Chapter 16

Drug Interactions

Mark G. Papich

Introduction

When providing anesthesia and analgesia to animals, veterinarians often administer combinations of drugs without fully appreciating the possible interactions that may and do occur. Many interactions, both beneficial and harmful, are possible, considering the number of drugs that are coadministered. Although most veterinarians view drug interactions as undesirable, modern anesthesia and analgesic practice emphasizes the use of drug interactions for the benefit of the patient (multimodal anesthesia or analgesia).

A distinction should be made between drug interactions that occur in vitro (such as in a syringe or vial) from those that occur in vivo (in patients). Interactions and incompatibilities may occur as a consequence of mixing drugs in the same vial or syringe prior to administration, or when drugs interact in patients. Veterinarians frequently mix drugs together (compound) in syringes, vials, or fluids before administration to animals. In vitro reactions, also called *pharmaceutical interactions*, may form a drug precipitate or a toxic product or inactivate one of the drugs in the mixture. In vivo interactions are also possible, affecting the pharmacokinetics (absorption, distribution, or elimination) or the pharmacodynamics (mechanism of action) of the drugs and can result in enhanced or reduced pharmacological actions or increased incidence of adverse events.

Drug interactions usually result from administration of (a) two drugs in one formulation, as a fixed-dose mixture; (b) two drugs in separate formulations simultaneously; (c) a second drug during prolonged use of the first drug; and (d) two drugs at specific time intervals. Drug interactions can be classified as either pharmacokinetic or pharmacodynamic. *Pharmacokinetics* refers to what the body does to drugs, and *pharmacodynamics* refers to what drugs do to the body. Pharmacokinetic interactions produce changes in drug concentration at the receptor site by altering absorption, elimination, or distribution. Pharmacodynamic interactions occur when one drug alters the response to another.

In vitro Drug Interactions

Acid-Base Interactions

Mixing drugs or solutions that vary in pH or acid-base characteristics may result in an incompatible mixture because of opposition of charge (anion-cation) or interference with the stability of a solution because of acid-base interactions. For example, drugs formulated as hydrochloride salt (HCl) are done so to maintain a pH balance that will ensure that the drug is soluble in an aqueous solution. The HCl may also be critical for the solubility and stability of the compound. If the solution is alkalinized by adding bicarbonate or other bases, the compound may become unstable or precipitate.

The pH of common intravenous fluids is lower than many clinicians appreciate. For example, 0.9% sodium chloride and 5% dextrose solutions can have a pH as low as 3 (Table 16.1).[1] A drug added to a bag containing an acidic solution may lose activity or precipitate if alkalinity is needed for drug stability or solubility. The pH values of common intravenous solutions are listed in Table 16.1.

Chemical Incompatibilities

These reactions occur as a result of chemical interactions among active ingredients, inactive ingredients, vehicles, and preservatives. Veterinarians should not admix drug solutions without first consulting a pharmaceutical reference[2,3] or the drug manufacturer. The drugs listed in Table 16.2 have often been cited as being incompatible with other drugs or solutions. Interactions with injectable drugs can be found in Trissel's book of interactions or the *USP Drug Information*, volume 1.[2,3] Signs of interactions and incompatibilities can include haziness of the solutions, precipitation, bubble formation, or a color change. Some interactions cause drug hydrolysis and oxidation, for example, sympathomimetic catecholamines, such as dobutamine, dopamine, or epinephrine may oxidize to a slight pink without significant loss of potency. However, if the color changes to brownish, it should not be used because this is a sign of significant oxidation.

Solutions

These may be incompatible with other solutions because of ionic interactions. For example, sodium bicarbonate ($NaHCO_3$) reacts with calcium-containing solutions, forming calcium carbonate. Admixing tetracyclines with calcium-containing solutions results in precipitation. In general, hydrochloride salts (e.g., dobutamine HCl, dopamine HCl, and epinephrine HCl) should not be mixed with alkaline solutions. Vitamin B_1 (thiamine hydrochloride) is unstable in alkaline solutions and should not be mixed with alkalinizing solutions, carbonates, or citrates.

Table 16.1. Common fluid solutions and components.

Fluid	Na^+	K^+	Ca^{2+}	Cl^-	pH
0.9% Saline	154	0	0	154	4.5–5.7
0.45% Saline	77	0	0	77	4–7
Ringer's solution	147	4	4.5	156	5.0–7.5
Lactated Ringer's	130	4	3	109	6.0–7.5
5% Dextrose (D_5W)	0	0	0	0	3.2–6.5

D_5W, 5% dextrose solution.

Table 16.2. Anesthetic drug in vitro incompatibilities with other drugs and solutions.

Drug	Compatibility with Other Drugs	Compatibility with Fluid Solutions	Important Considerations
Bupivacaine HCl	pH 4.0–6.5. Avoid strongly acid or alkaline solutions. Sodium bicarbonate has been added to local anesthetics just prior to administration to decrease pain from injection. Raising the pH will accelerate the onset of anesthetic action.	Compatible with fluid solutions.	Do not use if solution becomes cloudy, yellow, or pink. If pH is adjusted (e.g., pH 6–7) with alkalinizing solutions, the drug is stable if used soon after mixing.
Buprenorphine		Infuse with sodium chloride.	
Butorphanol	Do not mix with sodium barbiturates.		Protect from light.
Calcium chloride	Will precipitate with sodium bicarbonate.		Do not mix with compounds known to chelate with calcium.
Dexamethasone sodium phosphate	pH 7.0–8.5. Do not mix with acidifying solutions.	Compatible with most IV solutions.	
Diazepam	pH 6.2–6.9. Hydrolysis will occur if combined with low pH solutions. Precipitation will occur with aqueous solutions.	Precipitation occurs when mixed with water-based (aqueous) solutions. Ringer's based solutions and dextrose will cause precipitation.	Protect from light. There is no loss if stored in hard plastic syringe. However, if stored in soft plastic (PVC) infusion bags or tubing, significant sorption will occur (e.g., 80%–90% in 24 h).
Dobutamine HCl	pH 2.5–5.5. Do not mix with alkalinizing drugs.	Do not mix with alkaline solutions. Compatible with most fluid solutions.	Slight pink tinge to solution can occur without loss of potency, but do not use if solution turns brown.
Dopamine HCl	pH 2.5–5.0. Do not mix with alkalinizing solutions.	Do not mix with alkaline fluids. Compatible with most fluid solutions.	Do not use if solution turns color.
Epinephrine HCl	pH of solution is acidic. It is destroyed by mixing with alkaline drugs.	Incompatible with alkaline solutions and oxidizing solutions.	Do not mix with bicarbonates, nitrates, citrates, and other salts. It is compatible with plastic in syringes. When solution becomes oxidized, it turns brown. Do not use if this color change is observed.

