaluation of serum trough concentration (6–8 h after a dose) in patients at presumed steady state (i.e. 3–7 d after initiation or any change in dose). However, if a patient presents with signs of possible toxicity a serum level can be obtained immediately. The reported target therapeutic serum concentration is 1–2 ng/mL, where <0.5 ng/mL is subtherapeutic. However, some dogs will demonstrate signs of toxicity at serum levels of 2 ng/mL. Currently, most cardiologists aim for a serum concentration of 0.5–1.5 ng/mL. Serum concentrations above 2.5 ng/mL are considered toxic.

Starting dose

DOGS

- Because of the variability in pharmacokinetics from animal to animal and the narrow therapeutic range for serum concentration, digoxin administration to any animal should be viewed as a pharmacological experiment. An initial dose should be chosen and administered and serum concentration measured 3–5 d after starting treatment to determine if the chosen dose has resulted in a therapeutic serum concentration
- In dogs weighing less than 20 kg the initial starting dose of digoxin can be based on bodyweight at 5–10 μg/kg q.12 h PO (0.005–0.01 mg/kg q.12 h)
- In dogs weighing more than 20 kg, the dosage should be based on body surface area (so as not to overdose): 0.22 mg/m^2 of body surface area q.12 h PO

CATS (Rarely Used)

- The initial starting dose for normal cats is approximately 30 μg (0.03 mg) administered q.48 h for cats weighing less than 3 kg, 30 μg (0.03 mg) q.24 h for cats weighing 3–6 kg and 30 μg (0.03 mg) q.12–24 h for cats weighing more than 6 kg

Factors that alter dosage

Commonly, the initial starting dose of a digitalis glycoside needs to be modified because of factors that alter the pharmacokinetics of the drug. In one study in which digoxin dose (0.005–0.23 mg/kg/d) was plotted against serum concentration in dogs with heart failure, the correlation coefficient was only 0.39 (1.0 is a perfect correlation). This weak correlation was statistically significant, meaning that drug dosage is a factor determining serum concentration. However, the poor correlation indicates that the digoxin dose rate is only one factor among a number of other variables that determines serum concentration. These variables must be considered when administering digoxin.

- Renal failure reduces renal clearance, total body clearance and volume of distribution of digoxin, resulting in an increased serum concentration of the drug. There are no data to correlate degree of azotemia and serum digoxin concentration in dogs or cats. Consequently, whenever possible, digoxin should be avoided in dogs with any degree of renal failure. If digoxin must be administered, it is best to start at a very low dose and titrate upward, if necessary using the measured serum concentration as a guide.
- Because most of a digitalis glycoside is bound to skeletal muscle, dogs or cats that have lost significant muscle mass (decreased volume of distribution) have increased serum concentrations for any given dose. Consequently, for patients that are cachectic, the dose must be reduced. Older dogs commonly have decreased muscle mass and impaired renal function, so digoxin dosing in these patients must be performed cautiously.
- Digoxin is poorly lipid soluble. Consequently, dosing should be based on a lean bodyweight estimate. Lean bodyweight is an estimate of the weight that an obese patient *should* weigh.
- Digoxin does not distribute well into ascitic fluid. Consequently, the dose of digoxin must be reduced in patients with ascites if total bodyweight is used to calculate the dose. In general, patients with mild ascites should have their dose reduced by 10%, those with moderate ascites by 20% and patients with severe ascites by 30%.
- Hypokalemia predisposes to digitalis myocardial toxicity. Digitalis and potassium compete for the same binding site on the membrane Na^+,K^+-ATPase pumps. Hypokalemia leaves more binding sites available for digitalis. Hyperkalemia displaces digitalis from the myocardium.
- Hypercalcemia potentiates the positive inotropic and toxic effects of digitalis.
- Although hypothyroidism has been reported to reduce renal clearance of digoxin in humans, this does not appear to be the case in dogs. In one study, acute and chronic digoxin pharmacokinetics were measured in dogs before and after experimental induction of hypothyroidism. There was no difference between the groups. Consequently, it is not necessary to adjust the digoxin dose in hypothyroid dogs.
- Myocardial failure increases the sensitivity of the myocardium to the toxic effects of digitalis. Failing myocardial cells are usually thought to be overloaded with calcium. Digitalis may cause further calcium loading. Calcium-overloaded cells may

become electrically unstable, resulting in ectopic tachyarrhythmias.

- The administration of other drugs concurrently with digitalis may affect the serum concentration of digoxin.
  - Quinidine is the classic example. It displaces digoxin from skeletal muscle binding sites and reduces its renal clearance, resulting in an increased serum digoxin concentration. Quinidine probably also displaces digoxin from myocardial binding sites. This may lessen the direct cardiac toxicity of digoxin and decrease its positive inotropic effect. In general, the combination of digoxin and quinidine should be avoided. If both drugs must be used together, the rule of thumb in human medicine is to reduce the digoxin dosage by 50%. Since serum digoxin concentration approximately doubles following quinidine administration in dogs, this recommendation appears to be valid in veterinary patients.
  - In humans, there are reports of numerous other drugs that increase the serum concentration of digoxin, including oral aminoglycosides (neomycin), amiodarone, anticholinergics, captopril, diltiazem, esmolol, flecainide, ibuprofen, indomethacin, nifedipine, tetracycline and verapamil.
- Digoxin pharmacokinetics are not significantly altered in cats with compensated heart failure receiving furosemide and aspirin. This is despite increases in serum urea and creatinine concentrations.

