CHAPTER

4

Guidelines and Precautions for Drug Therapy in Cats

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OUTLINE

Drug therapy in feline patients has many potential roadblocks: differences in drug metabolism between cats and other species, which make dose extrapolations difficult; a paucity of good safety and dose optimization studies in cats; the relative lack of approved drugs with associated efficacy data in cats compared with dogs; the need for reformulation of many drugs designed for larger patients; and the difficulty in administering medications to many cats.

DIFFERENCES IN DRUG METABOLISM IN CATS

Cats have important differences in drug metabolism compared with humans and dogs, two species from which feline dosages are often extrapolated. It is well known that cats are deficient in glucuronidation of some xenobiotics; for example, UDP-glucuronosyltranferase (UGT) activity for acetaminophen is tenfold lower in cats compared with dogs and humans.[20] This is due to a nonfunctional feline pseudogene for UGT1A6,[21] the UGT isoform that metabolizes acetaminophen in humans. This same enzyme glucuronidates morphine and serotonin[48] and contributes to the metabolism of silybin (in milk thistle).[55] Glucuronidation is therefore deficient for many drugs in cats (Table 4-1). However, cats are able to normally glucuronidate endogenous compounds such as thyroxine[41] and bilirubin.[87]

Cats are also deficient in the enzyme thiopurine methyltransferase, which metabolizes thiopurine drugs such as azathioprine. The activity of this enzyme, which can be measured in red blood cells, is 80% to 85% lower in cats than in dogs.[29,79,100] This may explain why cats treated with azathioprine are especially sensitive to myelosuppression,[3] which is a dose-dependent side effect of this drug. Further individual variability in thiopurine methyltransferase among cats (almost tenfold) can be attributed to genetic polymorphisms in the feline gene, such that there is overlap between some "high-activity" cats and some "low-activity" dogs.[45,79] However, a relationship between polymorphisms in thiopurine methyltransferase and azathioprine response has not yet been established in either cats or dogs.

DOSAGE ADJUSTMENTS FOR RENAL INSUFFICIENCY

Renal insufficiency leads to decreased filtration of renally eliminated drugs and their active metabolites, as well as impaired tubular secretion of some drugs, including famotidine, ranitidine, trimethoprim, and digoxin.[86] These drugs are ionized at physiologic pH and in humans

TABLE 4-1 Xenobiotic Glucuronidation Capacity in the Cat

Compounds	UGT Enzyme Responsible in Humans	Glucuronidation in Cats	Clinical Consequences and Dosing in Cats
Acetaminophen	UGT1A6 (pseudogene in cats)[21]	Hepatic activities tenfold lower in cats compared with dogs and humans[20]	Acetaminophen toxicity at threefold to fourfold lower doses in cats (≥60 mg/kg) versus dogs (≥200 mg/kg)[81]
Morphine	UGT2B7 and others in humans	No glucuronide metabolites in dogs in vivo[50] Not evaluated in cats	Elimination half-life of morphine in cats (1-1.5 h)[91] is similar to that in dogs (1.2 h)[50]
Chloramphenicol	UGT2B7[15]	Not directly evaluated in cats	Slightly longer elimination half-life in cats (~4-8 h) compared with dogs (1.1-5 h)[71]
Aspirin	Several isoforms (UGT1A6 has high affinity)[49]	Not directly evaluated in cats	Longer elimination half-life in cats (22 h)[69] compared with dogs (5-6 h)[61] Dosed fourfold less frequently in cats versus dogs
Thyroxine	UGT1A1 and others[104]	Thyroxine is glucuronidated in cats[63]	Comparable daily thyroxine dosages in dogs and cats
Carprofen	Glucuronidated in humans[78]	Glucuronidated in dogs[78]	Oral elimination half-life in cats (20 h)[69] prolonged compared with dogs (8 h) (Rimadyl label)
	Isoform not identified	Not directly evaluated in cats	Increased susceptibility to carprofen toxicity in cats (gastrointestinal signs at 8 mg/kg in cats versus 20 mg/kg in dogs)[58]

require active transport in the renal tubules for elimination in the urine. Renal insufficiency is also associated with less obvious effects on drug disposition, such as decreased renal cytochrome P450 and conjugative metabolism of some drugs, impaired binding to albumin of acidic drugs (e.g., furosemide, sulfamethoxazole, and aspirin), and reduced tissue binding of digoxin.[97] All these effects can lead to drug accumulation in renal insufficiency.

Dosage reductions in renal insufficiency are indicated for any drug with a relatively narrow margin of safety that either is primarily eliminated by the kidneys or has an active metabolite that is eliminated by the kidneys (Table 4-2). There is little information in cats to guide dosage adjustments for renal insufficiency. In humans dose adjustments are typically made when glomerular filtration rate (GFR), as measured by creatinine clearance, drops to about 0.7 to 1.2 mL/kg/min, depending on the drug's therapeutic index.[66] Based on the demonstrated relationship between GFR and serum creatinine in cats,[60] this is equivalent to serum creatinine concentrations of approximately 2.5 to 3.5 mg/dL (221 to 309 µmol/L). In the absence of specific data in cats, it is therefore reasonable to consider dosage adjustments for renally cleared drugs when the serum creatinine reaches this range.

For many renally excreted drugs, a crude dose reduction can be made by multiplying the standard dose by a normal serum creatinine concentration (e.g., 1.0 mg/dL) divided by the patient's serum creatinine concentration. This results in less drug given at the same intervals and is based on the finding that serum creatinine is inversely related to GFR in early to moderate renal insufficiency in cats.[60] For example, in a cat with a serum creatinine concentration of 2 mg/dL (twice a typical normal value of 1 mg/dL), cephalothin would be given at 10 mg/kg every 8 hours rather than 20 mg/kg every 8 hours. An alternative approach is to multiply the dosing interval (e.g., every 12 hours) by the patient's serum creatinine concentration, divided by a normal creatinine level. This results in the same individual dose given at less frequent intervals. For example, for the same cat enrofloxacin would be given at a dosage of 5 mg/kg every 48 hours, rather than every 24 hours. Dosage adjustments using this method may be roughly accurate for serum creatinine concentrations up to 4 mg/dL (354 µmol/L), after which the relationship between creatinine concentration and GFR becomes nonlinear in cats.[60] In humans dosages for renally cleared drugs in renal failure are typically 25% to 75% of the standard daily dosage.[66]

Ampicillin and amoxicillin are renally excreted but have wide safety margins, so dose adjustments are probably not clinically necessary. Cephalothin can cause lipid peroxidation and nephrotoxicity in animal models[105] and can be nephrotoxic in combination with aminoglycosides in older human patients.[105] Therefore dosage reductions of this cephalosporin may be indicated in veterinary patients with renal insufficiency.

