CHAPTER 23

Adverse Drug Reactions*

Alastair E. Cribb, DVM, PhD, FCAHS
Mathieu Peyrou, DVM, MSc

An adverse drug reaction (ADR) is any noxious or unintended response to a drug that occurs at appropriate doses used for prophylaxis, diagnosis, or therapy. They may vary from minor annoyances to severe, life-threatening events. Because ADRs are an ever-present threat when drugs are used in clinical practice, communication with owners about risk and response to ADRs are an important part of client education. The frequency with which ADRs occur in the average clinical veterinary practice or in teaching hospitals is not known, but it is generally accepted that an ADR is a significant contributor to patient morbidity and mortality.

Drug toxicity includes all toxicity associated with a drug, including that observed in overdose situations (e.g., poisonings with drugs). *Side effects,* on the other hand, generally refers to relatively minor adverse effects that occur during therapy, such as polydipsia or polyuria in dogs on corticosteroids. Lack of therapeutic efficacy may also be an ADR. However, lack of response may also be caused by an incorrect diagnosis or inappropriate treatment and so is not necessarily an ADR.

When using a drug, the veterinarian has an obligation to minimize the likelihood of an ADR occurring, to be aware of the potential clinical signs of an ADR so that a prompt diagnosis can be made, and to know the appropriate clinical care to administer should an ADR occur. The veterinarian should educate clients as to the risk of ADRs associated with the drug so that they can rationally balance this risk against the expected therapeutic benefit of the drug for their animal. The owners must also be informed of the clinical signs expected should an ADR occur and what steps they should take on observing these signs (e.g., stop the drug, transport the patient to the clinic).

Assessment of Risk

The decision to use a drug is based on a risk-benefit analysis for the individual patient. No drug is without some risk; however, the willingness of the owner and the veterinarian to accept the risk associated with a therapy depends on the relative risks and benefits of the drug compared with the risk of no treatment or the risk associated with alternative treatments, such as surgery. A drug should not be used without a specific therapeutic goal, so that efficacy and toxicity can be balanced appropriately.

When assessing risk, the veterinarian needs to look at the population risk (how frequent and severe is the ADR?) and the individual risk (does this patient have any characteristics that increase or decrease risk?). Assessing the risks of an ADR may be frustrating because the information necessary to truly assess risk is not available. Veterinarians are often using

*FDA Adverse Event Reporting System; +1 888 463-6332; +1 301 796-3400; druginfo@fda.hhs.gov
FDA Adverse Event Reporting System website: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm

drugs with limited published clinical data in veterinary species and what information is available on ADRs is often vague. Finding information on the actual frequency and severity of ADRs is often difficult. Therefore, an understanding of the mechanism or pathogenesis of ADRs is often helpful, as discussed in detail in this chapter.

Although mechanisms are in place for reviewing and recording ADRs of licensed products, information for drugs used off-label is less readily available. Many standard veterinary textbooks list adverse reactions that have been reported to drugs without incorporating information on species differences or indeed noting if the adverse reactions have been reported in veterinary species. Furthermore, information on the frequency and severity of ADRs is often lacking. For licensed animal products, the company marketing the product is a good source of information, either through information on the package insert or through direct contact with the company. The Center for Veterinary Medicine, U.S. Food and Drug Administration (FDA) and the Veterinary Drugs Directorate, Health Canada, maintain a record of adverse events that have been reported and use this information to recommend changes in drug labels when appropriate. The FDA's database is available through its website (see the "Animal and Veterinary" section of the FDA website) and is a good source of up-to-date information on potential ADRs that have been reported.

Once an animal is receiving treatment, the identification and response to an ADR becomes important. The same caveats for prospectively assessing risk for the patient apply to deciding if a clinical event represents an ADR. That is, we often rely on cross-species extrapolation and a rather limited database to decide if an ADR has occurred. We must often rely on our knowledge of the pharmacologic and toxicologic characteristics of the drug in making a rational decision as to whether a clinical event is potentially drug-related and in deciding appropriate therapy. The diagnosis and response to ADRs is discussed in the following sections.

In summary, to make the most use of the information available, to tailor our decisions to the individual patient, and to make rational clinical decisions, an understanding of the basic principles of ADRs is invaluable. Therefore this chapter first presents general principles that can be applied in many clinical situations to guide therapeutic decisions. This is followed by a brief overview of hepatic and renal ADRs.

Classification of Adverse Drug Reactions

Several different systems for classifying ADRs exist, based on either clinical presentation or mechanism of toxicity. The clinical presentations of ADRs depend on the pharmacologic and chemical properties of the drug and the target organ damaged. In many cases, the exact mechanism of toxicity is not known or understood. This can make classification of drug toxicities difficult but does not prevent us from employing a broad mechanistic classification that will assist in making clinical decisions.

