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REVIEW

Pharmacotherapy of feline cardiomyopathy: chronic management of heart failure



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Abstract The natural progression of cardiomyopathy in cats can lead to congestive heart failure. This review enumerates commonly and uncommonly used medications that can be used for the long-term treatment of cats that have positively responded to initial management of acute heart failure. The advantages, drawbacks, and authors' preferred approach are presented for each medication.

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Introduction

Congestive heart failure (CHF) requiring chronic management is a common sequela of a variety of feline cardiomyopathies (CM).^{1–3} Most feline CHF is characterized by diastolic dysfunction with preserved contractility secondary to a variety of common CM, such as hypertrophic cardiomyopathy without or with obstruction (HCM/HOCM), and some phenotypes of unclassified cardiomyopathy (UCM).^{1–4} In humans, this form of heart failure has

traditionally been referred to as heart failure with preserved ejection fraction, but ejection fraction is not routinely measured in feline patients; instead, assessments of left ventricular systolic function derived from calculations of fractional shortening percentage (FS%) are measured. Thus, for the purpose of this manuscript, feline nondilated cardiomyopathies will be referred to as diseases that can cause heart failure with preserved FS% (HFPPFS). By contrast, CHF characterized by reduced FS% is much less common in cats and is typically associated with idiopathic dilated cardiomyopathy (DCM),⁵ arrhythmogenic right ventricular cardiomyopathy (ARVC),⁶ and some phenotypes of UCM.⁴

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Abbreviations

ACE	angiotensin-converting enzyme
ARVC	arrhythmogenic right ventricular cardiomyopathy
CHF	congestive heart failure
CM	cardiomyopathy
DCM	dilated cardiomyopathy
FS%	fractional shortening percent
HCM	hypertrophic cardiomyopathy without obstruction
HFPFS	heart failure with preserved FS%
HOCM	hypertrophic cardiomyopathy with obstruction
LV	left ventricular
LVOTO	left ventricular outflow tract obstruction
NSAIDS	non-steroidal anti-inflammatory drugs
RAAS	renin–angiotensin–aldosterone system
SAM	systolic anterior mitral valve motion
UCM	unclassified cardiomyopathy

There are too few published prospective clinical trials and retrospective clinical studies that offer peer-reviewed evidence to guide recommendations for the chronic management of CHF secondary to feline CM, and natural variability of disease evolution can mask or falsify the appearance of drug efficacy. In a published survey titled 'Is treatment of feline hypertrophic cardiomyopathy based in science or faith?', most respondents prescribed medications because of theoretical benefits, extrapolations from human HCM therapy, peer consensus, or because it 'probably doesn't hurt and might help.'⁷

The present report summarizes expert opinion gleaned from case series, the published survey cited above,⁷ scientific rationale, and the authors' combined clinical experience; it predominantly focuses on medication(s) selection for the treatment of CHF. Many other medications, including antithrombotics and antiarrhythmics, are used adjunctively in feline CHF patients, and the reader is referred to appropriate articles elsewhere in this issue for information pertaining to them.

Standard care

Furosemide

Furosemide is a diuretic that remains a cornerstone of treatment of CHF due to any etiology. As a loop diuretic, it leads to systemic depletion of

sodium, potassium, chloride and magnesium in a dosage-dependent manner and can also cause hypovolemia, systemic hypotension, azotemia, and metabolic alkalosis,⁸ although potassium excretion is reportedly absent or severely blunted in the cat as compared with other species.⁹ It is the primary diuretic used in cats with CHF secondary to all cardiomyopathic phenotypes⁷ and it can be used in combination with other standard CHF medications. Normal cats reportedly respond to IM furosemide administration, within the effective dosage range (1.25–10 mg/kg), with a stronger and more rapid natriuresis and diuresis than in the dog; however, effects in the dog are apparent over a slightly broader range of dosages (0.625–10 mg/kg).⁹ Increases in urine volume are comparable between normal cats and normal dogs when dosages of 1.25–10 mg/kg IM are administered.⁹ The difference in response between the dog and cat suggests a different dosage–response relationship and, possibly, a difference in mode of action. These differences, in combination with underlying diseases characterized predominantly by HFPFS, might explain why cats commonly require no more than 1–2 mg/kg PO q 12–24 h for chronic treatment of CHF. However, higher dosages may be needed in cats with severe, acute CHF because this state is characterized by reduced renal blood flow.

Why use

Furosemide is a high-ceiling diuretic (higher dosages elicit a greater response)⁸ that is consistently well tolerated by clinically ill cats and is not surpassed by any other diuretic in terms of subjective clinical efficacy and safety. It can be delivered parenterally or orally.

Why not use

Although no prospective studies have confirmed efficacy, its efficacy has never been questioned. With respect to furosemide use for the treatment of CHF, users must be satisfied with the fact that they have 'faith' in its efficacy, where 'faith' is defined as 'belief, in the absence of proof'. The liquid alcohol-based oral formulation is unpleasant tasting to many cats; however, the tablets are well tolerated and can be made into an oral suspension and used in lieu of the liquid alcohol-based preparation.

Authors' approach

We use furosemide in the treatment of clinically- and radiographically-confirmed chronic CHF secondary to any form of heart disease in all cats. After the acute CHF episode has been well

controlled and the patient discharged and stable (normal mentation, appetite, and respiration), we attempt to use the minimum dosage in mg/kg/day and longest dosing interval (ideally, q 24 h, if possible) that is sufficient to keep the cat free of clinical signs and radiographic evidence of CHF. Doing so requires a cooperative and insightful owner, and many feline patients cannot have exact dosage titrations if financial, time/lifestyle, or other limitations on the owner's part are prohibitive. Even with optimal owner and cat compliance, dosage adjustments (usually increases) are often required over time as the heart disease progresses. Such adjustments are guided by the results of follow-up evaluations and home monitoring of the resting respiration rate by owners that are able to do so.