TABLE 4-2 Drugs Requiring Precaution or Dosage Adjustment in Renal Insufficiency

Drug	Adverse Outcome	Recommendations
Cephalothin	Possible dose-dependent nephrotoxin in humans[105]	Avoid or consider adjusting dosage
Aminoglycosides	Dose-dependent nephrotoxin in cats	Avoid in renal insufficiency If unavoidable, extend dosing interval Maintain hydration Monitor urine for granular casts Minimize duration of treatment
Fluoroquinolones	Dose-dependent retinotoxicity in cats	Use fluoroquinolones with wide safety margin for retinotoxicity (e.g., marbofloxacin or orbifloxacin) Extend dosing interval
Trimethoprim–sulfadiazine	Can precipitate as obstructive sulfadiazine crystals and uroliths in humans[14]	Use more soluble sulfamethoxazole Maintain hydration Avoid urinary acidifiers
Furosemide	Causes dehydration and hypokalemia	Avoid in renal insufficiency unless strong rationale (e.g., overt heart failure) Use careful clinical monitoring
H_2 blockers	Confusion or mania in elderly human patients	Extend dosing interval or reduce individual dose
Metoclopramide	Tremors resulting from dopamine antagonism	Empiric dosage reductions (decrease constant-rate infusion daily dose by ~50%)
Enalapril	May cause renal decompensation[98]	Consider using benazepril, which does not accumulate in moderate renal insufficiency in cats[46]
Nonsteroidal antiinflammatory drugs	Gastric ulceration, renal decompensation	Substitute other analgesics whenever possible

For more expensive beta lactam derivatives, such as meropenem, dose adjustments are recommended in humans when creatinine clearance dips below 0.7 mg/mL/kg; initial prolongation of the dosing interval is recommended.[105]

Aminoglycosides are dose-dependent nephrotoxins and should be avoided, whenever possible, in preexisting renal insufficiency. For patients with renal insufficiency that develop resistant gram-negative infections, other antimicrobials (e.g., fluoroquinolones, cefotetan, meropenem, ticarcillin) should be considered whenever possible. When aminoglycosides are necessary, rehydration and concurrent fluid therapy (intravenous or subcutaneous) are recommended because hypovolemia is a risk factor for aminoglycoside nephrotoxicity in humans.[65] In addition, amikacin should be considered (Figure 4-1) because it is less nephrotoxic than gentamicin in human patients[89] and may be less nephrotoxic in cats as well.[17]

The dosage of aminoglycosides is routinely adjusted for human patients with renal insufficiency. Aminoglycosides are concentration-dependent antimicrobials (i.e., bacterial kill correlates with peak concentrations, not time above the minimum inhibitory concentration), and nephrotoxicity correlates with trough, not peak, drug concentrations.[74] Therefore aminoglycosides should be given at the same dose, but less frequently, in renal insufficiency.[92] For example, for a cat with a serum creatinine concentration of 2 mg/dL, amikacin or gentamicin would be dosed every 48 hours instead of every 24 hours, assuming that no alternative antimicrobials were available.

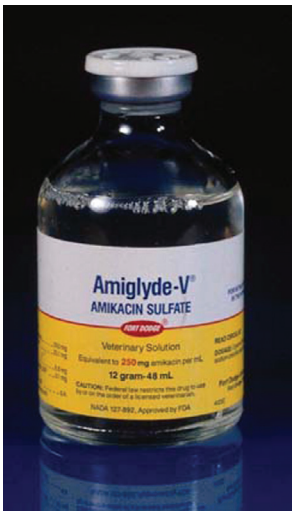

FIGURE 4-1 Aminoglycosides should be avoided whenever possible in cats with renal insufficiency. Administration of subcutaneous or intravenous fluids, avoidance of concurrent nonsteroidal antiinflammatory or furosemide therapy, and monitoring urine sediments daily for granular casts may decrease the risk of dose-dependent nephrotoxicity.

In humans aminoglycoside drug dosages are adjusted to keep trough plasma drug concentrations below 2 µg/mL.[36] Measurement of trough drug concentrations is ideal in patients with underlying renal insufficiency; however, rapid turnaround of serum drug concentrations is necessary for therapeutic drug monitoring to be useful in real-time clinical decision making. One practical monitoring alternative is to examine daily fresh urine sediments for granular casts, which can be seen days before azotemia develops.[82] Granular casts indicate renal proximal tubular damage and if observed suggest that the drug should be discontinued, unless the infection is life threatening. Toxicity in cats is lessened if aminoglycoside therapy can be limited to 5 days or less, whenever possible.[38] Aminoglycosides are contraindicated in combination with furosemide[1] or a nonsteroidal antiinflammatory drug (NSAID),[65] both of which can exacerbate nephrotoxicity.

Fluoroquinolones, like aminoglycosides, are renally cleared. Although they do not cause cartilage toxicity in growing kittens at the label dosage, they do cause dose-dependent retinal toxicity in cats.[101] Therefore dosage adjustments for fluoroquinolones may be important in cats with renal insufficiency, although this has not been directly evaluated. Dosage adjustments may be particularly important for enrofloxacin, which appears to be more retinotoxic in cats (retinal lesions at four times the label dosage) compared with other veterinary fluoroquinolones (orbifloxacin, retinal lesions at 18 times the label dose; marbofloxacin, no retinal lesions at 20 times the label dose).[101] Although the optimal method for dose adjustment is not established in cats, extending the dosing interval may be most appropriate,[23] insofar as fluoroquinolones are also concentration-dependent antimicrobials.

Potentiated sulfonamides should also be used with caution in azotemic patients, owing to decreased renal clearance and decreased protein binding. Dosage reductions for the human generic drug, trimethoprim–sulfamethoxazole, are recommended in human patients.[96] Dose reductions may be even more important for trimethoprim–sulfadiazine (found in Tribrissen) because sulfadiazine is reported to cause hematuria, urolithiasis, and even acute renal failure in humans.[14] This is due to the relative insolubility of sulfadiazine, which can precipitate as drug crystals in the renal tubules, especially at high concentrations or in acid urine.[66] Although comparable studies in feline patients are not available, this author recommends rehydration and discontinuation of urinary acidifiers before the use of trimethoprim–sulfadiazine in cats.

Furosemide is renally cleared and can cause significant dehydration and hypokalemia, which can lead to further renal decompensation. Furosemide should not be used in cats with underlying renal insufficiency unless there is a good rationale (e.g., fulminant congestive heart failure). Cats treated with furosemide should be monitored closely for dehydration, hypokalemia, and worsened azotemia, with routine evaluation of skin turgor, body weight, body condition score, packed cell volume and total protein values, serum potassium levels, and renal indices at each recheck.

Histamine 2 (H_2)–blocker antacids such as cimetidine, ranitidine, and famotidine are cleared by the kidneys, and dosage reductions are recommended for human patients with renal insufficiency.[62] H_2 blockers can also lead to central nervous system disturbances (mania, confusion), particularly in elderly patients, although it is not clear whether decreased GFR is a factor.[11] Therefore the dosage of H_2 blockers may merit reductions in cats with renal insufficiency, especially geriatric cats. Either reductions in the individual dose or extensions of the dosing interval are used in humans. Metoclopramide is also renally cleared. As a dopaminergic antagonist, metoclopramide can lead to tremors in some human patients.[85] Standard constant-rate infusion (CRI) dosages (1 to 2 mg/kg per day) can cause tremor and ataxia in azotemic patients (observed in dogs), and lower doses (e.g., 0.25 to 0.5 mg/kg/day as a CRI) appear anecdotally to be better tolerated.

Angiotensin-converting enzyme (ACE) inhibitors are recommended to reduce proteinuria in cats with renal insufficiency (International Renal Interest Society Guidelines; http://www.iris-kidney.com, accessed February 25, 2010). Benazepril does not depend solely on renal elimination and does not require dose adjustment in moderately azotemic cats.[46] Benazepril therefore may be preferable to enalapril in cats with substantial azotemia. Although ACE inhibitors typically do not cause systemic hypotension at therapeutic dosages in cats, they can adversely affect GFR at high dosages, particularly in a dehydrated patient or with concurrent furosemide administration. It is therefore important to monitor blood urea nitrogen, creatinine, and electrolytes in cats treated with ACE inhibitors: for example, initially after 1 week, after 1 month, and then every 3 months, depending on clinical status.