Table 16.2. Anesthetic drug in vitro incompatibilities with other drugs and solutions (*continued*).

Drug	Compatibility with Other Drugs	Compatibility with Fluid Solutions	Important Considerations
Fentanyl citrate		Compatible with most fluid solutions.	No loss measured when stored in plastic infusion sets.
Furosemide	pH of solution, 8.0–9.8. Stable with alkaline drugs, but do not mix with acidifying drug solutions with pH < 5.5	Do not mix with acidic solutions.	Compatible in plastic syringes and infusion sets.
Glycopyrrolate	Acidic pH (2–3). Do not mix with drugs that will alkalinize the solution.	Do not mix with alkaline solutions (pH > 6.0). Compatible with most other fluids.	
Heparin sodium	Heparin is acidic and will react with some basic compounds.	Infuse with dextrose solutions.	No loss occurs in various solutions. No sorption to plastic has been reported.
Hydromorphone HCl	Do not mix with diazepam or bicarbonate.	Stable in most fluid solutions.	
Isoproterenol HCl		Compatible with dextrose and saline solutions.	Degradation occurs at pH > 6.0.
Ketamine HCl	Acidic solution. Do not mix with alkaline solutions such as barbiturates. Avoid mixing ketamine and diazepam.	Compatible with saline and dextrose solutions.	Solution may turn slightly dark, which does not affect potency.
Lidocaine	pH of solution, 5–7. Compatible with most drugs. It can be alkalinized to pH 7.2 without loss of stability.	Stable in fluids, including dextrose solution.	Aqueous solution is stable in mildly acid and alkaline conditions. If pH is adjusted (e.g., pH 6–7) with alkalinizing solutions, the drug is stable if used soon after mixing. No sorption to plastic syringes has been reported.
Lorazepam		Compatible with fluid solutions such as dextrose and saline.	Dilute solution for IV use. There is significant sorption to PVC containers.
Meperidine HCl	Compatible with most drugs.	Compatible with most fluid solutions.	Compatible with plastic syringes.
Midazolam HCl	pH of solution, ca. 3.0. Increasing the pH to >7 will result in drug loss.	Compatible with fluid solutions.	No sorption with plastic or fluid containers is reported.
Morphine sulfate	pH of solution, 3.5–7.0. Stable at low pH, but degradation will occur at pH > 7.	Stable in most fluids (dextrose and saline solutions).	No sorption to plastic has been reported.
Nitroglycerin	pH of solution, 3.0–6.5. Do not mix with other drugs.	Compatible with most fluid solutions.	Sorption to containers, especially PVC plastic, is extensive and will result in significant loss.
Oxymorphone HCl	pH of solution, 2.7–4.5. Compatible with most drugs.	Compatible with most fluid solutions.	
Pentobarbital sodium	pH of solution is 9.0–10.5. It will precipitate if combined with most hydrochloride-based drugs or anything with low pH. Alkaline solution will affect other coadministered drugs.		Aqueous solutions are not stable. Will precipitate readily in solutions with low pH.

(*continued*)

Table 16.2. Anesthetic drug in vitro incompatibilities with other drugs and solutions (*continued*).

Drug	Compatibility with Other Drugs	Compatibility with Fluid Solutions	Important Considerations
Phenobarbital sodium	pH of solution, 9.2–10.2. It will precipitate if combined with most hydrochloride-based drugs or anything with low pH. Alkaline solution will affect other coadministered drugs.		Will precipitate readily in solutions with low pH.
Phenytoin sodium	pH of solution, 10.0–12.3. Do not mix with acidifying drugs.		Will precipitate readily in solutions with low pH.
Propofol	pH of solution, 7.0–8.5 and lower (depends on manufacturer).	Compatible with fluid solutions such as dextrose and saline.	Oil and water emulsion formulation that will encourage microbe growth. Do not freeze. More stable in glass than in plastic.
Sodium bicarbonate	Alkaline solution; pH 7.0–8.5. Do not mix with acid solutions.	Do not mix with solutions that contain calcium (e.g., Ringer's) or precipitation may occur.	
Sodium nitroprusside	pH of solution, 3.5–6.0.	Dextrose solution is recommended for infusion.	Very sensitive to light. Cover with foil during infusion.
Thiopental sodium	pH of solution, 10–11. If not kept at alkaline pH, precipitation will occur.		Reconstituted solution is stable for only 3 days at room temperature or 7 days refrigerated.

HCl, hydrochloride; IV, intravenous; and PVC, polyvinyl chloride.

Diazepam

Diazepam is notorious for its instability in solutions and its ability to adsorb to plastic containers. Diazepam is formulated in organic solvents (e.g., propylene glycol, ethanol, and benzyl alcohol) and is not soluble in aqueous solutions. If the diazepam solution is added to an aqueous solution, it will become hazy or precipitate unless the solution is very dilute (e.g., 1:50 to 1:100). In addition, diazepam is known to adsorb to soft plastic containers, such as those composed of polyvinyl chloride (e.g., PVC infusion bags and plastic tubing). Heparin, when used in flush solutions, is physically incompatible with diazepam.

Changes in pH That Affect Drug Stability or Solubility

According to the *USP-NF*,[3] improper pH ranks with exposure to elevated temperature as a factor most likely to cause a clinically significant loss of drug efficacy. A drug solution or suspension may be stable for days, weeks, or even years in its original formulation, but when mixed with another liquid that changes the pH, it can degrade in minutes, hours, or days. A pH change of 1 unit might decrease drug stability by a factor of 10 or greater. These types of interactions are more likely at the extremes of pH, for example outside the range of 4 to 8 (see Table 16.2 for pH values of commonly used anesthetic and adjunctive drugs). Some drugs undergo epimerization (steric rearrangement) when exposed to a pH range higher than the optimum for the drug. Other drugs are oxidized, which is catalyzed by high pH, rendering the drug inactive. Oxidation is often visible through a color change.

Some drugs are alkaline when in solution and will raise the pH of other admixed drugs, resulting in instability or precipitation. Examples of drugs that will increase the pH of solution above 6 are sodium bicarbonate, barbiturates, alkaline-buffered antibiotics, and aminophylline. Barbiturates are notable because the alkalinity of their solutions. Sodium salts of barbiturates in solution (e.g., pentobarbital sodium, phenobarbital sodium, or sodium thiopental) have a pH of approximately 10. If mixed with any solution that lowers the pH, for example, a hydrochloride-based solution, precipitation will occur instantly.