Furosemide use in acute CHF is discussed elsewhere in this special issue (See: Management of Acute Heart Failure in Cats). The line between acute and chronic CHF may be blurred by various factors: a well-recognized scenario is the cat with acute CHF but with mild clinical and radiographic signs, and that can be managed on an outpatient basis (possibly compounded by financial or logistical restrictions). In the latter situation, we typically administer 1–2 mg/kg IV or IM and have the owner begin to administer oral furosemide at home later that day. Many cats with HCM can be adequately controlled once stable with q 24-h dosing, and the decision to increase the interval to this length is reserved for patients whose second recheck (typically 2–4 weeks after acute CHF) shows a stable patient, especially if the cat's appetite is not impaired by the use of sodium-restricted foods and treats. Cats with DCM or other heart diseases characterized by systolic myocardial failure (cardiomyopathies characterized by reduced FS%) often appear to require higher dosages and/or q 12-h dosing.

In cats with a large volume of cardiogenic pleural effusion or ascites, we manually remove fluid via centesis, using sedation (e.g. butorphanol 0.1–0.3 mg/kg IV or IM once) if needed. Caution is exercised by some cardiologists when quickly removing large volumes (>120 mL) of chronic pleural fluid, especially with grossly chylous effusions, because of the possible risks of iatrogenic barotrauma (bronchopleural fistula, re-expansion pulmonary edema).¹⁰ However, these theoretical risks must be weighed against the anticipated benefits of greater volumes of fluid being withdrawn. We then prescribe long-term oral furosemide to delay the rate of fluid reaccumulation. Typically, furosemide dosages for this indication

are the same as those used for preventing recurrence of pulmonary edema.

At the first onset of CHF, or any recurrence, the furosemide dosages may need to be higher than those required for longer-term chronic management. The maximum chronic dosage rarely exceeds 3 mg/kg PO q 12 h. Furosemide tolerance (diuretic resistance/braking effect¹¹) should be considered in cats requiring dosages in excess of this. Higher dosages typically lead to hypokalemia, which may need to be addressed with a supplement or by adding spironolactone. In some cases, when diuretic resistance or cat/owner compliance issues are suspected with oral formulations, one oral dose per day can be exchanged for one SQ dose (same mg per dose). Presumably, if this works, it is either related to improved compliance or overcomes problems associated with enteric absorption. Our experience has shown us that owners can be easily trained to deliver SQ furosemide and, subjectively, many cats experience improved diuresis with this approach.

Pericardial effusion in cats with CHF rarely causes tamponade; rather, the pericardial effusion is the result, not the cause, of CHF and intrapericardial pressures can be expected to be lower than intracardiac pressures in essentially all cats with CHF. Therefore, pericardiocentesis is not indicated. Instead, treatment is the judicious use of furosemide as part of CHF treatment.

Non-steroidal anti-inflammatory drugs (NSAIDs) can decrease renal perfusion and, thus, potentiate toxicity of furosemide while reducing the efficacy of furosemide (presumably through inhibition of vasodilatory prostaglandins).⁸ The negative renal effects of NSAID–furosemide cotreatment can be exacerbated if there is coadministration of an angiotensin-converting enzyme (ACE) inhibitor. Therefore, this combination should be avoided if possible, or adjusted and the patient carefully followed if no better substitute is available for a given case.

Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme (ACE) inhibitors are a well-established component of CHF treatment in many species.^{12–15} In cats with CHF, ACE inhibitors are used routinely in practice: >98% of veterinarians say that they would prescribe an ACE inhibitor as part of CHF treatment in cats.⁷ The rationale for use of ACE inhibitors in CHF is based on important observations: diuretic administration, which is indispensable in the management of most cases of CHF, increases

renin–angiotensin–aldosterone system (RAAS) activity,¹⁶ the lynchpin of which is ACE; ACE inhibition in humans and dogs with CHF confers a longer disease-free interval than treatment without ACE inhibition^{12,13}; and preliminary evaluation of treatment with a diuretic and an ACE inhibitor, enalapril, in cats with CHF, revealed a trend towards improved outcomes compared to treatment with a diuretic and either atenolol or sustained-release diltiazem, but no convincing benefit over furosemide alone.^d In a study of cats with HCM that grouped occult (preclinical, ‘asymptomatic’) cases together with CHF cases, selected parameters improved with ACE treatment.¹⁵ ACE inhibitors are considered to be safe in cats¹⁷ and are pharmacologically active, inasmuch as plasma ACE activity is significantly reduced in cats treated with an ACE inhibitor like ramipril.¹⁸ These effects could possibly confer additional benefits, including renoprotective effects in cats with coexistent kidney disease,¹⁷ and a delay in first onset of CHF. Unfortunately, a profound limitation exists: no study has shown that cats receiving ACE inhibitors during CHF treatment live longer and/or better as a result of ACE inhibition.¹⁹

Why use

By extrapolation from dogs and humans with CHF, and based on an unpublished feline case series, ACE inhibitors may extend the duration of well-controlled CHF in cats. As a class, they are safe drugs and could have beneficial side effects. They can be formulated into a suspension and the dosing interval is once a day.

Why not use

Positive effects in cats with CHF are unproven. They would rarely be inherently harmful, but they may add to the treatment burden that a client must carry, and cause negative effects simply due to administration of more oral medications to uncooperative cats.