The use of NSAIDs can adversely affect GFR in patients with hypovolemia or underlying renal disease by blocking the elaboration of renal prostaglandins that otherwise autoregulate renal blood flow.[44] Although meloxicam was generally well tolerated for chronic use in cats with osteoarthritis in one study (at 0.01 to 0.03 mg/kg daily), relatively few cats with chronic renal disease (3 of 46 treated cats) were enrolled.[35] In addition, meloxicam has been implicated in episodes of acute renal failure in cats (Metacam label). Coxibs (cyclooxygenase-2 [COX-2]– selective NSAIDs) have the same potential for adverse renal events as do other NSAIDs.[70] This is because COX-2 is expressed in the kidney and is important for regulating renal blood flow.[39] For analgesia in renal insufficiency, buprenorphine

provides an alternative to NSAIDs, with comparable analgesic efficacy in cats.[88] If an antiinflammatory effect is needed, NSAIDs should be dosed conservatively and cats should be monitored frequently for dehydration, inappetence, evidence of gastrointestinal ulceration, or increases in blood urea nitrogen and creatinine levels.

DRUG THERAPY CONSIDERATIONS IN HEPATIC INSUFFICIENCY

In humans with inflammatory liver disease without failure, hepatic drug metabolism appears to be fairly well conserved. With hepatic dysfunction or cirrhosis, however, drugs that are normally extensively metabolized by the liver are not efficiently cleared. This leads to decreased first-pass clearance and increased oral bioavailability of certain drugs, such as propranolol and benzodiazepines. For these drugs 50% dosage reductions are recommended for human patients with impaired liver function.[26] Other drugs that require dosage reductions (to 25% to 50% of regular dosages) in humans with cirrhosis are listed in Box 4-1. Although cirrhosis is uncommon in cats, significant hepatic dysfunction is common with fulminant hepatic lipidosis or portosystemic shunts. In these patients dosage reductions for the drugs listed in Box 4-1 may be indicated, although we do not have comparable studies in cats.

Some therapies can worsen hepatic encephalopathy and are not recommended for cats at risk. Stored whole blood generates ammonia, which increases with time of storage (Figure 4-2).[51] Although time-course studies of ammonia generation have not been performed for feline whole blood or packed red blood cell units, stored blood should be used with caution in cats with liver failure, such as those with lipidosis or acute hepatotoxicity. Screening blood units for high blood ammonia before transfusion, using an in-house analyzer, is one option, as is using an in-house blood donor to obtain fresh whole blood.

NSAIDs have the potential to exacerbate hepatic encephalopathy, either by causing gastrointestinal bleeding (which is a protein load in the gut) or renal decompensation (which increases blood urea nitrogen that subsequently recycles to ammonia).[28] Furosemide can cause hypokalemia, dehydration, azotemia, and alkalosis, all of which can worsen hepatic encephalopathy.[28] Finally, glucocorticoids, which lead to muscle catabolism,[28] can enhance deamination of proteins and release of ammonia (NH_3). Glucocorticoids also enhance peripheral lipolysis, which could exacerbate hepatic lipidosis, although this has never been directly evaluated in cats. The safest course is to stabilize clinical signs, control hepatic encephalopathy, and provide nutritional support before considering glucocorticoids in cats with any type of liver disease.

BOX 4-1

Drugs that Require Dosage Reductions in Humans with Severe Impairment in Hepatic Function[37]

Buspirone
Butorphanol
Cisapride
Cyclophosphamide
Diazepam
Doxorubicin
Fluconazole
Fluoxetine
Itraconazole
Lidocaine
Loratidine
Metronidazole
Midazolam
Mirtazapine
Omeprazole
Prednisone
Propranolol
Theophylline
Vincristine

THERAPEUTIC CONSIDERATIONS IN NEONATES AND KITTENS

The neonatal period in dogs and cats has been defined as the first 4 weeks of life, with the pediatric period defined as up to 12 weeks of age.[34] Although drug therapy of neonates is common in human medicine, very few pharmacokinetic studies have been performed in newborns and infants. Given that neonatal pharmacology is even less well studied in cats, specific and valid recommendations are difficult to make. However, there

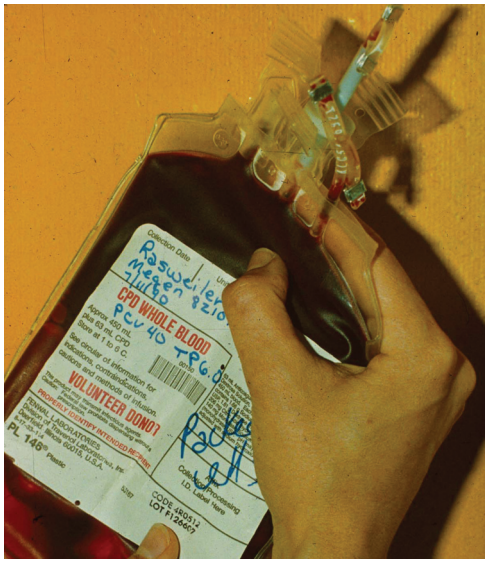

FIGURE 4-2 Whole blood and packed red blood cells can generate ammonia during storage. Transfusion of older units could exacerbate hepatic encephalopathy in cats with hepatic lipidosis or acute hepatotoxicities.

are certain physiologic differences between neonates and adults (based on studies in humans, dogs, rodents, and occasionally in cats) that can help guide rational drug therapy in these tiny and rapidly changing patients.

Oral absorption may be different in newborn kittens compared with adult cats. Immaturity of gastric parietal cells leads to a relatively high gastric pH in neonates; for example, gastric pH is greater than 3.0 through 5 weeks of age in puppies.[54] High gastric pH may decrease the bioavailability of drugs that require an acid environment for absorption, such as ketoconazole, itraconazole, and iron supplements.[54] Fluconazole may be better absorbed in these neonates because its absorption is not affected by gastric pH, at least in humans.[106] Oral absorption of some drugs may be affected by nursing because of the binding of drugs by milk components such as calcium. For example, the bioavailability of enrofloxacin, which is chelated by calcium, is low in nursing kittens, with overall bioavailability less than 35%.[84] The subcutaneous route provides more reliable absorption in nursing kittens, with bioavailability closer to 85% for enrofloxacin.[84]

Hepatic cytochrome P450 activities are low in newborns but approach and even exceed adult levels by 7 weeks of age, as shown in puppies[90]; this is likely an evolutionary response to a wider variety of dietary chemicals encountered at weaning. Immature cytochrome P450 content is associated with delayed hepatic clearance of some drugs in neonates. For example, lidocaine and theophylline have prolonged elimination half-lives in very young puppies (less than 1 to 2 weeks old).[2,40] However, by the time most feline patients are brought to the veterinarian for their first vaccination, hepatic function has greatly matured.

Newborn kittens have decreased GFR rates before 9 weeks of age, when GFR reaches rates found in adult cats.[43] Before this age, kittens may be at greater risk for fluid overload because of impaired solute and water excretion and for toxicity resulting from renally eliminated drugs such as aminoglycosides. Classic early warning signs of nephrotoxicity, such as granular casts, are not consistently observed in neonatal pups given gentamicin, despite the development of renal tubular lesions and impairment of GFR.[22] Aminoglycosides therefore should be avoided whenever possible in very young patients. In contrast, enrofloxacin, despite its renal excretion, is cleared efficiently in kittens as young as 2 weeks of age[84] and does not appear to require dosage reductions in this age group.