In vivo Drug Interactions

These are reactions that occur in patients when more than one drug is administered. Studies in people have demonstrated that, as the number of drugs coadministered to a patient increases, the incidence of drug interactions also increases. The consequences of drug interactions are most severe for drugs that have a narrow therapeutic index (i.e., when the ratio of toxic dose to effective dose is small). In vivo drug interactions may change drug absorption, drug disposition, biotransformation, and excretion (pharmacokinetic interactions).

Pharmacokinetic Drug Interactions

These interactions include (a) alteration in absorption, (b) alteration in drug-biotransformation enzymes, (c) alteration in protein binding, (d) changes in renal or hepatic clearance, and (e) changes in drug distribution.

Absorption (Systemic Availability)

Most patients undergoing anesthesia are fasted; however, oral medications are occasionally administered in the immediate perioperative period (e.g., orally administered nonsteroidal anti-inflammatory drugs [NSAIDs]). Most anesthetic and anesthetic adjunctive drugs (e.g., opioids) slow gastrointestinal motility and can delay passage of drugs to the small intestine, where most oral drugs are absorbed. Some drugs require an acidic environment to dissolve before gastrointestinal absorption. Antacid compounds, proton-pump inhibitors (omeprazole), or H_2-receptor blockers (famotidine, ranitidine, and cimetidine) can suppress stomach acid production, which may decrease the absorption of other drugs. There are few documented examples where this type of interaction has affected analgesic or anesthetic drug efficacy, however. It is well documented that orally administered antifungal and antibiotic drugs are affected by stomach acidity. It should be noted that fasted animals have a higher stomach pH than normal and often in the same range as animals administered an H_2 blocker or proton-pump inhibitor.[4]

Divalent cations (Mg^{2+} and Ca^{2+}) in antacid drugs will bind to tetracyclines and prevent absorption from the gastrointestinal tract. Divalent and trivalent cations, especially Fe^{3+}, Ca^{2+}, Mg^{2+}, and Al^{3+}, can bind to and prevent absorption of fluoroquinolone antibiotics. Gastrointestinal protectants, such as sucralfate (which contains aluminum) and antacids (containing Mg^{2+} and/or Al^{3+}), will decrease absorption of fluoroquinolone antibiotics (e.g., enrofloxacin and ciprofloxacin) and tetracyclines.

Alteration in absorption as a desirable drug interaction is best demonstrated by the practice of adding epinephrine to local anesthetic solutions. Epinephrine prolongs the duration of local anesthetic action by reducing blood flow (secondary to epinephrine-induced vasoconstriction) and thus delaying systemic absorption of the local anesthetic. The second gas effect represents enhanced absorption from the alveoli of volatile anesthetics administered with nitrous oxide. Rapid absorption of nitrous oxide concentrates the other anesthetic in the alveoli, thereby enhancing absorption of the volatile agent.

EMLA cream (lidocaine 2.5% and prilocaine 2.5%) is an interesting example of a physical change that occurs when two drugs are mixed with a resulting favorable impact on absorption. The cream contains equal parts of the local anesthetics lidocaine and prilocaine that combine to produce a eutectic mixture. Neither local anesthetic is effective when applied to unbroken skin, but the eutectic mixture can penetrate skin.

Interactions Involving the Multidrug Resistance Efflux Pump

The multidrug resistance (MDR) efflux pump, also known as P glycoprotein (P-gp), is coded for by the MDR gene(s) and can be involved in several important drug interactions.[5,6] The P-gp is located in membranes and is responsible for pumping drug compounds across a membrane and out of the cell. P-gp can be protective (e.g., removing ivermectin from the central nervous system [CNS]) or lead to decreased drug effectiveness (e.g., chemotherapeutic drug resistance in cancer cells).

Table 16.3. Substrates and inhibitors of P glycoprotein that may affect anesthetic drug actions.

P-glycoprotein substrates
Opiates (loperamide, morphine)
Digoxin
Quinidine
Ivermectin
Verapamil
Antihistamines
Cyclosporine
Doxorubicin
Diltiazem
P-glycoprotein inhibitors
Ketoconazole
Erythromycin
Cyclosporine
Grapefruit juice
Fluoxetine
St. John's wort
Paroxetine
Verapamil
Quinidine

P-gp is responsible for pharmacokinetic changes because it is located in the intestine, biliary tract, liver, placenta, and blood-brain barrier (BBB). The best-known pharmacokinetic effects are (a) the pumping of drugs into the intestinal lumen, thereby decreasing systemic absorption and increasing drug clearance from the body; and (b) the P-gp, located in the BBB, that affects the CNS uptake and elimination of certain compounds. P-gp is an integral part of the BBB and participates in neuroprotection of the brain by regulating drug entry.[7] Because P-gp is located also in the gastrointestinal tract, placenta, and kidneys, among other organs, inhibition of P-gp by ketoconazole, cyclosporine, calcium-channel blockers (diltiazem), and antiarrhythmics (lidocaine and quinidine) may have a variety of consequences.[8] In some cases, drugs such as cyclosporine can be both a substrate and an inhibitor of P-gp (see Table 16.3). Rifampin and corticosteroids can act as inducers (they increase the activity) of P-gp.

Ketoconazole can inhibit P-gp in the intestine and increase oral absorption of other drugs, including cyclosporine. Concurrent administration of ketoconazole has been known to decrease dose requirements for cyclosporine by one-third. Cyclosporine may inhibit P-gp in the BBB and increase the CNS concentration of some drugs, such as those within the avermectin group. There are anecdotal reports of dogs developing clinical signs consistent with avermectin toxicosis after having received both cyclosporine and avermectin-like drugs.

There have been no reports of anesthetic drugs affecting P-gp

interactions. However, because inhibition of P-gp influences the BBB, clinicians should be aware of the potential for exaggerated CNS anesthetic effects when an animal has received a P-gp inhibitor. Some opiates are substrates for P-gp in the BBB, although this is less established in the veterinary species of interest. However, an exaggerated CNS response (e.g. sedation or respiratory depression) might result from administration of an opiate and an inhibitor of P-gp.

Interactions That Affect Hepatic Drug Clearance

Changes in hepatic clearance are usually a consequence of changes in hepatic blood flow, although other actions (e.g., effects on microsomal enzyme activity) can result from one drug influencing the metabolism of another. Blood-flow changes are most noted when the liver extracts a high fraction of drug from the blood presented to it. Drugs most affected are those known as *high clearance drugs*. Lidocaine, meperidine, and opiates (e.g., morphine, oxymorphone, and hydromorphone) are examples of analgesic drugs that have high hepatic extractions. Inhalational anesthetics, such as halothane, can reduce liver blood flow.