Authors’ approach

To offset the RAAS-potentiating effects of furosemide, we co-prescribe an ACE inhibitor with furosemide in all cases of feline CHF.¹⁶ We initiate ACE inhibitor treatment when the patient is stable

and eating (rule of thumb: not initiated when patient has uremia/clinically significant azotemia, nor while the patient is receiving furosemide by parenteral injection only). We stop ACE inhibitor treatment when a cat is anorectic and restart it when appetite is restored. We use enalapril or benazepril, 0.5 mg/kg PO q 24 h, reducing the dosage if the cat shows evidence of intolerance such as inappetence, hypotension, or significant azotemia (e.g. increase of 15% or more in serum creatinine concentration not caused by increase in diuretic dosage or inappetence). Enalapril is available as 2.5 mg tablets, whereas the smallest benazepril tablet size is 5 mg, so the smaller size can favor enalapril, especially in very small cats. Benazepril is eliminated via both hepatic and renal routes, which might be preferable over enalapril in cats at high risk of oliguria/anuria (e.g. low-normal arterial blood pressure, marked azotemia; a small proportion of cases).

Used in selected cases/investigational

Atenolol

As a class, beta-blockers have multimodal effects and can be used alone or in combination with other medications for the treatment of a variety of feline cardiovascular diseases. Atenolol is a beta-1 selective adrenergic antagonist and is the most commonly used beta-blocker for cats with heart disease.⁷ Traditionally, such beta-blockers as atenolol were considered to be indirect positive lusitropes (via slowing of heart rate) and class II antiarrhythmics.²⁰ More recently, there has been increasing evidence of the cardio-protective properties of beta-blockers in some forms of human heart disease that are a result of their neuroendocrine modulatory potential.²⁰ However, it is primarily for prevention of heart-rate-mediated compromises in diastolic filling time and possibly the reduction in frequency and severity of mild supraventricular and ventricular arrhythmias that beta-blockers are clinically used in cats with both occult (preclinical, ‘asymptomatic’) and overt (clinical, ‘symptomatic’) heart disease.²¹ In particular, they have been used for the treatment of cardiomyopathies characterized by LV dysfunction with preserved FS% with or without left ventricular outflow tract obstruction (LVOTO), and arrhythmias that appear to be exacerbated by high adrenergic tone. In a published survey, practitioners rarely prescribed beta-blockers to cats as part of the treatment of heart disease that was causing CHF.⁷

^d Fox PR, for the Multicenter Feline Chronic Heart Failure Study Group. Prospective, double-blinded, multicenter evaluation of chronic therapies for feline diastolic heart failure: interim analysis. In: Proceedings, 21st Annual American College of Veterinary Internal Medicine Forum, 2003. Available at: www.vin.com/doc/?id=3848031 (last accessed 16 October 2014).

Why use

Longstanding veterinary dogma maintains that cats with cardiomyopathies could benefit from beta-blockade. Such putative benefits would be greatest when HCM exists with evidence of LVOTO secondary to systolic anterior mitral valve motion (SAM) with or without regional basilar septal hypertrophy, and the proposed mechanism is severity reduction of LVOTO and improvement in diastolic filling time. The premise for this treatment strategy is based on extrapolation from HCM and HCM + LVOTO in human patients and remains unproven in the cat; therefore, any potential benefits remain theoretical at this time.²² Potential benefits relate to atenolol's ability to blunt a number of the adverse effects (e.g. severity of LVOTO and associated mitral regurgitation, increased myocardial oxygen consumption, impaired diastolic function) that would be expected with chronic beta-adrenergic stimulation in cats with HCM, HOCM, and LVOTO.²¹

Why not use

There are concerns that initiation of beta-blockade could result in: worsening of CHF in cats with active clinical signs; decompensation to CHF in stable cats or asymptomatic cats; potentially increasing the risk of arterial thromboembolism as a consequence of impaired left atrial systolic function.²³ In one prospective clinical study of cats with CHF secondary to HCM (with or without LVOTO) or UCM, the treatment group that received atenolol in combination with furosemide had a negative survival trend; however, the small sample size resulted in a low power and no definitive conclusions were reached.^c

Authors' approach

Although there are limited data to support the concerns regarding the adverse effects of using atenolol in the treatment of cats with CHF, concerns remain.²³ These concerns, in combination with the lack of proof of efficacy, have dampened our enthusiasm for the widespread use of atenolol in cats with CHF secondary to HCM with or without LVOTO, and, therefore, we use it infrequently in this setting. Our current approach is to stabilize cats with CHF by using furosemide and an ACE inhibitor. In cats with a documented LVOTO gradient >50 mmHg, especially if there is a further increase with provocation of sinus tachycardia, and normal left auricular function,²⁴ we recommend uptitration with atenolol once the cat is free of clinical and radiographic signs of CHF. Our initial dosage is 6.25 mg per cat PO q 12 h, then recheck and adjustment based on stimulated heart rate in

7–14 days (stimulation consisting merely of the cat being in the exam room, i.e. not resting heart rate at home). Some cardiologists prescribe atenolol q 24 h, to be given in the evening, such that a daytime recheck is >12 h post pill; this method subjectively appears to identify 25–33% of cats that have beta-blockade that is sustained >12 h and therefore that can continue to receive q 24-hourly treatment. Other cardiologists systematically prescribe atenolol q 12 h, and no proof exists to favor one approach over the other. With either strategy, the target heart rate with stimulation is 140–160 beats/min. If the heart rate is still in excess of this target, we increase the dosage to 12.5 mg per cat PO q 12 h (or first increase to 6.25 mg/cat q 12 h if the initial dosage interval was q 24 h). We have not had to use more than 12.5 mg/cat PO q 12 h to achieve this target heart rate, and this uptitration should not be associated with recurrence of signs of CHF, a heart rate <140 beats/min, or onset of inappetence or other adverse effects. If it is, the atenolol dosage should be reduced to the previous level. Some cats do have a dramatic reduction in echocardiographically demonstrated LVOTO gradient when receiving atenolol. During uptitration of atenolol, we strongly encourage the owner to be diligent with monitoring for signs of decompensation. We do not currently initiate atenolol treatment in cats with CHF secondary to HCM not characterized by LVOTO, unless there is concurrent ventricular or supraventricular tachyarrhythmia, or an inappropriate sinus tachycardia, always in the setting of well-controlled ('dry') HF/PFS. In cats that were receiving atenolol prior to the development of CHF, we tend to continue the atenolol at the same dosage if the cat has preserved FS%, is not in fulminant CHF, has a heart rate >140 beats/min, and has a systolic arterial blood pressure >130 mmHg. In cats that have, or have developed, reduced systolic function or those in fulminant CHF, the dosage of atenolol can be acutely reduced by 50% and often continued at that dose if the cat stabilizes, but may still need to be discontinued at some point during the treatment of chronic CHF if hypotension, relative bradycardia, or both, persist(s).