THERAPEUTIC CONSIDERATIONS IN SENIOR AND GERIATRIC CATS

Adverse drug reactions are reported to be two to three times higher in elderly human patients than in younger adults.[94] Some of this risk can be attributed to patient confusion and errors in self-dosing; however, pharmacokinetic and pharmacodynamic factors are also involved. Geriatric veterinary patients have been defined as those that have reached 75% of their expected life span (Figure 4-3).[12] In both geriatric cats and humans, changes in renal function, hepatic blood flow, body composition, and compensatory physiologic responses alter drug response.

Age-related renal insufficiency is the most important factor affecting drug dosing in geriatric human patients.[94] Even patients without overt azotemia are likely to have decreased GFR associated with aging. The prevalence of renal insufficiency in older cats has not been established but appears to be relatively high, at least according to anecdotal reports. This may lead to decreased elimination and increased toxicity of renally cleared drugs (see Table 4-2) in older cats. Enrofloxacin has been associated with retinal toxicity in elderly cats at the label dose of 5 mg/kg per day.[32] Because this ocular toxicity is dose-dependent,[101] cases seen in older cats are likely due to decreased renal clearance of the drug. Although orbifloxacin and marbofloxacin are also cleared by the kidneys, they are less retinotoxic at higher dosages in young healthy cats[101] and may be safer for geriatric cats. Older patients also tend to have decreased total body and interstitial water,[94] which may contribute to increased susceptibility to dehydration when elderly patients are given diuretics such as furosemide.

Aging is associated with decreased liver mass, with variable reductions in cytochrome P450 function in elderly human patients.[27] Decreased liver blood flow also occurs with aging and can lead to decreased clearance of certain drugs.[83] For example, propofol is a "blood flow–limited" drug, and its clearance is diminished in

FIGURE 4-3 Geriatric cats have been defined as those that have reached 75% of their expected life span. This 17-year-old cat almost certainly has some degree of renal insufficiency, which may require dosing adjustments for some drugs.

older humans[95] and geriatric dogs, with higher plasma drug concentrations and apnea seen in some older dogs given standard dosages.[75] Other drugs that show impaired clearance in elderly human patients, owing to renal or liver impairment or other factors, are listed in Box 4-2. Although comparable feline studies are not available, these drugs probably should be dosed conservatively in older cats, and the owner should be taught to carefully monitor their pet for adverse effects.

Middle-aged to older cats may be overweight, which can affect drug distribution. For relatively polar drugs with poor fat distribution, such as digoxin, dosing should be based on lean body weight (ideal body weight).[16] For cats ideal body weight can be estimated from the patient's body conformation or from previous medical records when the patient had a normal body condition score. For the polar drug gentamicin, dose reductions of 15% to 20% are indicated in obese cats, based on differences in pharmacokinetics between obese and lean cats.[103] For lipid-soluble drugs, such as propofol and benzodiazepines, single or loading dosages are based on total body weight (lean body weight plus fat) in humans.[13]

DRUG COMPOUNDING FOR CATS

Custom veterinary pharmacies abound in the United States and provide reformulation options such as flavored liquid suspensions, capsules, chew tabs, and compressed minitablets. Pharmacists in the United States are legally allowed to compound veterinary or human drugs for individual veterinary patients if no appropriate approved veterinary formulation exists.[67] Pharmacists are not legally allowed to mass-produce compounded drugs, and as for all prescriptions, there must be a valid doctor–client–patient relationship.

Practitioners often assume that because a custom formulation is available, it must be safe and effective; this is not always true. Unfortunately, the stability and bioavailability of veterinary custom-compounded drugs are usually not tested. In addition, owners may perform their own reformulations at home to ease administration, such as crushing pills in food or water or combining medications in a capsule. Veterinarians usually have inadequate information to advise owners about these manipulations. However, some basic principles can help determine the advisability of a given reformulation.

Crushing medications is not always benign. Sustained-release tablets, such as theophylline (Theo-Dur), diltiazem (Cardizem CD), enteric-coated fluoxetine (Prozac Weekly), and tramadol (Ultram ER), should never be crushed. Crushing of extended-release formulations can lead to rapid, high peak plasma concentrations and potential side effects. In addition, tablets that are enteric coated should not be crushed because this may lead to a bitter taste and degradation in the stomach. Examples include budesonide (Entocort), erythromycin, omeprazole capsules, and potassium citrate tablets. Antineoplastic drugs, such as cyclophosphamide and chlorambucil, should never be crushed by clients or by clinic staff because this results in aerosols and dust that can lead to systemic exposure.[31] These drugs should be reformulated only by a licensed pharmacist, with an appropriate ventilated cabinet.

Mixing drugs with water can also cause problems. Drugs in a blister pack, which are often moisture sensitive, should not be mixed with water,[67] nor should lipophilic drugs, such as itraconazole and diazepam. The veterinarian should check the product insert to see whether a drug is highly lipophilic. Irritating drugs, such as doxycycline or clindamycin, should not be given as capsules to cats because capsules tend to lodge in the midcervical esophagus in cats.[33] This can lead to esophagitis and even esophageal stricture from doxycycline or clindamycin in cats (Figure 4-4).[4,6] Capsules can be chased with an ounce of food or a 6-mL bolus of water after each dose to ensure passage into the stomach.[33,99] However, this may be impractical in inappetent or fractious cats. In these cases oral suspensions of doxycycline or clindamycin may be safer.

Drugs that contain aluminum or other cationic minerals should not be crushed and combined with other drugs. For example, the aluminum in sucralfate or aluminum hydroxide forms complexes with many other drugs in the gastrointestinal tract and can markedly impair the absorption of fluoroquinolones, doxycycline, theophylline, digoxin, and amitriptyline.[56] In addition, aluminum can decrease peak plasma concentrations of azithromycin in humans.[30] Other cationic minerals, such as calcium, iron, zinc, and magnesium, found in multivitamins, may also chelate fluoroquinolones and impair their absorption.[52] Similarly, the

BOX 4-2

Drugs that Show Decreased Clearance (by 20% or More) in Elderly Human Patients[95]

Amikacin
Amlodipine
Atenolol
Ciprofloxacin
Diazepam
Digoxin
Diphenhydramine
Famotidine
Furosemide
Gentamicin
Lidocaine
Methylprednisolone
Metoclopramide
Midazolam
Omeprazole
Ondansetron
Piroxicam
Propofol
Terbutaline
Theophylline