Dosing strategy

In general, patients should be evaluated carefully before digoxin is administered. Factors that alter the dosage should be noted and an initial dose chosen. The patient should be monitored during the initial course of therapy for signs of toxicity or improvement. A decrease in heart rate or resolution of an arrhythmia are measurable benefits in patients with tachycardia or arrhythmia.

Clinical responsiveness due to improved hemodynamics in patients with heart failure is the desired endpoint of digitalis administration but can be difficult to identify, for several reasons. First, other drugs are generally administered with digoxin, so it may be impossible to identify the beneficial drug. Second, many dogs do not respond to digoxin, so clinical resolution may never occur. The dosage in the latter case should not be increased unless the serum concentration has been measured and documented to be subtherapeutic (i.e. less than 0.5 ng/mL).

Each case should have a serum digoxin concentration measured 3–7 d after initiating therapy and 6–8 h after the last dose (trough concentration) or immediately any time toxicity is suspected. The therapeutic range for serum digoxin concentration is somewhat controversial, although it is generally considered to be between 0.5 and 2.0 ng/mL. However, some dogs will demonstrate toxicity at serum concentrations of 2 ng/mL. A serum concentration above 2.5 ng/mL should be regarded as toxic. If such an elevation is identified in a patient, digoxin administration should be discontinued until the serum concentration is below 1.5 ng/mL. The dosage should be reduced accordingly several days later.

Pharmacokinetics

Approximately 60% of digoxin tablet formulations is absorbed, while about 75% of the elixir is absorbed. There is very little hepatic metabolism, so that almost all of the absorbed drug reaches the vascular system. In serum, an average of 27% of digoxin is bound to albumin. The volume of distribution is 12–15 L/kg. In normal young dogs, serum half-life of digoxin is 23–39 h although much interpatient variability exists. Theoretically, it takes about five half-lives to reach steady state, so it is commonly thought that five half-lives are required to achieve serum concentrations of between 1.0 and 2.0 ng/mL (which is generally considered to be the therapeutic range). However, this is not the case.

The canine maintenance dose of digoxin generally achieves a serum concentration of 1.5–2.0 ng/mL. The serum concentration after two half-lives (75% of steady state) should be 1.1–1.5 ng/mL and after three half-lives (87.5% of steady state) 1.3–1.75 ng/mL. Consequently, maintenance doses should theoretically achieve a therapeutic serum concentration within 2–4 d. In one study of dogs given 0.022 mg/kg digoxin every 24 h, the serum concentration was within therapeutic range by the second day. On the basis of these data, maintenance doses of digoxin in dogs should be used to achieve a therapeutic serum concentration in almost all situations. Loading doses designed to achieve a therapeutic concentration within a shorter period are not recommended in dogs and cats.

Digoxin is primarily excreted via glomerular filtration and renal secretion. About 15% is metabolized in the liver. Bile duct ligation increases the half-life of digoxin from an average of 26 h to 35 h in experimental dogs.

The half-life is extremely variable from cat to cat, ranging from 25 h to 50 h in one study and from 39 h to 79 h in another report. In a more recent study, the half-life in a group of six normal cats ranged from 30 h to 173 h with a mean half-life of 82 h. The half-life of digoxin increases dramatically with prolonged oral administration. The elixir form results in serum concentrations approximately 50% higher than those achieved with the tablet. However, cats generally dislike the taste

of the alcohol-based elixir. When digoxin tablets are administered with food to cats, serum concentration is reduced by about 50% compared to the concentration without food.

Adverse effects

In normal beagle dogs, a serum concentration of digoxin that exceeds 2.5 ng/mL generally produces clinical signs of toxicity. However, dogs and cats may show clinical evidence of toxicity at a serum concentration less than 2.5 ng/mL and occasionally a dog will show no clinical signs of toxicity at a serum concentration greater than 2.5 ng/mL.

The incidence of digoxin toxicity in veterinary medicine is not well documented. In one canine study, 25% of dogs receiving digoxin had a serum concentration in the toxic range while 24% had a subtherapeutic concentration. In this author's experience, clinically significant digitalis toxicity such as anorexia is common but may be minimized if lower doses targeting lower serum concentrations are employed. Doberman pinschers may be particularly sensitive to the anorectic side effects of digoxin. Toxicity may occur even in patients that were previously documented to be in a therapeutic range due to progressive muscle wasting, progressive azotemia or accidental overdose. This highlights the importance of good client communication with respect to dosing instructions.

Clinical signs of toxicity

Problems from digitalis intoxication fall into three general classes: those referable to the central nervous system (common), those to the gastrointestinal system (most common) and those to the myocardium – arrhythmias (common). Most dogs intoxicated with digoxin appear depressed. Humans experience malaise and drowsiness and have headaches. Anorexia and vomiting are the common manifestations of digitalis intoxication and are probably due to the direct effect of the digitalis molecule on the chemoreceptor trigger zone (CTZ). In one study, normal dogs with a serum concentration of digoxin in the 2.5–6.0 ng/mL range decreased their food intake to about 50% of normal while maintaining a normal water intake while dogs with a serum concentration above 6.0 ng/mL stopped eating, decreased their water intake to less than one-third of normal and vomited. In clinical practice, a serum concentration of digoxin above 3.0–4.0 ng/mL usually produces anorexia and vomiting. Body temperature also decreases in digitalis intoxication. In one study of healthy beagle dogs, body temperature decreased by approximately 1°C in dogs with moderate toxicity and 1–3°C in dogs with severe toxicity.