Diltiazem

In a landmark study comparing diltiazem with propranolol, which is a beta-blocker, this calcium-channel blocker was found to delay recurrence of signs of CHF in cats with HCM.²⁵ The results were particularly engaging because the cats that stopped receiving propranolol and were switched to

diltiazem then improved: the left atrial to aortic ratios were significantly lower, and both clinical and radiographic signs of CHF resolved. However, the study involved a small number of cats ($n = 17$), a logistical limitation of medication administration was three-times daily dosing of diltiazem, and the study was not duplicated or surpassed, which raised the question of repeatability of the results. Later, some veterinarians and veterinary cardiologists who addressed the limitation of three-times daily dosing switched to a sustained-release form of diltiazem that could be given to cats once a day. Regrettably, the pharmacokinetic properties of the sustained-release formulation were subsequently elucidated, revealing that 30 mg sustained-release diltiazem PO q 24 h produced plasma concentrations of diltiazem considered to be subtherapeutic (by extrapolation from human cardiology), whereas 60 mg sustained-release diltiazem PO q 24 h produced an unacceptable number of adverse clinical effects including general malaise, inappetence, and reversible hepatotoxicosis (complications that also occurred with the lower dosage).²⁶ In one unpublished clinical trial assessing three different treatments, or placebo, added to furosemide for treatment of cats with CHF, the cats that received sustained-release diltiazem had the highest withdrawal rate as a consequence of drug intolerance.^e Given the limitations of toxicosis with sustained-release formulations and the limited practicality of medication administration every 8 h for the non-sustained release formulation, diltiazem currently is used very little in cats; 15–30% of veterinarians report that they would prescribe it in cats with CHF.⁷ An important clinical trial in humans with HCM is evaluating whether diltiazem slows the evolution of the cardiomyopathic process,^f and results, if favorable, could spur further investigation of diltiazem use in feline HCM.

Why use

The reported positive lusitropic (diastolic function enhancing) properties of calcium-channel blockers could support their use in cats, although such properties have not been confirmed with diltiazem in cats; the results of the original feline HCM

study suggested that non-sustained-release diltiazem is safe and efficacious²⁵, and no other study, to date, has been published that refutes these findings.

Why not use

Medication administration q 8 h (non-sustained release) and risk of adverse effects and lack of clear proof of efficacy (sustained release) make the current formulations of this drug injudicious for use in cats. This limited practicality in combination with its unconfirmed lack of efficacy has caused the drug to fall into disfavor among most cardiologists.

Authors' approach

We do not prescribe it. Our feline patients who are receiving diltiazem had it initiated by another veterinarian, and these cats either continue to receive it if q 8-hourly administration is acceptable to the owner and the cat (non-sustained-release formulation) or go off the diltiazem on our recommendation (sustained-release formulation). The authors would consider its use (or the use of atenolol) for the management of atrial fibrillation with a rapid ventricular response.

Pimobendan

Pimobendan is a positive inotrope that also causes arterial and venous dilation (inodilator). Its efficacy for the treatment of DCM and chronic valvular disease causing CHF is recognized in dogs²⁷ and it has been reported to prolong symptom-free life in Dobermans with occult DCM based on an echocardiogram.²⁸

The first small retrospective reports of pimobendan use in feline CHF were limited to cats with ventricular myocardial failure.^{9,29} Since most feline cardiomyopathies are characterized by preserved ventricular ejection fraction – negating the value of one of pimobendan's fundamental properties – the scientific rationale for its use is not straightforward. Two retrospective studies offer important insights. In one study of 170 cats with a variety of cardiomyopathies and other forms of heart disease (HCM, $n = 68$; UCM, $n = 63$; DCM, $n = 27$; other, $n = 12$) four cats were reported to have concurrent LVOTO.³⁰ Five cats were reported to have experienced potential side effects (unusual agitation, $n = 2$; anorexia, $n = 1$;

^e Fox PR, for the Multicenter Feline Chronic Heart Failure Study Group. Prospective, double-blinded, multicenter evaluation of chronic therapies for feline diastolic heart failure: interim analysis (oral communication). 21st Annual American College of Veterinary Internal Medicine Forum, Charlotte, NC; June 4–8, 2003.

^f <http://clinicaltrials.gov/ct2/show/NCT00319982> (last accessed 16 October 2014).

^g Sturgess CP, Ferasin L. Clinical efficacy of pimobendan in 11 cats with systolic heart failure (abstract). In: Proceedings, 17th European College of Veterinary Internal Medicine-Companion Animals Congress, 2007. Available at: www.vin.com/doc/?id=3861038 (last accessed 16 October 2014).

vomiting, $n = 1$; constipation, $n = 1$), and in one of these cats the side effect was considered severe enough (unusual agitation) to discontinue the pimobendan – it resolved when pimobendan was discontinued. More recently, a retrospective case–control study of 54 cats with HCM characterized by preserved ejection fraction reported a significant survival benefit with adjunctive pimobendan therapy: the median survival was 626 days when pimobendan was added to standard CHF therapy versus 103 days when it was not ($P = 0.024$).³¹ Cases and controls were matched for certain important criteria, including presence and magnitude of LVOTO. Based on the sum of these retrospective data, pimobendan appears to be well tolerated in cats with CHF due to most forms of cardiomyopathy that are not associated with LVOTO (e.g. HOCM), regardless of the presence or absence of ventricular systolic dysfunction. However, based on available data, safety in cats with LVOTO (e.g. HOCM) cannot be assumed, as too few cats with LVOTO have been included and adverse-effect-specific monitoring has not been undertaken (prospective evaluation). In one study, one cat with LVOTO secondary to SAM experienced tachycardia and hypotension two hours after the initial oral dose of pimobendan, which was therefore discontinued. The cat experienced no lasting adverse effects.²⁹ Thus, treatment for CHF characterized by LVOTO should be carried out with caution and predominantly used as a rescue treatment for these cats until additional safety data are available. Likewise, in cats with no echocardiographic diagnosis, LVOTO cannot be ruled and therefore pimobendan should be reserved for use as rescue therapy at most.