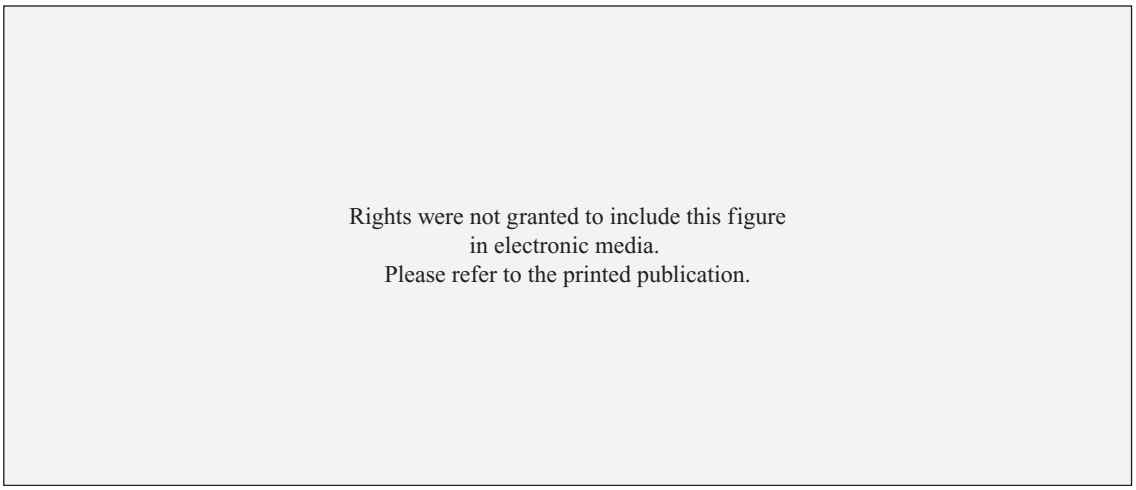

FIGURE 4-4 This male neutered Persian **(A)** developed an esophageal stricture **(B)** after administration of clindamycin capsules. *(From Trepanier L: Acute vomiting in cats, rational treatment selection,* J Feline Med Surg *12(3):225-230, 2010.)*

calcium in dairy products can decrease the absorption of doxycycline.[59]

Drugs that *can* be readily reformulated into capsules include cyclosporine emulsion, potassium chloride beads, omeprazole enteric-coated beads, and itraconazole beads; the number of beads in one original capsule can be counted and divided as needed for the desired dose. For cats with hypertension, amlodipine and benazepril can be reformulated in a single capsule without affecting bioavailability.[9] Fluoroquinolones are reportedly quite stable in most vehicles and flavorings, such as molasses, fish sauce, or corn syrup.[67] It is important, however, to make sure that the vehicle does not contain cationic minerals (e.g., iron, calcium) that will impair fluoroquinolone absorption. Other reformulated suspensions with demonstrated stability are summarized in Table 4-3.

TABLE 4-3 **Pediatric Suspensions with Demonstrated Stability**[64]

Drug	Formulation	Stability
Aminophylline	5 mg/mL in bacteriostatic water	1 week refrigerated
Chlorambucil	2 mg/mL in methylcellulose and syrup	1 week refrigerated; protect from light
Cyclophosphamide	2 mg/mL in aromatic elixir (from injectable)	2 weeks refrigerated
Hydralazine	2 mg/mL in bacteriostatic water	24 hours at room temperature
Metronidazole	20 mg/mL in purified water USP and syrup	10 days refrigerated
Phenobarbital	10 mg/mL in bacteriostatic water (from injection)	3 months refrigerated
Sucralfate	200 mg/mL in purified water USP	2 weeks refrigerated Shake well

ALTERNATIVE FORMULATIONS/ ROUTES FOR MEDICATING CATS

Transdermal drug formulations are a common compounding product in the United States. Transdermal administration, in which the goal is therapeutic drug concentrations in the systemic circulation, is distinct from topical administration, in which the goal is local therapeutic drug concentrations in surface organs (skin, eye, ear canal). Effective transdermal drug delivery is much harder to achieve.

Transdermal drugs are attractive because of their many potential advantages, which include better acceptance compared with pilling or injections, decreased gastrointestinal irritation, avoidance of first-pass intestinal and hepatic degradation, possible longer duration of action without peak side effects, and the ability to custom formulate the drug concentration to the patient's size. However, there are significant disadvantages and limitations to transdermal drug formulations as available through custom compounders. The transdermal route is inappropriate for drugs acting locally in the gastrointestinal tract and may be ineffective for prodrugs dependent on hepatic biotransformation for efficacy. There is a lack of immediate effect for most drugs needed in an emergency setting (nitroglycerin is an exception), and some cats resent the sensation of a transdermal gel. Compounding of transdermal drugs can add significantly to the prescription cost. Most important, many drugs are poorly absorbed transdermally and never reach therapeutic plasma concentrations.

Transdermal drugs that are effectively absorbed in humans tend to have relatively high lipid solubility (so that they can traverse the waxy stratum corneum) and a low melting point (i.e., they are readily converted from a solid to a liquid at body temperatures). Very polar compounds, such as aminoglycosides and many peptides, are poorly absorbed without additional interventions, such as an electric field, microneedles, or ultrasonic disruption of the stratum corneum.[73] Approved transdermal drugs for humans are typically small compounds (i.e., molecular weight less than 500 g/mol or 500 Da [daltons]).[7,8] Small drugs advertised for transdermal formulations in cats include methimazole (114 g/mol), nitroglycerin (227 g/mol), fentanyl (336 g/mol), and amitriptyline (277 g/mol). Larger drugs that are less likely to be absorbed but are still offered by veterinary compounding pharmacies include itraconazole (705 g/mol), ketoconazole (531 g/mol), and amikacin (585 g/mol). Amikacin has the additional disadvantage of being poorly lipid soluble.

Transdermal drugs that are approved for human patients tend to be those that are effective at very low dosages. For example, for fentanyl, lidocaine, nicotine, nitroglycerin, scopolamine, oxybutynin, and contraceptive hormones, total daily dosages range from 0.1 to 32 mg per day.[73] Transdermal dosing is constrained by the physical limitations of permeation enhancers, as well as by practical limitations in the amount of skin coverage that patients will accept. Transdermal formulations of veterinary drugs that require higher total daily dosages (i.e., more than 50 mg per patient per day) are unlikely to be adequately absorbed, especially through the relatively small surface area of a cat's pinna.

Veterinary transdermal drugs are typically formulated in a permeation enhancer such as pluronic lecithin organogel (PLO), which increases the fluidity of the stratum corneum and enhances the formation of drug micelles. PLO also leads to exfoliation of the stratum corneum and low-grade inflammation with chronic use, which likely contributes to drug penetration. PLO separates at cold temperatures and should be discarded if this occurs. Another available permeation enhancer is Lipoderm, a commercial product with proprietary ingredients. Lipoderm is comparable to PLO but is less greasy and does not separate at cold temperatures. A second proprietary permeation enhancer, VanPen, is used for more lipophilic drugs. There are essentially no data to compare the efficacy of PLO, Lipoderm, and VanPen in the delivery of veterinary drugs. Dimethyl sulfoxide (DMSO), although an excellent permeation enhancer, is not recommended because it can be quite irritating.

Several drugs have shown low bioavailability (less than 10% compared with oral) when given transdermally to cats as single doses: fluoxetine, diltiazem, dexamethasone, buspirone, and amitriptyline.[18,25,57,102] Glipizide in PLO has about 20% bioavailability (relative to oral administration) after a single dose in cats. Despite relatively low absorption, transdermal glipizide was associated with a delayed decrease in blood glucose in some cats,[5] and multiple-dose studies in diabetic cats are warranted. Multiple doses of transdermal methimazole in PLO were effective at lowering serum T_4 in hyperthyroid cats and had fewer gastrointestinal side effects than oral methimazole.[80] However, the risk of idiosyncratic drug toxicity (facial pruritus, hepatotoxicity, blood dyscrasias) appeared to be the same for both routes. Similar responses have been observed for transdermal carbimazole (a prodrug of methimazole) in Europe.[10] Modest efficacy has been reported for transdermal atenolol (6.25 mg once daily, in propylene glycol–glycerin–Tween) in reducing heart rate in cats[53] and for transdermal amlodipine (0.625 mg daily in Lipoderm) in reducing blood pressure in hypertensive cats (although the transdermal route was inferior to oral amlodipine).[42] The transdermal route is *not appropriate* for empiric dosing of antimicrobials because of the considerable risk of poor absorption, subtherapeutic plasma concentrations, and potential selection for resistant bacterial strains.