Many drugs must be biotransformed by microsomal enzymes in the liver to make them more water soluble for excretion into the bile or urine. Drugs metabolized by the liver can undergo phase I or phase II reactions. Phase I reactions metabolize the drug to a more water-soluble compound. These reactions often are oxidative, but other reactions, such as reduction, also occur. Phase II reactions occur via conjugation. The best-known example is that of conjugation with glucuronic acid, but other conjugation reactions with amino acids, acetyl groups, and sulfates are possible. Drugs that affect the liver's biotransformation enzymes can cause clinically significant drug interactions.

Cytochrome P-450 Family of Enzymes

The cytochrome P-450 (CYP) enzymes have been studied in great detail in humans, and a family of these enzymes have been identified that participate in the metabolism of drugs. The CYP-3A4 enzymes are probably the most important of this group because they have the largest number of substrates (about half the drugs currently prescribed clinically). However, CYP-2D6, CYP-1A2, CYP-2C9, and CYP-2C19 also can be important for drug metabolism. The presence and significance of these enzymes in domestic animals have not been documented nearly as well. Animals also have these families of enzymes, although the activity of each group is not the same.[9] Of the species compared (dogs, cats, and horses), none of them resemble the same pattern as humans.

Microsomal Enzyme Induction

Drugs and compounds can increase hepatic microsomal (cytochrome P-450) enzyme activity. Since some of these enzymes are found in intestine as well as the liver, enzyme induction can cause faster biotransformation, resulting in lower oral bioavailability and/or faster plasma clearance. The enzymes most commonly affected by induction are the mixed-function oxidases (phase I oxidation reactions). Enzyme induction causes an increase in activity as well as an increase in enzyme content within the endoplasmic reticulum.

Table 16.4. Cytochrome P-450 inducers.

Chlorinated hydrocarbons
Diazepam (Valium)
Diphenhydramine
Estrogens
Griseofulvin
Hyperthyroidism
Pentobarbital
Phenobarbital
Phenylbutazone
Phenytoin (Dilantin)
Progestogens
Rifampin

Some drugs are specific in their inducing ability. For example, a drug may induce one group of enzymes without affecting another. The drugs that are most affected by enzyme inhibition are those that undergo metabolism by hepatic enzymes and are lipid soluble. Affected drugs usually have a low hepatic extraction ratio. The time for induction to occur is usually 2 to 3 weeks after initial exposure, and it may take weeks to months for enzyme activity to return to normal after the inducing drug is withdrawn. Potential enzyme inducers are listed in Table 16.4.

Microsomal Enzyme Inhibition

Hepatic microsomal enzymes responsible for drug biotransformation may be inhibited by certain drugs and compounds. Inhibition usually occurs via competitive binding to form an inactive drug-enzyme complex. Inhibition almost immediately follows drug exposure. In many cases, a metabolite of the drug is responsible for enzyme inhibition. Noncompetitive inhibition is also possible when a drug is not a substrate for the enzyme, but alters its function in some manner.

Examples of drugs that inhibit microsomal enzymes are listed in Table 16.5. Some of the microsomal enzyme inhibition–mediated drug interactions that have been described in veterinary patients include cimetidine inhibition of theophylline metabolism, chloramphenicol inhibition of barbiturate metabolism, ketoconazole inhibition (by as much as 85%) of cyclosporine metabolism, ketoconazole inhibition of prednisolone metabolism, and ethanol or 4-methyl-pyrazole inhibition of alcohol dehydrogenase, which converts ethylene glycol to toxic metabolites (this effect is used to treat toxicosis). One well-known example of enzyme inhibition that has clinical consequences in people is the inhibition of acetaminophen metabolism following alcohol consumption. This inhibition can lead to accumulation of hepatotoxic metabolites that form via other pathways.

During the anesthetic period, the nature of enzyme inhibition is important to patients that receive drugs requiring hepatic biotransformation to terminate their effect. For example, if there is concurrent enzyme inhibition, the risks of anesthesia may be altered. Veterinarians should be cognizant of the potential prob-

Table 16.5. Cytochrome P-450 enzyme inhibitors.

Chloramphenicol
Cimetidine
Cyclophosphamide
Erythromycin
Interferon (vaccines)
Ketoconazole
Morphine
Organophosphates
Quinidine
Tetracycline
Verapamil

lems that may occur if they administer or prescribe a drug that has enzyme-inhibiting effects when also administering anesthetics. Fortunately, clearance of inhalant anesthetics and drugs cleared via renal excretion are usually not directly affected.

Interactions That Involve Drug Protein Binding

Alterations in protein binding occur but are rarely of clinical significance. Drugs exist in unbound (free) and bound forms in the blood. The free form is generally immediately available to exert pharmacological effects, but the bound form is not. Drug displaced from protein distributes rapidly into tissue and is available for biotransformation and excretion. The net effect of a displacement interaction is usually small, transient, and frequently unrecognized.

Some drugs are known to compete for binding sites on albumin and other proteins, altering the unbound fraction of a second drug. For most drugs, the amount of protein (and protein-binding sites) in the plasma greatly exceeds the number of drug molecules in the plasma, and binding is rarely saturated. Interactions that involve displacement of protein-bound drugs are therefore rare unless there is severe hypoproteinemia or the drug is so highly protein bound that it occupies most of the binding sites. Only drugs that are highly protein bound (usually defined as approximately 80% to 85% or greater bound), exhibit high clearance rates, and have a low therapeutic index are likely to be involved in protein-binding interactions of clinical significance. Two recent reviews illustrate that drug protein-binding interactions have minimal consequences in most situations of multiple-drug administration.[10,11] Although changes in plasma protein binding may have an important influence on individual pharmacokinetic parameters, changes in plasma protein binding will usually not greatly influence the clinical exposure of a patient to a drug.[11]

Pharmacodynamic Drug Interactions

These interactions include drug interactions at the same receptor sites or at different sites. In anesthesiology, pharmacodynamic interactions are frequently used clinically, and pharmacokinetic interactions much less often. Pharmacodynamic interactions of marked clinical significance can affect the cardiovascular, respiratory, and central nervous systems, as well as the neuromuscular junction and metabolism.