The chronic median oral dosage reported in retrospective studies is approximately 0.25 mg/kg PO q 12 h (range 0.18–0.35). A feline pharmacokinetic study reported that a single oral dose of pimobendan (mean \pm standard deviation 0.28 mg/kg \pm 0.04) was rapidly absorbed, with an absorption half-life of 0.2 ± 0.08 h (mean \pm standard deviation) and an elimination half-life of 1.3 ± 0.2 h. The model predicted the maximum plasma concentration to occur 0.9 h after oral administration.³²

Review of these studies encourages us to think longer about why a drug like pimobendan may be advantageous in cats with CHF characterized by preserved ejection fraction. Some potential reasons include: enhanced inotropy of the left atrium that may improve atrial contribution to LV filling and reduce risk of arterial thromboembolism; by way of phosphodiesterase III inhibitory effects, it may have some ability to limit platelet aggregation

and reduce the risk of ATE;³³ in the LV myocardium, inhibition of PDEIII may directly improve relaxation;³⁴ and lastly, its endothelial-derived relaxation properties (separate from PDEIII inhibition in vascular smooth muscle) may also contribute to enhanced myocardial perfusion and reduced preload and afterload. Taken together, if these properties exist in the cat and the positive inotropy is tolerated, then the overall effect could be beneficial. The last caveat is that the combination of inotropy and afterload reduction must not lead to the development or worsening of LVOTO obstruction.

Why use

Together, several retrospective studies^{29–31,f} have provided some information on safety and tolerability, with rare adverse effects reported. A pharmacokinetics study proved that it is orally absorbed and helped to better define the oral dosage in cats. There is sound scientific rationale for its use in heart failure secondary to diseases characterized by ventricular systolic dysfunction/myocardial failure; however, diseases of this nature are uncommon (DCM) or poorly characterized (UCM) in the cat. Limited formulations (i.e. no suspensions are known to be stable) pose somewhat of a limitation in some cats.

Why not use

Safety is unproven, and legitimate concerns exist regarding current approaches to administering pimobendan to cats. The pharmacokinetic properties of pimobendan are substantially different in cats than in dogs: elimination half-life is three times longer, and peak serum concentration is nine times higher in cats given the same mg/kg dosage as dogs.³² Despite such findings, the dosage that is approved for dogs is routinely given to cats.^{29–31,f} The risk–benefit ratio of such an approach is unknown, either in the short term or long term. Studies that do not involve systematic questioning of subjects regarding adverse effects are known to underreport adverse effects, sometimes by many fold,³⁵ and yet an unsupported implication of safety begins to emerge when adverse effects of pimobendan are reported as being uncommon in retrospective studies.³⁰ Regardless of the echocardiographic findings, the existence and variability of systolic anterior motion of the mitral valve and LVOTO cannot be predicted day-to-day in an individual cat, and yet vasodilators like pimobendan are contraindicated when LVOTO exists.³⁶ Finally, since all clinical evidence that is currently available is retrospective, it is methodologically difficult or impossible to separate

negative patient outcomes caused by adverse medication effects from negative patient outcomes caused by natural progression of disease. Most other medications described in the present article suffer from the same lack of prospective clinical safety evaluations, but none have pharmacokinetic properties in cats that are so markedly different from those in dogs, even as the feline dosage remains the same as the canine dosage.^{37–39} Therefore, the main reason for not using pimobendan in cats is that existing information suggests a real potential for harm, which has not been characterized and, therefore, which cannot be anticipated or managed using current approaches.

Authors' approach

With new information continuing to emerge, and incompletely defined benefits and risks, no single approach can be considered to be optimal for using pimobendan in cats. The following strategies represent two options that are pursued by cardiologists who use pimobendan in their feline patients with CHF.

Option 1

We recommend pimobendan in combination with other traditional heart failure medications (ACE inhibitor, furosemide ± antithrombotic) in every cat with current or historical CHF characterized by ventricular systolic dysfunction and no LVOTO based on an echocardiogram. In cats with preserved ventricular ejection fraction and no LVOTO that are not rapidly and easily stabilized on traditional CHF medication, we historically withheld pimobendan until they decompensated or were not clinically doing well (i.e. reserved it for rescue therapy), but in light of the most recent retrospective case–control study, we are offering it as adjunctive therapy as per the myocardial-failure cats outlined above. However, cats with LVOTO and preserved ejection fraction are not candidates for pimobendan until they are refractory to optimized traditional therapy (i.e. in this scenario, it can be considered rescue therapy). In all cases, we present our recommendations to the owner with the goal of helping them make an 'informed decision', especially in cats with LVOTO. In these cases, we typically begin treatment in the hospital and we check heart rate and blood pressure before and 2–3 h after the first oral dose to be sure it is well tolerated. A significant decrease in blood pressure, increase in heart rate, or both, could indicate worsening LVOTO and warrant discontinuation of pimobendan. In addition, blood work, blood pressure, and heart rate should be

rechecked 10–14 days after initiating pimobendan in any cat.