In general digoxin toxicity is potentiated by agents that reduce GFR (e.g. enalapril), hypokalemia, azotemia and in cachetic patients.

Autonomic manifestations

Autonomic tone of the heart is increased with digitalis toxicity. Increased vagal tone can result in a decrease in sinus node rate and altered AV nodal conduction and refractoriness, although compensatory increased sympathetic tone can counter these effects. Consequently, sinus node rate is variable in dogs with digitalis intoxication. In one study of normal dogs administered toxic doses of digoxin for 2 weeks, the heart rate initially decreased from baseline values of 90–130 beats/min to 50–90 beats/min after intravenous administration of digoxin but returned to baseline by 24–48 h after dosing. Despite continued administration of toxic doses, the heart rate remained at baseline values or was mildly decreased. During the periods of most severe toxicity, the heart rate increased to 130–190 beats/min.

However, it should be remembered that increased vagal tone predominates at the AV nodal level. Consequently, regardless of baseline heart rate, first-degree AV block is a common finding in dogs with digoxin toxicity. Second-degree AV block may also occur, especially after prolonged intoxication, while third-degree AV block is rare.

Myocardial toxicity

Myocardial toxicity is the most serious complication of digitalis administration. A toxic serum concentration disrupts the normal electrical activity of the heart in several ways. Increased sympathetic nerve activity can result in increased normal automaticity and exacerbate other arrhythmic mechanisms. In dogs, blockade of the sympathetic nervous system increases the dose of digitalis required to produce arrhythmias. Digitalis also slows conduction and alters the refractory period, making it easier for re-entrant arrhythmias to develop.

Late (delayed) afterdepolarizations, where the diastolic membrane potential oscillates, eventually reaches threshold potential and depolarizes the cell, appear to be the most important reason for the development of arrhythmias in digitalis intoxication. The ECG counterpart of this depolarization would be a premature beat. Late afterdepolarizations are attributed to cellular calcium overload and are more easily induced in myocardium that has been stretched (analogous to a ventricle with an increased end-diastolic pressure) and in a hypokalemic environment. Myocyte calcium overload occurs when too many Na^+,K^+-ATPase pumps are poisoned. Digitalis cardiotoxicity occurs when 60–80% of Na^+,K^+-ATPase pumps are inhibited.

Clinically, myocardial toxicity can take the form of almost every known rhythm disturbance. In the dog,

ventricular tachyarrhythmias and bradyarrhythmias are most common. The ventricular tachyarrhythmias consist of ventricular premature depolarizations, ventricular bigeminy and trigeminy and ventricular tachycardia. The common bradyarrhythmias are second-degree AV block, sinus bradycardia and sinus arrest, which occur because of increased vagal tone. Digitalis can also induce supraventricular and junctional tachyarrhythmias, as well as other arrhythmias.

Digitalis intoxication also appears to cause abnormal myocardial function and myocyte damage. In isolated hearts, digitalis intoxication results in an increase in diastolic tension (diastolic dysfunction) and a decrease in developed (systolic) tension (myocardial failure). In normal dogs, severe digoxin toxicity results in an increase in serum creatine kinase concentration and histological evidence of myocardial degeneration and necrosis.

Renal toxicity

Digoxin toxicity also causes renal damage. In one study, there was hydropic degeneration and epithelial necrosis in the proximal tubules and in the medullary collecting ducts. This resulted in increases in serum concentrations of urea nitrogen and creatinine. There was a direct correlation between the degree of elevation in serum concentration and the severity of the tubular damage.

Electrolyte abnormalities

A digitalis overdose can produce hyperkalemia and hyponatremia. In one study, moderate toxicity (serum digoxin concentration 2.5–6.0 ng/mL) resulted in a serum concentration of sodium between 130 and 145 mEq/L with a normal serum potassium concentration. Severe toxicity (serum digoxin concentration >6.0 ng/mL) produced a serum sodium concentration in the 110–130 mEq/L range and serum concentration of potassium anywhere from 3.2 to 7.7 mEq/L. These electrolyte abnormalities are probably caused by digitalis inhibition of the Na^+,K^+-ATPase pumps throughout the body.

Treatment of digitalis intoxication

The mainstay of treating digitalis intoxication is discontinuing drug administration. Because the half-life of digoxin in a normal dog is between 24 and 36 h, it should take between 1 and 1.5 days for the serum concentration to decrease to one-half the original concentration. Half-life is commonly prolonged in older animals and diseased animals. Consequently, the time to reach one-half the original concentration is prolonged.

Gastrointestinal signs related to a digitalis overdose are treated by drug withdrawal and correction of fluid and electrolyte abnormalities. Conduction disturbances and bradyarrhythmias usually require only digitalis withdrawal, although atropine administration is occasionally needed. Ventricular tachyarrhythmias are generally treated aggressively, especially when ventricular tachycardia is present. Lidocaine is the drug of choice for treating these ventricular tachyarrhythmias. It decreases sympathetic nerve traffic and can abolish reentrant arrhythmias and late afterdepolarizations.

Phenytoin can be used to treat digitalis toxicity in the dog. It has similar properties to lidocaine. When administered intravenously, the drug vehicle can produce hypotension and exert a depressant effect on the myocardium. The total intravenous dose is 10 mg/kg, given in 2 mg/kg increments over 3–5 min. Phenytoin can also be administered orally (35 mg/kg administered q.8 h) either to treat a digitalis-induced ventricular tachyarrhythmia or to prevent these tachyarrhythmias.