It is also common to give drugs that interact to produce complementary effects, to reduce side effects, or to terminate an effect of a drug. Some examples of these types of desirable interaction are (a) the systemic administration of an opioid to reduce the concentration of inhalation agent required to prevent patient response to a noxious stimulus, (b) atropine administration to reduce or prevent the muscarinic effects (e.g., salivation or bradycardia) of anticholinesterases (e.g., neostigmine) when used to counter the action of nondepolarizing neuromuscular blocking agents, (c) administration of an opiate partial agonist or agonist/antagonist (e.g., buprenorphine or butorphanol) to blunt the effects of a pure opiate agonist, and (d) the use of anticholinesterase compounds to antagonize the action of nondepolarizing neuromuscular blocking agents by blocking the hydrolysis of endogenous acetylcholine.

Interactions are possible with the concomitant use of stimulants and sedatives and/or anesthetics. Among the commonly encountered stimulants are the sympathetic amines (phenylpropanolamine, ephedrine, and pseudoephedrine) and other drugs that exert their effects through dopaminergic mechanisms. Selegiline is a monoamine oxidase B (MAO-B) inhibitor at low doses (MAO-A *and* B inhibitor at high doses) that has been administered to animals for treatment of canine hyperadrenocorticism and cognitive disorder. In addition to its indirect dopaminergic effects, it is metabolized to *l*-amphetamine and *l*-methamphetamine in animals.[12] The amphetamine *l*-isomer is not as pharmacologically active as the d-isomer (e.g., dextroamphetamine), but high doses of selegiline (3 mg/kg) have caused excitement and restlessness in dogs, presumably via amphetamine effects.[13] MAO-B inhibitors are generally less likely than MAO-A inhibitors to cause severe anesthetic drug interactions, but they still may exacerbate CNS toxicity of other excitatory drugs. Of the interactions reported in humans, coadministration of selegiline with selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine and paroxetine has caused CNS reactions and the potential for the *serotonin syndrome* characterized by muscle rigidity, tremors, restlessness, and altered mental status.[14] Other signs of serotonin syndrome may not involve the CNS and include dysfunction of the respiratory and cardiovascular system and hyperthermia. Such reactions associated with selegiline have not yet been documented in veterinary medicine. There does not appear to be a larger potential for severe interactions between selegiline and sympathomimetic amines (e.g., phenylpropanolamine and ephedrine) because selegiline does not inhibit MAO-A at clinically relevant doses. Nevertheless, when prescribing selegiline with sympathetic amines or MAO inhibitors such as amitraz (Mitaban), one should advise owners of the potential interaction and clinical manifestations. There have been reported serotonin-mediated reactions in humans when selegiline has been administered with the opiate meperidine, but documentation of the clinical occurrence of these reactions in veterinary patients is lacking. Because this reaction is caused by a metabolite of meperidine, other opiates are considered less likely to cause this reaction.

Nonsteroidal Anti-inflammatory Drug Interactions

NSAIDs such as carprofen, meloxicam, etodolac, tepoxalin, firocoxib, and deracoxib are used to treat pain and inflammation. In large animals, flunixin meglumine, ketoprofen, and phenylbutazone are often used. The mechanism of action of an NSAID is primarily via inhibition of cyclooxygenase (prostaglandin endoperoxide synthase) isoenzymes. Prostaglandin synthase 1 (cyclooxygenase 1 [COX-1]) is primarily a constitutive enzyme expressed in tissues. Prostaglandins, prostacyclin, and thromboxane synthesized by this enzyme are in part responsible for normal physiological functions. Prostaglandin synthase 2 (COX-2) is synthesized by macrophages and inflammatory cells and is inducible after stimulation by cytokines and other mediators of inflammation. Contrary to initial beliefs, though, COX-2 may be constitutive in some tissues. This has recently raised concerns about the ability of COX-2–selective drugs to spare physiological prostaglandin production in some tissues and their safety in certain situations. NSAID development in the 1990s and early 2000s focused on selective inhibition of COX-2, with the goal of producing analgesia and suppressing inflammation without inhibiting physiologically important prostanoids. However, more profound inhibition of COX-2 may not always be beneficial, because COX-2 products appear to be beneficial in some tissues and disease states. For example, COX-2 products have biological importance in angiogenesis, renal function, regulation of bone resorption, reproductive function, and healing of gastroduodenal ulcers.[15] Prolonged COX-2 inhibition has also been associated with a higher risk of cardiovascular complications (stroke and myocardial ischemia) in humans, because it unbalances the production of endogenous prostanoids by preserving COX-1 function, which may promote platelet aggregation and vasoconstriction.[16] Consequently, COX-2–selective drugs (valdecoxib, celecoxib, and rofecoxib) used in humans have received increased scrutiny by the medical community in recent years, and two have been voluntarily withdrawn from the U.S. market. Unbalanced COX-2 enzyme inhibition appears to increase risk of adverse events in some patient populations, and, because of this concern, future directions of NSAID development may need to be reexamined.[17]

The action of NSAIDs in animals raises questions about the potential for adverse interactions. Some theoretical interactions are worthy of consideration. NSAIDs might interfere with prostaglandin-mediated vasodilation that may be necessary for tissue perfusion during anesthesia. Prostaglandins may be important for the action of cardiovascular drugs such as angiotensin-converting enzyme (ACE) inhibitors (e.g., captopril, enalapril, benazepril, and lisinopril). Prostaglandins may also mediate some of the pharmacological effects of diuretics such as furosemide. Furosemide and ACE inhibitors stimulate prostaglandin synthesis to increase renal blood flow and produce vasodilation and natriuresis. Consequently, NSAID inhibition of prostaglandin synthesis may decrease the action of ACE inhibitors and furosemide.[18] NSAIDs may decrease the antihypertensive effect of ACE inhibitors. For aspirin, this action appears to be dose related.[19,20] This warning is listed in the United States Pharmacopeia-Drug Information (*USP-DI* 2004) and has been reported in people, but its clinical significance has been debated.[19,20] The administration of an ACE inhibitor with the NSAID tepoxalin is not associated with adverse renal effects.

Because NSAIDs are generally highly protein bound, interactions with other highly protein-bound drugs are possible, but as discussed previously, unlikely.[21] Manufacturers' labels on veterinary NSAIDs have warned veterinarians that coadministration of NSAIDs (many of which are over 90% protein bound) could increase free fractions of coadministered drugs such as phenobarbital and produce adverse effects. However, despite the frequently cited potential protein-binding interactions between NSAIDs and other drugs, there are very few documented cases where this has resulted in an adverse outcome, and the clinical significance of protein-binding interactions has likely been exaggerated.

One last possible NSAID interaction worthy of consideration is the combination of an NSAID with a fluoroquinolone antibiotic, causing CNS toxicity in people.[22] This type of interaction with currently available fluoroquinolones used in animals (enrofloxacin, marbofloxacin, orbifloxacin, and difloxacin) has not been reported, however.