Option 2

Despite the concerns listed above we use pimobendan together with furosemide and an ACE inhibitor in 'nothing-to-lose,' 'rescue' situations, defined as cases where cats have: (1) radiographically confirmed signs of pulmonary edema, plus (2) overt dyspnea with or without clinical signs of forward heart failure, plus (3) HCM, restrictive cardiomyopathy, or UCM with extremely severe changes on echocardiography (systolic dysfunction and marked secondary changes – typically, a left atrial to aortic ratio >2.5:1). Pimobendan treatment is clearly presented to the owner as a last-resort option, but with potential benefits and with risks that might be outweighed by the risk of withholding pimobendan treatment from patients with such severe illness. If a cat responds well to pimobendan, we generally continue its administration indefinitely, even though the optimal duration of treatment is unknown.

Sotalol

Sotalol is an antiarrhythmic drug with class II (beta-blocking) and class III (potassium-channel-blocking, repolarization-extending) effects.⁴⁰ It is widely used in dogs, especially those with arrhythmogenic right ventricular cardiomyopathy, but sparingly in cats. In cases of ventricular arrhythmias where correction of the causative disorder is not possible (e.g. HCM) and the arrhythmia is very rapid, is associated with syncope/presyncope, or both, it would be preferred over a pure beta-blocker like atenolol. It has also been used in rapid, clinically overt feline supraventricular tachycardia.^{41,42} Anecdotally, sotalol is given to cats at 10–20 mg/cat PO q 12 h, beginning at the lower dosage and with caution or not at all if overt evidence of CHF is apparent. Evidence for its use in cats is extrapolated from other species or is based on single case reports.

Why use

In cats, it appears to be safe, and may be efficacious. There are few/no alternatives that are clearly superior.

Why not use

Unproven, no pharmacokinetic or pharmacodynamics data for the cat.

Authors' approach

We usually prefer atenolol for initial treatment of supraventricular or ventricular tachyarrhythmias in cats, but this choice may be influenced by

familiarity and habit. The cats for which we prescribe sotalol instead of atenolol generally receive it due to more rapid, persistent, morphologically complex, and/or syncopal ventricular tachycardia. We have not observed any adverse effect when sotalol is initiated at 10 mg/cat PO q 12 h and we only increase it later if the clinical need is perceived to be persistent. Efficacy is difficult to judge given the labile nature of cardiac arrhythmias, and the drug may have been effective at reducing the clinical impact of ventricular tachyarrhythmias in treated cats.

Spironolactone

Spironolactone, a simple and safe diuretic, exerts its effects by blocking aldosterone receptors, notably in the collecting ducts. The resultant inhibition of sodium reabsorption is responsible for its diuretic effect, while potassium retention may be beneficial for prevention, or correction, of mild hypokalemia. Its anatomic sites of action are numerous, and in other species, spironolactone is associated with reduced myocardial fibrosis.^{43,44}

In cats, spironolactone is of main interest as a second diuretic, typically in addition to furosemide, because the two may act synergistically by inducing natriuresis at different locations of the renal tubule. This theoretical advantage, called sequential nephron blockade, should allow a patient's CHF signs to be better controlled using lower dosages of each diuretic rather than diuretic monotherapy. Added benefits could include a decrease in interstitial myocardial fibrosis.⁴⁴ Regrettably, the positive and negative effects of spironolactone are poorly documented in cats with naturally occurring heart disease and CHF. The principal investigation of spironolactone in cats with HCM revealed that the drug did not cause significant change in LV mass, cardiac chamber and wall dimensions, nor in echocardiographic indices of diastolic LV function. Worse, treatment was associated with severe ulcerative facial dermatitis that required termination of treatment in 4/17 (31%) of treated cats.⁴⁵ Greater usage of this drug in Europe, where it is licensed for use in dogs and is costlier than in North America, suggests that this cutaneous adverse reaction in cats is uncommon, and might be more likely to occur in Maine Coon cats.

Why use

As a second diuretic it can act synergistically with furosemide; it could also have beneficial extrarenal

effects. These findings are largely extrapolated from human medicine.

Why not use

The risk of cutaneous adverse drug reactions, and lack of effect on myocardial hypertrophy make the value of spironolactone in cats with HCM unclear. Furosemide typically is an adequate diuretic in cats and, therefore, sequential nephron blockade is rarely indicated. The RALES study of human CHF that prompted an explosion of interest in spironolactone due to marked benefits⁴³ was more recently followed by an equally impressive study of human CHF with preserved ejection fraction, which more closely mimics feline CHF caused by HCM.⁴⁶ Unfortunately, the latter study found no significant benefit for the use of spironolactone, which calls into question the enthusiasm for (and expected efficacy of) spironolactone in feline CHF with underlying HCM.

Authors' approach

We prescribe spironolactone as a second diuretic, in addition to furosemide, when hypokalemia exists in a cat with CHF. We do not initiate spironolactone during acute CHF, but rather introduce it in a patient who is stable and well if a recheck renal profile reveals hypokalemia. If the cat is eating a high-sodium diet and/or we are suspicious of persistent pulmonary edema or pleural effusion, we add spironolactone (typically at 6.25 mg/cat PO q 12 h) to the existing treatment regimen. Conversely, if the cat is not eating a high-sodium diet and there is no evidence of pulmonary edema or pleural effusion, and especially if serum creatinine is 1.5 times the high-normal value or higher, then we begin at a lower dosage or else increase the interdosage interval to q 24 h. In such cases, we encourage the owner to monitor appetite and demeanor at home and return for periodic rechecks (history, physical exam, serum renal and electrolyte profile), or sooner if abnormalities arise.