In contrast to transdermal administration, transmucosal drug delivery is typically associated with rapid absorption and relatively high bioavailability. This is because the mucous membranes are highly vascular and lack the stratum corneum. Drugs can be administered transmucosally by several routes (Table 4-4). Like transdermal administration, transmucosal administration bypasses first-pass intestinal and hepatic metabolism and may prevent gastrointestinal upset resulting from direct gastric irritation. However, this route cannot be used for irritating medications.

Buprenorphine is often given by the transmucosal (buccal) route in cats. It is well accepted at 0.01 mg/kg of injectable solution in the buccal pouch and is absorbed as well as that administered by the intravenous route, with equivalent analgesia.[76] It is hypothesized that the higher bioavailability in cats (compared to humans) is due to the relatively high pH in the feline mouth (pH 8 to 9), in which buprenorphine is mostly uncharged, which favors absorption across the mucosa.[77]

Fluticasone, a trifluorinated glucocorticoid with potent antiinflammatory activity, can also be administered by the transmucosal (pulmonary aerosol) route in cats, using a metered-dose inhaler with a spacer. The goal is high topical potency in the lungs with few systemic side effects. Inhaled fluticasone has been associated with decreased lower airway inflammation in cats with bronchitis,[47] and dosages up to 220 µg every 12 hours have not been associated with adrenal suppression in cats.[19] Although local irritation can lead to acute bronchospasm, inhaled fluticasone is anecdotally well tolerated by many cats with reactive airway disease.

TABLE 4-4 Drugs that Are Effective When Given by the Transmucosal Route

Drug	Route of Administration	Indication
Apomorphine	Conjunctival sac	Emesis (dogs only; emetic dosages in cats cause unacceptable central nervous system side effects)[93]
Buprenorphine	Buccal cavity[77]	Analgesia[76]
Desmopressin (DDAVP)	Nasal mucosa Conjunctival sac	Diabetes insipidus (rare in cats)
Diazepam	Intrarectal[68] Nasal mucosa	Cluster seizures (efficacy demonstrated in dogs)[72]
Epinephrine	Pulmonary Through endotracheal tube	Cardiopulmonary resuscitation
Fluticasone	Pulmonary Via metered-dose inhaler	Reactive airway disease/feline asthma[47]

Finally, human recombinant regular insulin was recently marketed for transmucosal (pulmonary aerosol) administration in human diabetic patients (Exubera, Pfizer). This formulation was shown to lower blood glucose in healthy cats at high dosages (25 U/kg), with hypoglycemia even seen in some cats.[24] Although this drug had a short duration of action and was recently discontinued because of poor market performance, it demonstrates proof of the principle that peptide drugs can be administered without injection to cats, which is an exciting development.

CONCLUSION

The differences between cats and humans require the feline practitioner to be quite savvy when it comes to feline therapeutics. Dosage extrapolations to cats should always be made with attention to whether the drug is cleared by glucuronidation in humans and dogs. Drugs with narrow safety margins should be dosed with attention to the primary route of clearance in adult cats (or in other species if data in cats are lacking), young kittens, geriatric cats, or cats with renal or hepatic insufficiency. Drug compounding, although very appealing, should be undertaken with a critical eye toward factors such as original formulation (enteric coated or extended release), water solubility of the drug, and drug–drug and drug–mineral interactions. Transdermal drug administration should be reserved for drugs with good evidence of absorption or efficacy (or both) in cats.

References

1. Adelman RD, Spangler WL, Beasom F et al: Furosemide enhancement of experimental gentamicin nephrotoxicity: comparison of functional and morphological changes with activities of urinary enzymes, *J Infect Dis* 140:342, 1979.
2. Alberola J, Perez Y, Puigdemont A et al: Effect of age on theophylline pharmacokinetics in dogs, *Am J Vet Res* 54:1112, 1993.
3. Beale KM, Altman D, Clemmons RR et al: Systemic toxicosis associated with azathioprine administration in domestic cats, *Am J Vet Res* 53:1236, 1992.
4. Beatty JA, Swift N, Foster DJ et al: Suspected clindamycin-associated oesophageal injury in cats: five cases, *J Feline Med Surg* 8:412, 2006.
5. Bennett N, Papich MG, Hoenig M et al: Evaluation of transdermal application of glipizide in a pluronic lecithin gel to healthy cats, *Am J Vet Res* 66:581, 2005.
6. Bissett SA, Davis J, Subler K et al: Risk factors and outcome of bougienage for treatment of benign esophageal strictures in dogs and cats: 28 cases (1995-2004), *J Am Vet Med Assoc* 235:844, 2009.
7. Bos JD, Meinardi MM: The 500 Dalton rule for the skin penetration of chemical compounds and drugs, *Exp Dermatol* 9:165, 2000.
8. Brown MB, Martin GP, Jones SA et al: Dermal and transdermal drug delivery systems: current and future prospects, *Drug Deliv* 13:175, 2006.
9. Budde J, Head Pharmacist UoW-M, Veterinary Medical Teaching Hospital: Personal Communication, 2009.
10. Buijtels JJ, Kurvers IA, Galac S et al: [Transdermal carbimazole for the treatment of feline hyperthyroidism], *Tijdschr Diergeneeskd* 131:478, 2006.
11. Cantu TG, Korek JS: Central nervous system reactions to histamine-2 receptor blockers, *Ann Intern Med* 114:1027, 1991.
12. Carpenter RE, Pettifer GR, Tranquilli WJ: Anesthesia for geriatric patients, *Vet Clin North Am Small Anim Pract* 35:571, 2005.
13. Casati A, Putzu M: Anesthesia in the obese patient: pharmacokinetic considerations, *J Clin Anesth* 17:134, 2005.
14. Catalano-Pons C, Bargy S, Schlecht D et al: Sulfadiazine-induced nephrolithiasis in children, *Pediatr Nephrol* 19:928, 2004.
15. Chen M, Leduc B, Kerr SG et al: Identification of human UGT2B7 as the major isoform involved in the O-glucuronidation of chloramphenicol, *Drug Metab Dispos* 38:368, 2010.
16. Cheymol G: Drug pharmacokinetics in the obese, *Fundam Clin Pharmacol* 2:239, 1988.
17. Christensen EF, Reiffenstein JC, Madissoo H: Comparative ototoxicity of amikacin and gentamicin in cats, *Antimicrob Agents Chemother* 12:178, 1977.
18. Ciribassi J, Luescher A, Pasloske KS et al: Comparative bioavailability of fluoxetine after transdermal and oral administration to healthy cats, *Am J Vet Res* 64:994, 2003.