Serum potassium concentration should always be determined in patients intoxicated with digitalis. If serum potassium is less than 4.0 mEq/L, potassium supplements should be administered, preferably in intravenous fluids. Potassium competes with digitalis for binding sites on the Na^+,K^+-ATPase pumps and provides a more suitable environment for the antiarrhythmic agents to work.

Orally administered activated charcoal avidly binds digoxin and is useful after accidental ingestion or administration of a large oral dose. It decreases digoxin absorption up to 96%. Colestyramine, a steroid-binding resin, may also be useful early after digoxin ingestion but only decreases absorption 30–40%.

F_{ab} fragments of digoxin-specific antibodies (e.g. Digibind®) are used in humans to bind digoxin in the bloodstream and thus remove it from myocardial binding sites. This may be a useful means of treating life-threatening digitalis intoxication in veterinary medicine but it is very expensive. There have been two reports of its use in dogs. In one it cost US$1200 to treat a 23 kg Labrador retriever. The F_{ab} fragment binds with the antigenic epitope on the digoxin molecule. This complex cannot bind to Na^+,K^+-ATPase pumps and is cleared by glomerular filtration. This results in rapid resolution of clinical signs. The measured serum concentration of digoxin may increase or decrease after administration of Digibind®, depending on the type of assay used. Some assays measure total serum digoxin concentration and some measure primarily free serum concentration. Serum concentration of free digoxin decreases rapidly to very low concentrations after administration of Digibind® while total serum concentration of digoxin (free plus digoxin bound to F_{ab}) increases to 10–20 times the baseline after Digibind® administration. The dose of Digibind® can be calculated if either the dose of digoxin ingested or the serum digoxin concentration is known.

The body load of digoxin (mg) is calculated by one of the following methods:

Amount of ingested digoxin (mg) × bioavailability of digoxin = mg × 0.6 [Serum concentration (ng/mL) × volume of distribution (12 L/kg) × weight (kg)]/1000

The dose of Digibind® is then calculated as follows:

$$\frac{\text{mol. wt } F_{ab}\ (50000)}{\text{mol. wt digoxin}\ (781)} = 64 \times \text{body load (mg)}$$

$$= F_{ab} \text{ dose (mg)}$$

Each vial of Digibind® contains 40 mg of F_{ab} fragments, so the number of vials is calculated by dividing the F_{ab} dose by 40. For example, a 25 kg dog is presented with a serum digoxin concentration of 7.5 ng/mL and the owner thinks that it ingested 10 0.25 mg tablets. Using serum concentration, the body load is 2.25 mg. Using the owner's information, the body load is 2.5 mg. Using the serum concentration to calculate the body load gives a F_{ab} dose of 144 mg, or 3.6 vials. The four vials will cost approximately US$2000.

Combination antiarrhythmic therapy

At times, combinations of two antiarrhythmic drugs may be more effective than one drug alone. For example, the combination of digoxin and a β-blocker or digoxin and diltiazem is often more effective at controlling the ventricular rate in patients with atrial fibrillation than is digoxin alone. At times, using digoxin with quinidine may be more effective for converting primary atrial fibrillation to sinus rhythm than using quinidine alone. However, this is an example of a combination where toxicity can also be produced. Because quinidine decreases renal clearance of digoxin and displaces it from its non-CNS binding sites, serum digoxin concentration commonly doubles when quinidine is added. This can result in clinical signs of digoxin intoxication due to increased CTZ stimulation. Paradoxically, there may, however, be a concurrent reduction in digoxin's cardiac effects, as its capacity to bind to cardiac receptors will be reduced by the quinidine.

Another example of the combination of two drugs causing clinical problems is the combination of a β-blocker and a calcium channel blocker. Both drug types can produce negative inotropic effects. In combination, this effect is exacerbated and can result in a severe decrease in contractility, worsening of heart failure and even death.

Combination therapy may be more effective for treating some ventricular arrhythmias. Many veterinary cardiologists have for years had the clinical impression that the combination of a class I antiarrhythmic agent and a β-blocker is more effective at controlling ventricular arrhythmias than either agent alone. In one experimental study using dogs, the combination of quinidine and propranolol was more effective than either drug alone at preventing ventricular fibrillation. Most veterinary cardiologists prefer to use a combination of procainamide and propranolol or atenolol. In experimental studies, the combination of two class I agents may be more effective at controlling ventricular arrhythmias in dogs than either drug alone. An example is the combination of mexiletine and quinidine. In one study of experimental dogs with myocardial infarction, mexiletine controlled the ventricular arrhythmia in only one of 13 dogs and quinidine successfully suppressed the arrhythmia in only three of 13 dogs. The combination, however, was efficacious in eight of the 13 dogs.

Another example is the combination of mexiletine and sotalol. Mexiletine decreases the Q-T interval in experimental dogs that have a prolonged Q-T interval because of sotalol administration. One might think that this would counteract the antiarrhythmic efficacy of sotalol. However, in one study, the combination of these two drugs in experimental dogs was more effective at preventing ventricular tachycardia and more effective at slowing the rate of the ventricular tachycardia than was either drug alone. It is worth noting, however, that in this study sotalol was more effective than mexiletine at preventing ventricular fibrillation either alone or in combination with mexiletine.