Not routinely used

Digoxin

In humans with chronic CHF, digoxin is a positive inotropic, negative chronotropic, negative dromotropic drug that confers important neurohormonal benefits.^{47,48} These effects occur due to digoxin's action on the sodium–potassium-ATPase exchange pump, mainly in the heart and central

nervous system. Historically, digoxin was used for treatment of DCM and CHF, with emphasis on its positive inotropic properties, which are modest. More recently, Doberman dogs with DCM and CHF were found to have significantly reduced levels of ouabain, the same category of compound as digoxin (cardiac glycosides).⁴⁹ The concept of replacing a cardiac glycoside deficiency with low-dose digoxin during CHF has brought renewed interest in this drug. Currently, digoxin is used sparingly for cats, likely because DCM is uncommon in cats and because, historically, high dosages have led to digoxin toxicosis. Pharmacodynamic studies of cats receiving digoxin have shown a long half-life in this species, justifying q 48 h administration in feline CHF.^{50,51}

Why use

Negative dromotropic and positive inotropic properties make it the drug of choice for treating cats that have systolic dysfunction and concurrent supraventricular tachycardia; this combination of disorders, while recognized in cats, occurs much less commonly than it does in dogs.

Why not use

Unproven. Risk of toxicosis at high dosages and/or with individual susceptibility.

Authors' approach

Various approaches exist, including the absence of use of digoxin altogether, or its judicious use in specific cases. In the latter situation, low-dosage digoxin is prescribed to cats with obvious systolic dysfunction if they are still eating (because in an anorectic cat, a greater concern exists for digoxin toxicosis, and existing anorexia will be difficult to discern from anorexia occurring as a sign of digoxin toxicosis). It is the drug of choice for marked, persistent supraventricular tachycardia causing a persistently elevated ventricular response rate in a cat with ventricular systolic dysfunction (uncommon situation). Some cardiologists measure serum digoxin levels and others do not. For those who do not, and when a 0.03125 mg/cat dosage has not achieved the desired results, additional medications (e.g. beta-blocker) are added instead of raising the digoxin dosage, whereas if the concern exists that the dosage is too high and is causing toxicosis, the digoxin would be stopped regardless of serum levels.

Hydrochlorothiazide

Hydrochlorothiazide is a thiazide diuretic with a site of action that is more distal in the convoluted

tubule than that of furosemide.⁸ The potential adverse event profile is very similar and its efficacy likewise is dependent on adequate renal blood flow. In addition, hydrochlorothiazide may directly decrease the glomerular filtration rate. In the cat, the relative potency of hydrochlorothiazide is low compared to furosemide when it is used as monotherapy, but its duration of action might be longer; however, it is rarely used as a first-line diuretic in cats. It may have value in patients that develop resistance to furosemide. In this case, the addition of hydrochlorothiazide could result in a synergistic interaction with furosemide as a result of sequential nephron blockade and, thus, restore diuresis. Sequential nephron blockade results from potentiation of the effects due to upregulation of the specific exchange mechanism that is inhibited by hydrochlorothiazide in the distal convoluted tubule as a consequence of chronic furosemide therapy. When used in this manner, the risk of all adverse effects is also enhanced. The reported dosage range in cats is 2–4 mg/kg PO q 12 h.

Why use

Diuretic effect when furosemide appears to have poor efficacy. Available as tablet and stable in formulated suspension.

Why not use

Rarely required; other medications may suffice. Poorly evaluated in the cat.

Authors' approach

We rarely use hydrochlorothiazide in cats. When we do, it is in the context of perceived diuretic resistance. If torsemide is unavailable, and given the initial concerns (now reduced) about toxic dermatopathy in cats receiving spironolactone, we have used hydrochlorothiazide as a second, add-on diuretic in cats when there is evidence of diuretic resistance that cannot be explained by poor compliance alone (rare). A typical example would be recurrent CHF in a cat that is receiving an adequate dosage of furosemide (e.g. 3 mg/kg PO q 8–12 h) and yet in whom the urine specific gravity is >1.025, with or without recurrent signs of CHF.

Torsemide

Like furosemide, torsemide is a potent loop diuretic. It is used for diuretic-resistant CHF in dogs.⁵² It has superior properties compared to furosemide in cats: whereas furosemide produces a peak diuretic effect after 2–3 h and that diuretic effect is lost after 6 h, the peak diuretic effect of torsemide occurs 2–4 h after administration and it persists

after 12 h.³⁷ Clinical use in cats is limited, but likely due to lack of familiarity rather than adverse effects, which have not been reported in the cat. It should be used with caution in the cat until the systemic effects are better understood in this species. A logical use of this drug would be substitution (at 1/4–1/8 of the dosage of furosemide, given the greater potency of torsemide) when diuretic resistance is suspected based on recurrent CHF in a cat with good medication compliance.

Why use

Superior diuretic effect in cats compared to furosemide, less diuretic resistance in cats compared to furosemide, available by prescription (human use; off-label for veterinary use) in the U.S. but not Canada.

Why not use

Limited clinical experience (efficacy, safety) in cats.

Authors' approach

We have used torsemide very sparingly in cats (fewer than 10 cases cumulatively). We consider it for CHF cases with diuretic resistance, if poor compliance, abrupt sodium loading/dietary indiscretion, and alternative solutions (e.g. intermittent SQ furosemide) are not feasible or have been ineffective. Its greater, and longer-lasting, diuretic effect signifies that both the advantage of reduced signs of CHF, and the drawback of greater intravascular volume depletion and renal and electrolyte effects, must be anticipated and managed.

Non-pharmacotherapeutic options to enhance outcome

Pleurocentesis, abdominocentesis

Body cavity effusions may be mobilized through centesis or drainage, and such procedures reduce excess body fluid with greater efficacy and fewer side effects than increased dosages of diuretics in humans with ascites.⁵³ In cats, recurrent pleural effusion (common) and recurrent ascites (rare) can be managed with ongoing diuretic administration plus periodic centesis, especially when the fluid is chylous. There is no fixed time interval between centeses; rather, the procedure is performed as dictated by the recurrence of clinical signs. An advantage of the centesis approach over increasing diuretic dosage is that prerenal azotemia,

glomerular filtration rate, and systemic effects of vascular volume contraction are not negatively affected, and if anything can be improved by centesis bringing relief for abdominal compartment syndrome (tense ascites). This can be especially helpful in cats with chronic kidney disease.