19. Cohn LA, Declue AE, Cohen RL et al: Effects of fluticasone propionate dosage in an experimental model of feline asthma, *J Feline Med Surg* 12:91, 2010.
20. Court MH, Greenblatt DJ: Molecular basis for deficient acetaminophen glucuronidation in cats. An interspecies comparison of enzyme kinetics in liver microsomes, *Biochem Pharmacol* 53:1041, 1997.
21. Court MH, Greenblatt DJ: Molecular genetic basis for deficient acetaminophen glucuronidation by cats: UGT1A6 is a pseudogene, and evidence for reduced diversity of expressed hepatic UGT1A isoforms, *Pharmacogenetics* 10:355, 2000.
22. Cowan RH, Jukkola AF, Arant BS Jr: Pathophysiologic evidence of gentamicin nephrotoxicity in neonatal puppies, *Pediatr Res* 14:1204, 1980.
23. Czock D, Rasche FM: Dose adjustment of ciprofloxacin in renal failure: reduce the dose or prolong the administration interval? *Eur J Med Res* 10:145, 2005.
24. DeClue AE, Leverenz EF, Wiedmeyer CE et al: Glucose lowering effects of inhaled insulin in healthy cats, *J Feline Med Surg* 10:519, 2008.
25. DeFrancesco T: Transdermal cardiac therapy in cats: the NCSU experience. Annual Forum of the American College of Veterinary Internal Medicine, 2003.
26. Delco F, Tchambaz L, Schlienger R et al: Dose adjustment in patients with liver disease, *Drug Saf* 28:529, 2005.
27. El Desoky ES: Pharmacokinetic-pharmacodynamic crisis in the elderly, *Am J Ther* 14:488, 2007.
28. Faint V: The pathophysiology of hepatic encephalopathy, *Nurs Crit Care* 11:69, 2006.
29. Foster AP, Shaw SE, Duley JA et al: Demonstration of thiopurine methyltransferase activity in the erythrocytes of cats, *J Vet Intern Med* 14:552, 2000.
30. Foulds G, Hilligoss DM, Henry EB et al: The effects of an antacid or cimetidine on the serum concentrations of azithromycin, *J Clin Pharmacol* 31:164, 1991.
31. Gambrell J, Moore S: Assessing workplace compliance with handling of antineoplastic agents, *Clin J Oncol Nurs* 10:473, 2006.
32. Gelatt KN, van der Woerdt A, Ketring KL et al: Enrofloxacin-associated retinal degeneration in cats, *Vet Ophthalmol* 4:99, 2001.
33. Graham JP, Lipman AH, Newell SM et al: Esophageal transit of capsules in clinically normal cats, *Am J Vet Res* 61:655, 2000.
34. Grundy SA: Clinically relevant physiology of the neonate, *Vet Clin North Am Small Anim Pract* 36:443, 2006.
35. Gunew MN, Menrath VH, Marshall RD: Long-term safety, efficacy and palatability of oral meloxicam at 0.01-0.03 mg/kg for treatment of osteoarthritic pain in cats, *J Feline Med Surg* 10:235, 2008.
36. Hagen I, Oymar K: Pharmacological differences between once daily and twice daily gentamicin dosage in newborns with suspected sepsis, *Pharm World Sci* 31:18, 2009.
37. Hardman J, Limbard L: *Goodman and Gilman's the pharmacologic basis of therapeutics*, ed 10, New York, 2001, McGraw-Hill.
38. Hardy ML, Hsu RC, Short CR: The nephrotoxic potential of gentamicin in the cat: enzymuria and alterations in urine concentrating capability, *J Vet Pharmacol Ther* 8:382, 1985.
39. Harris RC: COX-2 and the kidney, *J Cardiovasc Pharmacol* 47(Suppl 1):S37, 2006.
40. Hastings CL, Brown TC, Eyres RL et al: The influence of age on lignocaine pharmacokinetics in young puppies, *Anaesth Intensive Care* 14:135, 1986.
41. Hays MT, Broome MR, Turrel JM: A multicompartmental model for iodide, thyroxine, and triiodothyronine metabolism in normal and spontaneously hyperthyroid cats, *Endocrinology* 122:2444, 1988.
42. Helms SR: Treatment of feline hypertension with transdermal amlodipine: a pilot study, *J Am Anim Hosp Assoc* 43:149, 2007.
43. Hoskins JD, Turnwald GH, Kearney MT et al: Quantitative urinalysis in kittens from four to thirty weeks after birth, *Am J Vet Res* 52:1295, 1991.
44. House AA, Silva Oliveira S, Ronco C: Anti-inflammatory drugs and the kidney, *Int J Artif Organs* 30:1042, 2007.
45. Kidd LB, Salavaggione OE, Szumlanski CL et al: Thiopurine methyltransferase activity in red blood cells of dogs, *J Vet Intern Med* 18:214, 2004.
46. King JN, Strehlau G, Wernsing J et al: Effect of renal insufficiency on the pharmacokinetics and pharmacodynamics of benazepril in cats, *J Vet Pharmacol Ther* 25:371, 2002.
47. Kirschvink N, Leemans J, Delvaux F et al: Inhaled fluticasone reduces bronchial responsiveness and airway inflammation in cats with mild chronic bronchitis, *J Feline Med Surg* 8:45, 2006.
48. Krishnaswamy S, Hao Q, Von Moltke LL et al: Evaluation of 5-hydroxytryptophol and other endogenous serotonin (5-hydroxytryptamine) analogs as substrates for UDP-glucuronosyltransferase 1A6, *Drug Metab Dispos* 32:862, 2004.
49. Kuehl GE, Bigler J, Potter JD et al: Glucuronidation of the aspirin metabolite salicylic acid by expressed UDP-glucuronosyltransferases and human liver microsomes, *Drug Metab Dispos* 34:199, 2006.
50. KuKanich B, Lascelles BD, Papich MG: Pharmacokinetics of morphine and plasma concentrations of morphine-6-glucuronide following morphine administration to dogs, *J Vet Pharmacol Ther* 28:371, 2005.
51. Latham JT, Jr, Bove JR, Weirich FL: Chemical and hematologic changes in stored CPDA-1 blood, *Transfusion* 22:158, 1982.
52. Lomaestro BM, Bailie GR: Absorption interactions with fluoroquinolones. 1995 update, *Drug Saf* 12:314, 1995.
53. Macgregor JM, Rush JE, Rozanski EA et al: Comparison of pharmacodynamic variables following oral versus transdermal administration of atenolol to healthy cats, *Am J Vet Res* 69:39, 2008.
54. Malloy MH, Morriss FH, Denson SE et al: Neonatal gastric motility in dogs: maturation and response to pentagastrin, *Am J Physiol* 236:E562, 1979.
55. Matal J, Jancova P, Siller M et al: Interspecies comparison of the glucuronidation processes in the man, monkey, pig, dog and rat, *Neuro Endocrinol Lett* 29:738, 2008.
56. McCarthy DM: Sucralfate, *N Engl J Med* 325:1017, 1991.
57. Mealey KL, Peck KE, Bennett BS et al: Systemic absorption of amitriptyline and buspirone after oral and transdermal administration to healthy cats, *J Vet Intern Med* 18:43, 2004.
58. Mensching D, Volmer P: Toxicology brief: managing acute carprofen toxicosis in dogs and cats, *Vet Med* 104(7):325, 2009.
59. Meyer FP, Specht H, Quednow B et al: Influence of milk on the bioavailability of doxycycline—new aspects, *Infection* 17:245, 1989.
60. Miyamoto K: Use of plasma clearance of iohexol for estimating glomerular filtration rate in cats, *Am J Vet Res* 62:572, 2001.
61. Morton DJ, Knottenbelt DC: Pharmacokinetics of aspirin and its application in canine veterinary medicine, *J S Afr Vet Assoc* 60:191, 1989.
62. Munar MY, Singh H: Drug dosing adjustments in patients with chronic kidney disease, *Am Fam Physician* 75:1487, 2007.
63. Myant NB: Excretion of the glucuronide of thyroxine in cat bile, *Biochem J* 99:341, 1966.
64. Nahata M, Hipple T: *Pediatric drug formulations*. ed 2, Cincinnati, 1992, Harvey Whitney Books.
65. Oliveira JF, Silva CA, Barbieri CD et al: Prevalence and risk factors for aminoglycoside nephrotoxicity in intensive care units, *Antimicrob Agents Chemother* 53:2887, 2009.