DRUGS USED TO TREAT BRADYARRHYTHMIAS

Anticholinergic drugs

EXAMPLES

Anticholinergic agents, such as atropine and glycopyrolate, can be used diagnostically and therapeutically in veterinary patients with bradyarrhythmias

Clinical applications

Increased vagal tone can cause sinus bradycardia, periods of sinus arrest and second-degree AV block. Whenever a patient presents with one of these abnormalities, an assessment of the response to the administration of an anticholinergic agent is indicated, especially if clinical signs are caused by the bradyarrhythmia. Generally, atropine is administered either subcutaneously or intravenously to determine if a bradyarrhythmia is vagally induced.

Dogs with vagally mediated sinus node depression (either sinus bradycardia or arrest) respond to atropine administration by increasing their sinus rate to more than 160 beats/min. Dogs with intrinsic sinus node disease (sick sinus syndrome) may have no response to

atropine administration or may have a partial response (e.g. the heart rate may increase to 110 beats/min). Second-degree AV block disappears following atropine administration to dogs with vagally mediated second-degree AV block. Although we commonly administer atropine to dogs with third-degree AV block to assess their response, we have never identified a dog that had a significant response.

Vagal tone can be increased by numerous factors. Anesthesia, central nervous system lesions, abnormal carotid sinus function (hypersensitive carotid sinus syndrome in humans), respiratory disease and abdominal disease are common. Often the cause is unknown (idiopathic). Parenteral anticholinergic therapy can be used to control bradyarrhythmias in situations where vagal tone is increased for only a short period (e.g. during anesthesia) or can sometimes be used for home therapy if the owner can administer an injection. This is no more involved than teaching a client to administer insulin to a pet with diabetes mellitus.

Oral administration of anticholinergic agents can also be tried in these patients. Some patients do very well on oral anticholinergic therapy. However, oral anticholinergic therapy is not always successful and parenteral administration, administration of a sympathomimetic or pacemaker implantation may be required. The oral anticholinergic drugs can be ranked in order of effect. Drugs with weak anticholinergic effects are commonly used as antidiarrheal drugs in veterinary medicine. They include isopropamide iodide and propantheline bromide. These drugs are only rarely effective for chronically treating vagally induced bradyarrhythmias. Atropine and glycopyrolate are more potent vagolytics and much more effective agents.

Formulations and dose rates

Atropine

When administered subcutaneously, 0.04 mg/kg should be administered and the dog should be placed in a cage for 30 min before reassessing the cardiac rhythm. For intravenous administration, 0.04 mg/kg is also administered but the rhythm can be reassessed in 5–10 min.

Atropine tablets used to be available and in the authors' experience were often effective. They are no longer manufactured but can occasionally be found. The parenteral atropine solution can also be administered PO but is extremely bitter. To administer it PO, it must be diluted in a sweet substance, such as corn syrup, to disguise the taste. The authors have found that a dose of 0.04 mg/kg q.8 h can be effective.

Glycopyrolate is available as 1 mg and 2 mg tablets. Although this product should be effective, the authors have little experience with its use.

Adverse effects

Vagolytic substances can produce side effects. These include:

- mydriasis
- constipation
- dry mouth
- keratoconjunctivitis sicca.

In the authors' experience, however, these side effects are often remarkably inapparent.

Sympathomimetic drugs

Isoprenaline (isoproterenol)

Clinical applications

Sympathomimetics can also be used to treat bradyarrhythmias. Isoprenaline (isoproterenol) is a pure β-agonist that stimulates both β_1- and β_2-adrenergic receptors (see Chapter 4). In so doing, it increases the sinus node rate, increases the rate of subsidiary pacemakers in the heart and increases conduction velocity in the AV node.

Isoprenaline can be used temporarily to increase the heart rate in dogs with sick sinus syndrome or third-degree AV block. This is done only in dogs that are severely bradycardic or are symptomatic. Isoprenaline is infrequently used in the author's clinic to increase the heart rate in dogs that are waiting to have a pacemaker implanted. It is more frequently used in dogs that become severely bradycardic under anesthesia prior to pacemaker implantation.

Formulations and dose rates

Isoprenaline is administered intravenously as a CRI at a dose of 0.05–0.2 μg/kg/min. The dose must be titrated and the lowest effective dose should be used. Oral administration of isoprenaline is not effective because it is almost completely metabolized by the liver before it reaches the systemic circulation.

Adverse effects

- Isoprenaline stimulates β-receptors in systemic arterioles, producing vasodilation. This can cause hypotension.
- Isoprenaline can also stimulate tachyarrhythmias.

β_2-Agonists

Clinical applications

Numerous drugs that stimulate β_2-receptors are available. These drugs are used as bronchodilators and are effective after oral administration. They are generally formulated not to produce many cardiac effects. However, this is impossible since β_2-receptors are present in the heart and play an important role in modulating the sinus rate. Consequently, these drugs can also

be used to treat bradyarrhythmias. Most of the authors' experience is with the use of terbutaline in dogs with vagally mediated sinus bradycardia and sinus arrest. In these dogs, terbutaline can be effective at increasing the sinus rate and eradicating the sinus pauses.

Formulations and dose rates

Terbutaline is supplied as tablets. The dose must be titrated, usually starting with 2.5 mg q.8 h per dog PO and increasing as needed. Side effects include hyperactivity and gastrointestinal disturbances.