Diet modification

On principle, dietary sodium can be said to negate the effects of diuretics because the diuretics used in veterinary medicine cause natriuresis. Logically, lower sodium intake can allow the CHF state to be controlled with lower dosages of diuretics. In addition, adequate caloric requirements, which are increased in CHF, must be met in order to limit the loss of lean muscle mass and prevent sarcopenia in cats with CHF.⁵⁴ Other cardio-supportive nutrients such as omega-3 fatty acids and taurine may also be beneficial if delivered in a palatable way as part of a diet, but their role is uncertain if a documented deficiency is not present.

Many cats' notoriously finicky appetites are an important limiting factor to dietary therapy, and no therapeutic diet justifies compromising the patient's appetite. Sodium restriction can be considered when the CHF state is stable: the respiratory rate and effort are normal, the patient is eating well, and the patient is alert and shows a normal behavior and level of activity in the owner's opinion. It should be gradually introduced; a common approach is to mix 25% of low-sodium food with 75% of the cat's regular food in a total portion that is the same as usual, and after one week, if this is accepted, to change to 50% of each, and so on until the diet consists of 100% sodium-restricted food. Another approach is to feed a veterinary nutritionist-designed and approved, balanced, home-cooked diet that deliberately restricts sodium content. This subject is a topic of great concern among veterinarians who see, time and again, that home-cooked diets prepared by owners with the best of intentions (but no consultation with a board-certified veterinary nutritionist) lead to nutritional deficiencies that can be harmful or devastating. Prepared properly, balanced home-cooked diets can be effective and safe.^{54,h}

Appetite stimulants

In cats with chronic CHF, inappetence or anorexia can be devastating complications. Every effort

^h Tufts Veterinary Nutrition Service. Available at: <http://vet.tufts.edu/heartsmart/diet/> (last accessed 16 October 2014).

should be made to identify and treat any inciting cause. Common causes include: azotemia, hepatopathy, poor perfusion/hypotension, food avoidance behavior, dental disease and cardiac cachexia. In cases where the primary cause of the reduced appetite cannot be adequately managed, an appetite stimulant can be considered, such as B vitamin-cobalamin (Note: do not use a multi-vitamin or B-complex) 250 µg per week SQ for 6 weeks then repeat in 30 days. Mirtazapine, 3–4 mg/cat PO q 72 h can be considered as adjunctive therapy,⁵⁵ especially in end-stage CHF. However, every effort should be made to identify and manage any primary contributing causes and not default to a diagnosis of cardiac cachexia.

Medication formulation options

Ptyalism is common in cats that are given oral medications, especially medications with strong and bitter tastes. In addition, cats can develop food avoidance behaviors when medications are hidden in food.⁵⁴ The treatment of a life-threatening condition like CHF requires a high degree of chronic compliance. Therefore, clinicians must stay diligent with respect to the role compliance plays in successful, long-term treatment. In cats that are difficult to stabilize or those that experience frequent episodes of deterioration or recurrence of clinical signs, the potential role of compliance should be discussed with a goal toward finding alternative strategies that will work for that cat and client. For some cats, pill pockets work well, and in some cases, repackaging tablets (or portions of tablets) into clear glycerin capsules or into suspensions (when possible) can improve compliance. To date, no CHF medication discussed herein has been demonstrated to be bioavailable and effective as a topical preparation and, currently, this route should be avoided for feline cardiovascular pharmacotherapy. In addition, not all medications are known to be bioavailable when reformulated, which means that caution should be used when selecting reformulated medications.

Resting home respiration rate

Objective evaluation of home resting or, ideally, sleeping breathing rate is widely used in the dog as a sensitive tool to identify the onset or recurrence (in the case of Stage C and D) of CHF.⁵⁶ Although it has not been proven to be similarly useful in the cat, there is reason to believe that it may be, and a reference interval for normal adult cats has been reported (≤ 30 breaths per minute).⁵⁷ Cats with

sleeping home respiration rates repeatedly >30 breaths/min are outside the reference interval and likely warrant re-evaluation by their veterinarians. There are a variety of free smartphone applications that have been developed to facilitate owner-observed resting/sleeping respiratory rates for the dog that could also be used for the cat. Home resting/sleeping respiratory rates should be measured approximately once a day in cats with a history of CHF. Utilization of owner-observed home respiration rate is a cost-effective way to empower the owner to be part of the cat's treatment plan, and it may limit life-threatening recurrence of fulminant CHF via early detection. Development of clinical signs, or an elevated home breathing rate >30 breaths/min, can then prompt an immediate re-evaluation or, minimally, a call to the veterinarian.

Summary

As our understanding of early treatment for occult/'asymptomatic' feline cardiomyopathy evolves, it will undoubtedly contribute to the advancement of CHF treatment. Some agents that are initiated will need to be carried forward into the overt/'symptomatic' (CHF) stage of treatment and some might need to be reduced or discontinued. However, even if treatment of occult cardiomyopathy can extend symptom-free survival, it is unlikely that it will result in a cure and, therefore, CHF treatment will still be necessary.

The lack of prospective data for the basis of recommendations for CHF treatment highlights the myriad of opportunities to investigate management approaches in the cat. However, the lack of data, to date, does not negate our responsibility to treat CHF in the cat, and it does emphasize the importance of critical analysis of retrospective studies, expert opinion, and clinical experience when making individual treatment decisions.

Conflicts of Interest

There are no known conflicts of interests associated with this publication. Over the past 5 years, the following Dr. Gordon served as a consultant and received support in the form of speaker honoraria, remuneration of travel expenses, research funding, programmatic support [intern or resident funding or equipment] from Boehringer Ingelheim Vetmedica. Dr.Cote has no disclosures relevant to

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