66. Olyaei AJ, Bennett WM: Drug dosing in the elderly patients with chronic kidney disease, *Clin Geriatr Med* 25:459, 2009.
67. Papich MG: Drug compounding for veterinary patients, *AAPS J* 7:E281, 2005.
68. Papich MG, Alcorn J: Absorption of diazepam after its rectal administration in dogs, *Am J Vet Res* 56:1629, 1995.
69. Parton K, Balmer TV, Boyle J et al: The pharmacokinetics and effects of intravenously administered carprofen and salicylate on gastrointestinal mucosa and selected biochemical measurements in healthy cats, *J Vet Pharmacol Ther* 23:73, 2000.
70. Pham K, Hirschberg R: Global safety of coxibs and NSAIDs, *Curr Top Med Chem* 5:456, 2005.
71. Plumb D: *Plumb's veterinary drug handbook*, ed 6, Ames, 2008, Blackwell.
72. Podell M: The use of diazepam per rectum at home for the acute management of cluster seizures in dogs, *J Vet Intern Med* 9:68, 1995.
73. Prausnitz MR, Mitragotri S, Langer R: Current status and future potential of transdermal drug delivery, *Nat Rev Drug Discov* 3:115, 2004.
74. Rea RS, Capitano B: Optimizing use of aminoglycosides in the critically ill, *Semin Respir Crit Care Med* 28:596, 2007.
75. Reid J, Nolan AM: Pharmacokinetics of propofol as an induction agent in geriatric dogs, *Res Vet Sci* 61:169, 1996.
76. Robertson SA, Lascelles BD, Taylor PM et al: PK-PD modeling of buprenorphine in cats: intravenous and oral transmucosal administration, *J Vet Pharmacol Ther* 28:453, 2005.
77. Robertson SA, Taylor PM, Sear JW: Systemic uptake of buprenorphine by cats after oral mucosal administration, *Vet Rec* 152:675, 2003.
78. Rubio F, Seawall S, Pocelinko R et al: Metabolism of carprofen, a nonsteroid anti-inflammatory agent, in rats, dogs, and humans, *J Pharm Sci* 69:1245, 1980.
79. Salavaggione OE, Yang C, Kidd LB et al: Cat red blood cell thiopurine S-methyltransferase: companion animal pharmacogenetics, *J Pharmacol Exp Ther* 308:617, 2004.
80. Sartor LL, Trepanier LA, Kroll MM et al: Efficacy and safety of transdermal methimazole in the treatment of cats with hyperthyroidism, *J Vet Intern Med* 18:651, 2004.
81. Savides MC, Oehme FW, Nash SL et al: The toxicity and biotransformation of single doses of acetaminophen in dogs and cats, *Toxicol Appl Pharmacol* 74:26, 1984.
82. Schentag JJ, Gengo FM, Plaut ME et al: Urinary casts as an indicator of renal tubular damage in patients receiving aminoglycosides, *Antimicrob Agents Chemother* 16:468, 1979.
83. Schmucker DL: Age-related changes in liver structure and function: implications for disease? *Exp Gerontol* 40:650, 2005.
84. Seguin MA, Papich MG, Sigle KJ et al: Pharmacokinetics of enrofloxacin in neonatal kittens, *Am J Vet Res* 65:350, 2004.
85. Sirota RA, Kimmel PL, Trichtinger MD et al: Metoclopramide-induced parkinsonism in hemodialysis patients. Report of two cases, *Arch Intern Med* 146:2070, 1986.
86. Somogyi A: Renal transport of drugs: specificity and molecular mechanisms, *Clin Exp Pharmacol Physiol* 23:986, 1996.
87. Spivak W, Carey MC: Reverse-phase h.p.l.c. separation, quantification and preparation of bilirubin and its conjugates from native bile. Quantitative analysis of the intact tetrapyrroles based on h.p.l.c. of their ethyl anthranilate azo derivatives, *Biochem J* 225:787, 1985.
88. Steagall PV, Taylor PM, Rodrigues LC et al: Analgesia for cats after ovariohysterectomy with either buprenorphine or carprofen alone or in combination, *Vet Rec* 164:359, 2009.
89. Sweileh WM: A prospective comparative study of gentamicin- and amikacin-induced nephrotoxicity in patients with normal baseline renal function, *Fundam Clin Pharmacol* 23:515, 2009.
90. Tanaka E, Narisawa C, Nakamura H et al: Changes in the enzymatic activities of beagle liver during maturation as assessed both in vitro and in vivo, *Xenobiotica* 28:795, 1998.
91. Taylor PM, Robertson SA, Dixon MJ et al: Morphine, pethidine and buprenorphine disposition in the cat, *J Vet Pharmacol Ther* 24:391, 2001.
92. Touw DJ, Westerman EM, Sprij AJ: Therapeutic drug monitoring of aminoglycosides in neonates, *Clin Pharmacokinet* 48:71, 2009.
93. Trulson ME, Crisp T: Behavioral and neurochemical effects of apomorphine in the cat, *Eur J Pharmacol* 80:295, 1982.
94. Turnheim K: Drug therapy in the elderly, *Exp Gerontol* 39:1731, 2004.
95. Turnheim K: Pharmacokinetic dosage guidelines for elderly subjects, *Expert Opin Drug Metab Toxicol* 1:33, 2005.
96. Van Scoy RE, Wilson WR: Antimicrobial agents in adult patients with renal insufficiency: initial dosage and general recommendations, *Mayo Clin Proc* 62:1142, 1987.
97. Verbeeck RK, Musuamba FT: Pharmacokinetics and dosage adjustment in patients with renal dysfunction, *Eur J Clin Pharmacol* 65:757, 2009.
98. Weinberg MS: Renal effects of angiotensin converting enzyme inhibitors in heart failure: a clinician's guide to minimizing azotemia and diuretic-induced electrolyte imbalances, *Clin Ther* 15:3, 1993.
99. Westfall DS, Twedt DC, Steyn PF et al: Evaluation of esophageal transit of tablets and capsules in 30 cats, *J Vet Intern Med* 15:467, 2001.
100. White SD, Rosychuk RA, Outerbridge CA et al: Thiopurine methyltransferase in red blood cells of dogs, cats, and horses, *J Vet Intern Med* 14:499, 2000.
101. Wiebe V, Hamilton P: Fluoroquinolone-induced retinal degeneration in cats, *J Am Vet Med Assoc* 221:1568, 2002.
102. Willis-Goulet HS, Schmidt BA, Nicklin CF et al: Comparison of serum dexamethasone concentrations in cats after oral or transdermal administration using pluronic lecithin organogel (PLO): a pilot study, *Vet Dermatol* 14:83, 2003.
103. Wright LC, Horton CR, Jr, Jernigan AD et al: Pharmacokinetics of gentamicin after intravenous and subcutaneous injection in obese cats, *J Vet Pharmacol Ther* 14:96, 1991.
104. Yoder Graber AL, Ramirez J, Innocenti F et al: UGT1A1*28 genotype affects the in-vitro glucuronidation of thyroxine in human livers, *Pharmacogenet Genomics* 17:619, 2007.
105. Zhanel GG: Cephalosporin-induced nephrotoxicity: does it exist? *DICP* 24:262, 1990.
106. Zimmermann T, Yeates RA, Riedel KD et al: The influence of gastric pH on the pharmacokinetics of fluconazole: the effect of omeprazole, *Int J Clin Pharmacol Ther* 32:491, 1994.