Adverse effects

Terbutaline should be used cautiously, if at all, in dogs with mitral regurgitation due to myxomatous mitral valve degeneration. The authors have not noted complications with this drug in this setting but have noted acute pulmonary edema, possibly secondary to ruptured chordae tendineae, in dogs treated with salbutamol (albuterol), another β_2-agonist.

ANTICOAGULANTS

EXAMPLES

Unfractionated heparin, low molecular weight heparin, warfarin

Unfractionated heparin

Unfractionated heparin (heparin), a water-soluble mucopolysaccharide, was first discovered in 1916. It was named heparin because of its abundance in liver. It was initially used to prevent the clotting of shed blood, which eventually led to its use in vivo to treat venous thrombosis.

Clinical applications

Heparin is used in the treatment of disseminated intravascular coagulation (DIC) and thromboembolic disease. Its prophylactic use has been recommended in severe immune-mediated hemolytic anemia (IMHA) to decrease the potentially harmful effects of thromboplastic substances released from hemolyzed red blood cells and to minimize the danger of developing pulmonary thromboembolism. However, controlled studies are lacking and the prophylactic use of heparin in IMHA is not universally accepted.

Heparin has been used in the management of cats with thromboembolic disease secondary to hypertrophic or restrictive cardiomyopathy. It has been given with acepromazine as an empirical, unproven treatment to promote collateral vasodilation and prevent growth of the thrombus.

In the management of DIC, heparin is used to activate antithrombin in blood products prior to administration to the patient. Antithrombin, an α_2-globulin acute-phase protein produced in the liver, is the natural inhibitor of serine proteases in the coagulation pathways (factors II, IX, X, XI, XII and kallikrein). It has little or no activity against factor VII. When a patient is in a hypercoagulable state and prothrombin is being actively converted to thrombin, the antithrombin concentration will be low (<80%). The affinity of antithrombin for serine proteases is enhanced 100-fold by administration of heparin.

Heparin has been reported to be ineffective in patients with DIC and to be the cause of hemorrhagic complications in these patients. However, it is believed that most of the poor responses to heparin are the result of its administration when there are inadequate circulating concentrations of antithrombin. In the absence of antithrombin, heparin has only weak antithrombotic effects. These are related to heparin–heparin cofactor II activity against thrombin. When administered alone (i.e. without additional antithrombin) heparin can actually diminish antithrombin concentrations.

Low-dose heparin has also been recommended as adjunctive therapy for severe pancreatitis in dogs but its efficacy is unknown and its use is not recommended in all cases.

Heparin can be administered to test for lipoprotein lipase activity. If serum lipids do not increase 15 min after intravenous administration of 100 U/kg heparin, this is suggestive of lipoprotein lipase deficiency.

Mechanism of action

Heparin inhibits coagulation by several mechanisms. It binds with and enhances the potency of plasma antithrombin III, which inhibits several coagulation factors (see above). Inhibition of thrombin and factor X probably accounts for most of heparin's anticoagulant effect. Antithrombin rapidly inhibits thrombin only in the presence of heparin. Heparin increases the rate of the thrombin-antithrombin reaction at least 1000-fold by serving as a catalytic template to which both the inhibitor and the protease bind. Binding of heparin also induces a conformational change in antithrombin that makes the reactive site more accessible to the protease.

Heparin also inhibits prothrombin activation and platelet aggregation. By inhibiting the activation of factor XIII (fibrin-stabilizing factor), heparin also prevents the formation of stable fibrin clots. While heparin will inhibit the reactions that lead to clotting, it does not change clotting factor concentration. Heparin will

prevent the growth of existing clots but will not lyse clots.

Formulations and dose rates

Heparin is available in ampoules in a range of concentrations (1000–40,000 U/mL) as well as in prefilled syringes (various concentrations and amounts) and premixed with saline and half-normal saline in 250 mL, 500 mL or 1000 mL containers.

Thromboembolic disease

- 100–200 U/kg IV loading dose then 100–300 U/kg SC q.6–8 h

Low-dose prophylaxis

- 50–75 U/kg SC q.8–12 h

DIC

- 50–200 U/kg into plasma or whole blood to be transfused then 50–100 U/kg SC q.8 h once the antithrombin concentration is greater than 60%

Pharmacokinetics

Heparin is not absorbed from the gut if given orally; it therefore must be given parenterally to be effective. If sufficient antithrombin is present, anticoagulant activity begins immediately after intravenous injection and up to 1 h after subcutaneous injection.

Heparin is extensively protein bound, primarily to fibrinogen, low-density lipoproteins and globulins. It does not cross the placenta or into milk in any appreciable amounts. Heparin in humans appears to be cleared and degraded primarily by the reticuloendothelial system. A small amount of nondegraded heparin also appears in the urine. In humans the serum half-life averages 1–2 h and is dependent on the dose administered. The half-life in humans may be shorter in patients with pulmonary thromboembolism and prolonged in patients with renal failure and hepatic cirrhosis.