Renal Interactions with NSAIDs and Anesthetics

In the kidney, prostaglandins play an important role in modulating the tone of blood vessels and regulating salt and water balance, especially during periods of renal stress. Renal injury caused by NSAID use has been described in people and horses. Reported cases of toxicity occur when high doses have been used or when there are other complicating factors (e.g., coadministration of methoxyflurane).[23] Renal injury probably occurs as a result of inhibition of renal prostaglandin synthesis and altered renal autoregulation during periods of renal stress or insult.[24] In animals that have decreased renal perfusion caused by dehydration, anesthesia, shock, or preexisting renal disease, this interference with prostaglandin synthesis can lead to renal ischemia.[25] Many cases of renal damage caused by anesthetic-NSAID interactions might be subclinical because of the reserve capacity of the kidney. Widespread nephron damage would be required (approximately 75%) before currently used laboratory benchmarks for renal function (blood urea nitrogen and creatinine) would significantly change.

Additional information is needed with regard to the safety of the effect of currently available COX-2 specific inhibitors on the kidney. Prostaglandins that play an important role in salt and water regulation and renal hemodynamics are synthesized by COX-2 enzymes.[26] Constitutive COX-2 is found in various sections of the kidney, and administration of drugs that selectively inhibit COX-2 may adversely affect overall renal function in some situations. Of the currently available NSAIDs, carprofen's effect on renal function has been the most extensively studied. Because carprofen is registered for use in perioperative situations in an injectable formulation, safety studies have been conducted to determine whether there is any evidence of an increased occurrence of renal toxicity with its use in the perioperative period, particularly during anesthesia. In one study, carprofen, ketorolac,

and ketoprofen were examined in healthy dogs undergoing surgery, but without intravenous fluid administration. There were minor increases in renal tubular epithelial cells in urine sediment, but, overall, carprofen had no adverse effect on renal function.[27] In contrast, some ketorolac-treated and ketoprofen-treated dogs had transient azotemia. In two similar studies, carprofen administered to anesthetized healthy dogs had no adverse effect on renal function.[28,29] The renal effects of deracoxib administration have been reported by the manufacturer. At high doses, there is a dose-dependent effect on renal tubules. At up to 10 mg/kg for 6 months, it is well tolerated in most dogs, but there is a potential for a dose-dependent renal tubular degeneration/regeneration at doses of 6 mg/kg or higher with long-term usage. It should be remembered that the clinically approved dose of deracoxib for long-term treatment is only 1 to 2 mg/kg per day. Tepoxalin at a dose of 10 mg/kg (currently registered dose) has been evaluated in anesthetized, healthy, normotensive, normovolemic dogs. It has also been evaluated in dogs receiving ACE inhibitors. In both studies adverse effects on renal function were not detected.[30] Despite the apparent safety of perioperative NSAID administration documented by these studies, intravenous fluid administration and vigilant monitoring during prolonged anesthesia are clearly warranted to reduce the risk of either subclinical damage or overt renal complications.

Gastrointestinal Interactions with NSAIDs

In the gastrointestinal (GI) tract, prostaglandins play an important role in maintaining a healthy mucosa and cytoprotection and in regulation of acid and mucous secretion. Administration of NSAIDs typically alters GI physiology and may increase the risk of GI injury. GI effects range from mild gastritis and vomiting to severe GI ulceration and bleeding and even death. These effects have been documented for the past 3 decades in the veterinary literature. GI toxicity is caused by two main mechanisms: direct irritation of the GI mucosa and prostaglandin inhibition.[15] Direct irritation occurs because an acidic NSAID can become more lipophilic in the acid milieu of the stomach and cause injury by enhancing diffusion into the gastric mucosa. Secondly, prostaglandins have a cytoprotective effect on the GI mucosa, and inhibition of these compounds causes decreased cytoprotection, diminished blood flow, decreased synthesis of protective mucus, and inhibition of mucosal cell turnover and repair. In healthy dogs, COX-1 is the primary COX enzyme that produces prostaglandins (primarily prostaglandin E_2).[31] An examination of published reports of GI toxicity from the administration of an NSAID in animals indicates that the most serious problems are caused from doses that are higher than recommended, but toxicity has been observed also from relatively mild doses in susceptible individuals. Some factors may increase the risk of GI toxicosis, including concurrent corticosteroids and other GI diseases. Corticosteroids in particular are known to increase the risk of GI toxicity caused by NSAIDs.[25,32,33] Even meloxicam, which is relatively COX-1 sparing in the canine GI tract, has been associated with increased risk of GI mucosal injury when administered with a corticosteroid.[32] Other events that stress the gastric mucosa, such as decreased perfusion caused by shock, anesthesia, or dehydration, increase risk of damage.[34] Clinical observations suggest that, although gastric ulceration can be significant with the administration of NSAIDs in some patients, catastrophic perforating ulceration can occur also in the proximal duodenum, especially in dogs.[34] Further investigation into the actions of NSAIDs on the duodenal mucosa are needed.

Opioid Interactions

Opioids are often administered with general anesthetics to provide analgesia and enhance their anesthetic action.[35] They are also commonly coadministered with sedative and tranquilizing agents to enhance sedation and analgesia. Clinical and research observations strongly support the concurrent use of opioids and anesthetic and anesthetic-adjunctive drugs; however, there is some evidence that this practice may actually decrease the magnitude and duration of opioid analgesic efficacy in some situations.[36,37]

As discussed previously in this chapter, there is a specific interaction between MAO inhibitors and meperidine described in people. The use of these drugs together has caused an unpredictable and sometimes fatal reaction, which includes excitation, sweating, rigidity, coma, and seizures. This reaction seems to be rather specific for meperidine because it is caused by one of its metabolites. If animals receive MAO inhibitors and another opiate, it is suggested first to administer a test dose of the opiate and observe the animal carefully. If there is no adverse reaction, subsequent doses can probably be administered safely. Although nonspecific MAO inhibitors are rarely used for treatment of depression in animals, other drugs with MAO-inhibiting properties are used in animals. For example, selegiline, a specific MAO type-B inhibitor, is used in dogs to treat canine hyperadrenocorticism and cognitive disorder. Amitraz, which is also an MAO inhibitor, is found in pet collars and dips to prevent and treat mite infestations. Although no adverse reactions in animals have been documented with amitraz or selegiline and opioid analgesic drugs, one should administer these drug combinations cautiously, at least for the first dose.