Adverse effects

- The most common adverse effects associated with heparin therapy are bleeding and thrombocytopenia. In human medicine, major bleeding occurs in 1–33% of patients receiving various forms of heparin therapy. Mild thrombocytopenia occurs in a small proportion of human patients 2–15 d after commencement of therapy; in these patients therapy can be continued if the platelet count does not fall below 100×10^6/L. In rare cases, severe immune-mediated thrombocytopenia can occur.
- Hypersensitivity reactions may occur if heparin is of bovine or porcine origin.
- Uncommon adverse effects reported in humans include:
  - osteoporosis and spontaneous vertebral fractures after long-term therapy
  - hyperkalemia as a result of heparin inhibiting the synthesis of aldosterone.
- In humans, mild increases in alanine aminotransferase enzyme concentrations are common.
- Intramuscular injection can result in hematoma formation. Hematomas, pain and irritation may also occur after deep SC injection.
- Because heparin does not cross the placenta and has not been associated with fetal abnormalities (in contrast to warfarin), it is used for anticoagulation in human pregnancies. However, its safety in pregnancy has not been established. Indeed, it has been reported that fetal mortality or prematurity occurs in one-third of pregnancies where heparin has been used.

Known drug interactions

- Heparin sodium is incompatible with the following solutions or drugs:
  - sodium lactate 1/6 mmol/L
  - aminoglycosides
  - chlorpromazine HCl
  - codeine phosphate
  - cytarabine
  - daunorubicin HCl
  - diazepam
  - doxorubicin HCl
  - droperidol HCl ± fentanyl citrate
  - erythromycin
  - hyaluronidase
  - levorphanol bitartrate
  - pethidine HCl (meperidine HCl)
  - methadone HCl
  - morphine sulfate
  - pentazocine lactate
  - phenytoin sodium
  - polymyxin B sulfate
  - vancomycin sulfate.
- There is conflicting information on compatibility, or compatibility is dependent on diluent or concentration, for:
  - dextrose-saline combinations
  - dextrose in water
  - lactated Ringer's solution
  - saline solutions
  - ampicillin sodium
  - cefalothin sodium
  - dobutamine HCl
  - hydrocortisone sodium succinate
  - methicillin sodium
  - oxytetracycline HCl
  - penicillin G sodium/potassium
  - tetracycline HCl.
- Heparin should be used with caution with other drugs that change coagulation status of platelet function, e.g.:

  - NSAIDs
  - warfarin.
- Heparin may antagonize the effects of:
  - corticosteroids
  - insulin
  - ACTH.
- Heparin may increase the plasma concentration of diazepam.
- Heparin's actions may be partially antagonized by
  - antihistamines
  - intravenous nitroglycerin
  - propylene glycol
  - digoxin
  - tetracyclines.
- Heparin decreases TSH and levothyroxine (thyroxine) concentrations, possibly as a result of interference with the binding of these hormones to proteins.

Low molecular weight heparins (LMWH)

EXAMPLES

Dalteparin (Fragmin®), enoxaparin (Lovenox®)

The LMWH or fractionated heparins represent an alternative to unfractionated heparin. These agents are similar in size to heparin but maintain a peptide sequence that prevents the activation of factor X. They inhibit thrombin IIa to a lesser degree and are frequently expressed as anti-Xa:anti-IIa activity ratios. Because they have less activity towards factor IIa, the PT will not be prolonged significantly and monitoring is not required. Instead, anti-Xa activity can be monitored. LMWH has a higher bioavailability and longer half-life than heparin in people, allowing q.12–24 h dosing. LMWH have minimal antiplatelet effects in humans compared to heparin. They do, however, exhibit fewer although similar proaggregating effects in humans with hypersensitive platelets. They are more expensive than heparin but can be administered subcutaneously. Both dalteparin and enoxaparin have been used in cats at 100 IU/kg SQ q.24–12 h and 1.0–1.5 mg/kg SQ q.24–12 h respectively. Efficacy can be monitored by determination of anti-Xa:anti-IIA ratios. The ratios for dalteparin and enoxaparin are 2:1 and 3:1 respectively. As with heparin, the most common side effect is bleeding.

One study reported the pharmacokinetics of dalteparin in normal cats. A dose of 100 IU/kg SQ q.24 h for 5 d achieved an anti-Xa activity in the human therapeutic range by 4 h after the dose was given and fell below the human therapeutic range by 4–8 h. Another study reported the effects of enoxaparin at 1 mg/kg SQ q.12 h and dalteparin at 100 IU/kg SQ q.12 h. Peak anti-Xa activity occurred by 4 h and returned to baseline by 8 h. However, peak anti-Xa activity was not within the human therapeutic range. Together, these studies suggest that a dosing interval of 8 h may be optimum. However, the correlation between thrombus prevention and therapeutic range of anti-Xa activity is not strong. Thus to better evaluate these agents in cats at risk for aortic thromboembolism (ATE), anti-Xa effects would need to be evaluated in this patient population and ultimately a prospective clinical trial would be required. One retrospective study failed to demonstrate a significant reduction in recurrence rate or improved survival in cats at risk for ATE receiving warfarin or dalteparin.

Warfarin

Clinical applications

Warfarin is used prophylactically to prevent thromboembolism in cats with hypertrophic and unclassified cardiomyopathy.

Mechanism of action

Warfarin interferes with the cyclic interconversion of vitamin K and vitamin K epoxide by inhibiting epoxide reductase (Fig. 17.2), thus inhibiting the production of vitamin K-dependent coagulation factors (II, VII, IX, X). These factors require activation from precursor coagulation proteins to activated coagulation proteins. Activation occurs via γ-carboxylation by carboxylase enzymes located in hepatocytes; vitamin K is an essential cofactor for this reaction.