In recent years, tramadol has become increasingly popular as an oral analgesic medication for managing chronic pain, but its analgesic efficacy may be partially attributed to serotonin reuptake inhibition. The potential to induce CNS excitation and even seizures when tramadol is coadministered with known CNS stimulants, such as the tricyclic antidepressants, the SSRIs such as fluoxetine, and mood-altering herbal medication such as St. John's wort, should be appreciated by veterinarians. These combinations should be administered to animals with caution.

Interactions Among Opioid Drugs

In recent years, there has been some confusion as to whether the administration of opioid agonists with opioid agonist/antagonists will produce an interaction that diminishes the analgesic effect of the combination. In theory, drugs such as butorphanol and pentazocine have antagonistic properties on the μ receptor, so they should partially reverse some effects of μ-receptor agonists when administered together. The clinical significance of this antagonism has been debated, however. In dogs, for example, although butor-

phanol reverses some respiratory depression and sedation produced by pure agonists, the analgesic efficacy may be preserved.[38] Similarly, in dogs given butorphanol for postoperative pain associated with orthopedic surgery, there was no diminished efficacy with subsequent administration of oxymorphone.[39] However, in another study, dogs that had not responded to butorphanol after shoulder arthrotomy responded to subsequent administration of oxymorphone, but the oxymorphone dose required to produce an adequate effect was higher than what would be required if oxymorphone was used alone, suggesting that some antagonism of analgesia may have been present.[40] When butorphanol and oxymorphone have been administered together to cats, a greater efficacy has been reported than when either drug was used alone.[41,42] These clinical observations taken together suggest that antagonism may indeed occur in some clinical patients, but in other patients coadministration actually results in a synergistic analgesic effect. These divergent results from one individual to the next may be due to a variety of factors, including (a) differences in the pain syndrome being treated, (b) species variation in response to opioids, (c) dosage ratios of the specific opioids being administered and (d) variation in opioid efficacy between genders. For example, when looking at the first of these factors in humans, whether antagonism or synergism occurs with the coadministration of butorphanol and a pure opioid agonist appears to depend on whether somatic pain versus visceral pain is present. These types of studies have not been performed to date in common pet species.

Nomenclature

Commonly used terms to describe drug interactions are addition, antagonism, synergism, and potentiation.

In purely pharmacological terms that have underlying theoretical implications, *addition* refers to simple additivity of fractional doses of two or more drugs, the fraction being expressed relative to the dose of each drug required to produce the same magnitude of response; that is, response to X amount of drug A = response to Y amount of drug B = response to $1/2X_A + 1/2Y_B$, $1/4X_A + 3/4Y_B$, and so on. Additivity is strong support for the assumption that drug A and drug B act via the same mechanism (e.g., on the same receptors). Confirmatory data are provided by in vitro receptor-binding assays. Minimum alveolar concentration (MAC) fractions for inhalational anesthetics are additive.

Synergism refers to the situation where the response to fractional doses as described previously is greater than the response to the sum of the fractional doses (e.g., $1/2X_A + 1/2Y_B$ produces more than the response to X_A or Y_B).

Potentiation refers to the enhancement of action of one drug by a second drug that has no detectable action of its own.

Antagonism refers to the opposing action of one drug toward another. Antagonism may be competitive or noncompetitive. In competitive antagonism, the agonist and antagonist compete for the same receptor site. Noncompetitive antagonism occurs when the agonist and antagonist act via different receptors.

Experimental approaches to determine additivity etc. have included dose-response analysis (Fig. 16.1) and isobolographic analysis (Fig. 16.2).

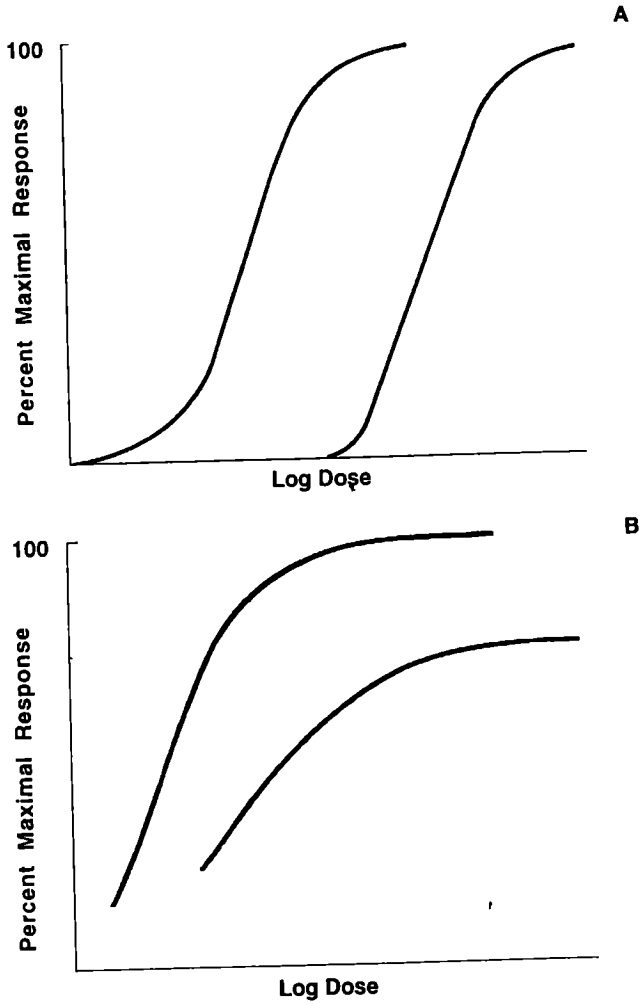

Fig. 16.1. Dose-response curve illustrating competitive antagonism **(A)** and noncompetitive antagonism **(B)**. In **A**, the dose-response curve is shifted to the right in the presence of an antagonist, but the shape of the curve is not changed. In **B**, the dose-response curve is shifted to the right in the presence of an antagonist, and the maximal response to the agonist is reduced.

Anesthetic Drug Interactions

The way anesthetic drugs are usually used raises special considerations with regard to drug interactions. For example, (a) drugs that act rapidly are usually used; (b) responses to administered drugs are measured, often very precisely; (c) drug antagonism is often relied upon; and (d) doses or concentrations of drugs are usually titrated to effect. Minor increases or decreases in responses are usually of little consequence and are dealt with routinely.