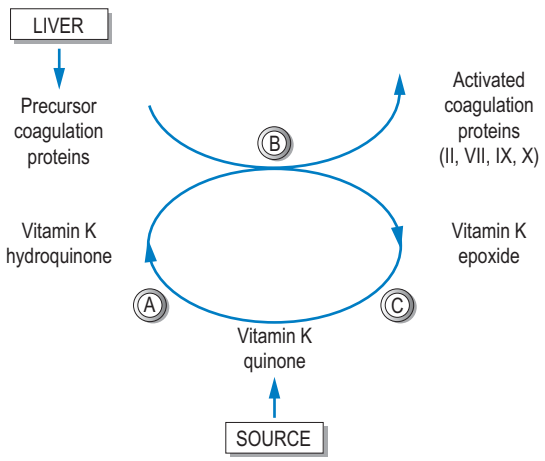

Fig. 17.2 Metabolic pathway for vitamin K. A, reductase reaction; B, linked γ-carboxylation and epoxidation reaction; C, epoxide reductase reaction.

Formulations and dose rates

There is a large interpatient variation in dose response to warfarin. A 20-fold variability in dose response has been reported in humans, and veterinarians using warfarin clinically have observed significant variability in cats. Thus careful patient monitoring is essential and initial hospitalization while the dose is being stabilized is recommended. One-stage prothrombin time is the most common coagulation test used to monitor warfarin therapy. Time of drug administration and blood sampling should be standardized to optimize interpretation of results. Veterinarians are advised to consult relevant references to ensure they are familiar with appropriate protocols for monitoring warfarin therapy.

Warfarin is available in tablet and injectable formulations. The initial dose in cats is 0.5 mg q.24 h PO. If used in dogs to prevent thromboembolism, an initial dose of 0.1–0.2 mg/kg PO has been recommended.

Pharmacokinetics

Pharmacokinetic data for warfarin in cats have not been determined. In humans it is rapidly and completely absorbed after oral administration. It is highly protein bound (approximately 99% in humans) but there are wide species variations in the degree of protein binding – for example, it is less protein bound in horses than in rats, sheep and swine. Comparative data are lacking for companion animal species.

Warfarin is predominantly metabolized in the liver to inactive metabolites that are excreted in urine and bile. Metabolites excreted in bile undergo enterohepatic recycling and are eventually eliminated in urine. The plasma half-life may be several hours to several days, depending on the patient and possibly on the species.

Adverse effects

Dose-related hemorrhage can be a serious complication.

Known drug interactions

Numerous drugs interact with warfarin and may affect the patient's response to the drug.

- In humans potentiated anticoagulant effects may occur with:
  - anabolic steroids
  - several antimicrobial drugs (chloramphenicol, erythromycin, metronidazole, tetracycline, trimethoprim/sulfamethoxazole)
  - several antifungal drugs (fluconazole, ketoconazole, miconazole)
  - antiulcer drugs (cimetidine and omeprazole)
  - thyroid medication (levothyroxine (thyroxine), propylthiouracil)
  - amiodarone
  - danazol
  - NSAIDs
  - quinidine.
- In humans decreased anticoagulant effects may occur with:
  - barbiturates
  - carbamazepine
  - corticosteroids
  - griseofulvin
  - estrogen-containing products
  - rifampicin (rifampin)
  - spironolactone
  - sucralfate
  - vitamin K
  - mercaptopurine.

ANTIPLATELET DRUGS

EXAMPLES

Aspirin, thienopyridines (clopidogrel (Plavix®), ticlopidine (Ticlid®))

ASPIRIN

See Chapter 13.

THIENOPYRIDINES

These agents induce specific irreversible platelet membrane ADP receptor antagonism. They are direct antiplatelet drugs and inhibit primary and secondary platelet aggregation in response to many agonists and thus prolong mucosal bleeding times. Antiplatelet effects are greater than those with aspirin. The ADP-induced conformational change of glycoprotein IIb/IIIa complex is also inhibited which reduces binding of fibrinogen and von Willebrand factor. Platelet release action is also impaired, decreasing the release of proaggregation and vasoconstrictive agents (e.g. serotonin, ADP, thromboxane).

Clopidogrel

Clopidogrel is a second-generation agent with increased potency relative to ticlopidine. A short-term pharmacodynamic study in normal cats reported that clopidogrel caused inhibition of platelet aggregation to ADP and serotonin by >90% and a 3.9-fold increase in mucosal bleeding time at 18.75, 37.5 and 75 mg/cat PO q.24 h. Maximum effects were present by 3 d and were lost 7 d following discontinuation of drug administration. No

adverse effects were noted in the study or in 30 clinical feline patients receiving daily therapy for 18 months. There was no difference in antiplatelet efficacy between doses and thus the lowest dose (1/4 of a 75 mg tablet (18.75 mg/cat q.24 h) is recommended.

Canine starting doses are reported to be 2 mg/kg once daily. Doses as low as 1 mg/kg may be sufficient for chronic therapy (i.e. after at least 3 weeks of therapy). If rapid platelet inhibition is desired (i.e. within 90 min) then a loading dose of approximately 10 mg/kg could be used and was found to be safe and effective in six dogs.

However, if there is a possibility of von Willebrand's deficiency, then von Willebrand's levels should be checked (bleeding times are not sufficient) before starting any antiplatelet drug, including clopidogrel.

Ticlopidine

This was the first drug in this class to be used in people. A short-term pharmacodynamics study in normal cats demonstrated good antiplatelet effects but most cats had severe gastrointestinal side effects, limiting clinical utility.

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