Commonly Used Anesthetic Drug Interactions

Two or more different kinds of injectable neuroactive agents are frequently used to induce anesthesia with the goal of achieving the highest quality of anesthesia with minimal side effects. The agents frequently have complementary effects on the brain, but

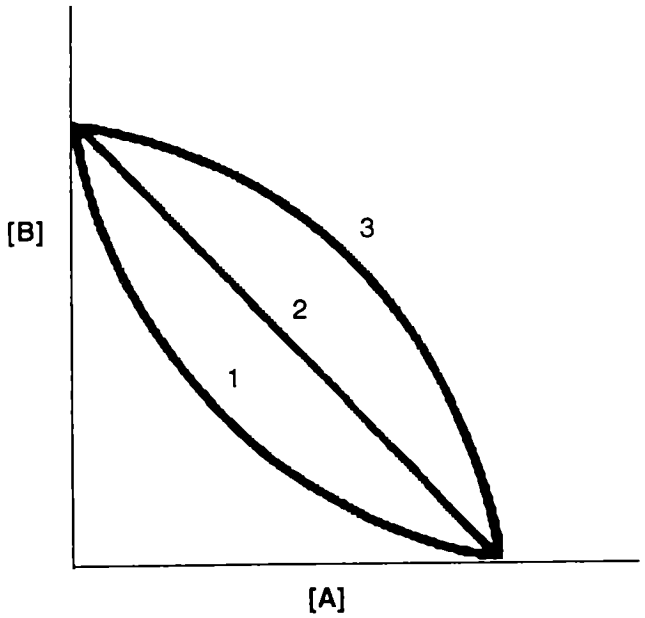

Fig. 16.2. Isobolograms for the response to mixtures of drugs. The sets of concentrations of drugs A and B, which as mixture produce an effect (e.g., 50% of a maximal response), are plotted. Strict additivity, which means [A] + [B] = a constant, results in a curve of slope –1 (2). If the curve is concave (3), some antagonism is present; if the curve is convex (1), synergism is present.

one agent may also antagonize an undesirable effect of the other. An example of such a combination is tiletamine and zolazepam (Telazol [tiletamine hydrochloride 50 mg/mL and zolazepam hydrochloride 50 mg/mL], an arylcycloalkylamine and a benzodiazepine).

Tiletamine produces sedation, immobility, amnesia, and marked analgesia, but may also produce muscle rigidity and grand mal seizures. Zolazepam produces sedation, reduces anxiety, and prevents muscle rigidity and seizures. Another arylcycloalkylamine-benzodiazepine combination commonly used is ketamine with either midazolam or diazepam. Ketamine is also frequently used in combination with xylazine, a potent sedative with central muscle relaxant and analgesic properties.

Acepromazine is often used as a preanesthetic agent. In addition to calming patients, acepromazine reduces the dose of anesthetic required to produce anesthesia and reduces the sensitivity of the myocardium to catecholamines, thereby reducing the risk of ventricular arrhythmias. On the other hand, acepromazine possesses α_1-adrenergic blocking activity such that the cardiovascular depressant effects of general anesthetics may interact to produce further vasodilation and hypotension.

Volatile anesthetics may potentiate cardiovascular depression in patients. Because nitrous oxide produces relatively less cardiovascular depression than does an equivalent dose of a volatile agent (it may even stimulate), at any given depth of anesthesia, the amount of cardiovascular depression is less with nitrous oxide plus a volatile agent than with the volatile agent alone at the same depth of anesthesia achieved.

To manage pain associated with surgical procedures better, it is becoming increasingly common to combine the use of regionally administered analgesics and light general anesthesia. An example of such an approach is to administer a local anesthetic alone or in combination with an opioid or an α_2-adrenergic agonist into the epidural space before or during general anesthesia. Benefits sought with this approach are reduction in the amount of general anesthetic required and the provision of preemptive analgesia. Reducing the amount of general anesthetic required reduces the magnitude of systemic side effects of the general anesthetic.

References

1. Papich MG. Incompatible critical care drug combinations. In: Bonagura JD, ed. Current Veterinary Therapy XII, 1995:194–198.
2. Trissel LA. Handbook on Injectable Drugs, 11th ed. Bethesda, MD: American Society of Health-System Pharmacists, 2001.
3. US Pharmacopeia. USP-DI, vol 1: Drug Information for the Health Care Professional. Rockville, MD: US Pharmacopeia, 2004.
4. Bersenas AME, Mathews KA, Allen DG, Conlon PD. Effects of ranitidine, famotidine, pantoprazole, and omeprazole on intragastric pH in dogs. Am J Vet Res 66:425–431, 2005.
5. Lin JH. Drug-drug interaction mediated by inhibition and induction of P-glycoprotein. Adv Drug Deliv Rev 55:53–81, 2003.
6. Mealey KL. Therapeutic implications of the MDR-1 gene. Vet Pharmacol Ther 27:257–264, 2004.
7. Lechardeur D, Phung-Ba V, Wils P, Scherman D. Detection of the multidrug resistance of P-glycoprotein in healthy tissues: The example of the blood-brain barrier. Ann Biol Clin (Paris) 54:31–36, 1996.
8. Preiss R. P-glycoprotein and related transporters. Int J Clin Pharmacol Ther 36:3–8, 1998.
9. Chauret N, Gauthier A, Martin J, Nicoll-Griffith DA. In vitro comparison of cytochrome P450-mediated metabolic activities in human, dog, cat, and horse. Drug Metab Dispos 25:1130–1136, 1997.
10. Toutain PL, Bousquet-Melou A. Free drug fraction vs free drug concentration: A matter of frequent confusion. J Vet Pharmacol Ther 25:460–463, 2002.
11. Benet LZ, Hoener B. Changes in plasma protein binding have little clinical relevance. Clin Pharmacol Ther 71:115–121, 2002.
12. Milgram NW, Ivy GO, Murphy MP, et al. Effects of chronic oral administration of L-deprenyl in the dog. Pharmacol Biochem Behav 51:421–428, 1995.
13. Head E, Milgram NW. Changes in spontaneous behavior in the dog following oral administration of L-deprenyl. Pharmacol Biochem Behav 43:749–757, 1992.
14. Mahmood I. Clinical pharmacokinetics and pharmacodynamics of selegiline. Clin Pharmacokinet 33:91–102, 1997.
15. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. N Engl J Med 340:1888–1899, 1999.
16. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. J Am Med Assoc 286:954–959, 2001.
17. Topol EJ. Failing the public health: Rofecoxib, Merck and the FDA. N Engl J Med 351:1707–1709, 2004.
18. Wilson TW. Renal prostaglandin synthesis and angiotensin-converting enzyme inhibition. J Cardiovasc Pharmacol 19(Suppl 6):S39–S44, 1992.
19. Nawarskas JJ, Spinler SA. Does aspirin interfere with the therapeutic efficacy of angiotensin-converting enzyme inhibitors in hyperten-