Dose-Dependent Adverse Drug Reactions

Most ADRs are dose-dependent. That is, the larger the dose, the greater the number of patients affected and the more severe the reaction. These types of ADRs or toxicities are generally predictable and can be reproduced in experimental models. The majority of patients experience a dose-dependent ADR if the drug is given at a sufficient dose or for a sufficient time period. In a clinical setting, the frequency of these reactions depends largely on the care with which the products are used and knowledge of specific dose adjustment that may be required. They can occur at therapeutic doses or plasma concentrations in some individuals, but they are commonly associated with elevated drug plasma concentrations resulting from altered pharmacokinetics in the patient caused by concurrent disease, pregnancy, age, or a drug interaction. This is particularly true for drugs with a narrow therapeutic index, in which changes in pharmacokinetics result in a functional overdose despite use of a normally safe therapeutic dosage regimen. The majority of dose-dependent toxicities can be avoided by careful and appropriate selection of the dose, taking into consideration patient characteristics and concurrent drug use.

Box 23-1 Examples of Pharmacologic Toxicities

Digoxin-induced cardiac arrhythmias
Ulcers associated with inhibition of cyclooxygenase activity by nonsteroidal antiinflammatory drugs
Pancytopenia from estrogens in dogs
Hypotension from acepromazine (α-1 antagonism)
Iatrogenic Cushing's from excessive corticosteroid use
Ivermectin neurotoxicity

Box 23-2 Examples of Intrinsic Toxicities

Aminoglycoside nephrotoxicity and ototoxicity
Acetaminophen methemoglobinemia and hemolytic anemia
Acetaminophen hepatotoxicity
Sulfonamide-induced hypothyroidism
Doxorubicin cardiotoxicity

Patients may be hypersusceptible to a dose-dependent ADR, so that they have a reaction at doses (or plasma concentrations) lower than typically observed. Hypersusceptibility may result from altered pharmacokinetics, either through disease, genetic variation, or a drug interaction, that leads to higher than expected drug concentrations in the circulation or at specific sites for a given drug dose. Alternatively, there may be a receptor or target organ sensitivity that results in an adverse reaction at a lower concentration.

The occurrence of a dose-dependent toxicity in a patient is not necessarily an absolute contraindication to future use of the drug. If possible, the reason for the occurrence of the ADR should be ascertained. For example, was a dosing error made or was the ADR the result of a drug interaction?

Dose-dependent ADRs can be further subdivided into pharmacologic toxicity or intrinsic toxicity. The general principles of dose-dependent ADRs apply, but the diagnosis and treatment of these two different classes of ADRs may differ.

Pharmacologic Toxicity

Pharmacologic toxicity (also referred to as *mechanism-based, receptor-mediated, augmented,* or *Type A adverse reactions*) is a form of dose-dependent ADR that arises through exaggerated or undesirable pharmacologic effects of a drug (Box 23-1). Pharmacologic toxicity depends on an interaction of the parent drug or a pharmacologically active metabolite with a specific target or receptor. These effects may be related to the intended therapeutic target or to additional, inseparable secondary pharmacologic actions. In the latter instance, the ADRs are often called "side effects." For example, a minor side effect is mydriasis associated with the use of atropine as a preanesthetic agent.

Intrinsic Toxicity

Intrinsic toxicity is determined by the chemical properties of the drug, not its pharmacologic properties. That is, the toxicity depends on the intrinsic chemical properties of the drug—hence the term *intrinsic toxicity.* The drug or its metabolites do not bind to specific receptors to cause these toxicities, but instead bind nonspecifically to a variety of proteins or nucleic acids or disrupt membranes or organelle function (Box 23-2). Intrinsic toxicity may have a short course (e.g., acetaminophen toxicity) or a longer course (e.g., bone marrow suppression with chemotherapy). It is also referred to as *Type A (augmented)* or *Type C (chronic)* adverse reactions, depending on the nature and course of the reaction.

Intrinsic toxicity frequently depends on the metabolism of the parent drug to toxic metabolites, a process referred to as *bioactivation.* The site of toxicity therefore depends on the sites of accumulation of the toxin, the localization of enzymes necessary for metabolism

of the compound, and the susceptibility of specific cells to the toxic effects. A typical intrinsic toxin is acetaminophen. Acetaminophen is metabolized to reactive metabolites that cause methemoglobinemia, hemolytic anemia, or liver damage, the primary clinical manifestations depending on the species of animal affected. Drugs or chemicals with carcinogenic properties, which bind to deoxyribonucleic acid (DNA) or damage DNA through other mechanisms, would be included in this category.

Clinical Pharmacologic Characteristics of Dose-Dependent Adverse Drug Reactions

Dose-dependent ADRs have the potential to occur in all patients, but they may be avoided in many instances by careful selection of the dose, taking into account the patient characteristics. Patient evaluation becomes very important in deciding whether an adjustment in the recommended standard dose is required or if it is safe to use the drug. In some cases, sex and age (e.g., fluoroquinolone-induced cartilage changes) are important characteristics that must be considered. Susceptibility to dose-dependent ADRs can be enhanced through factors that lead to greater drug exposure (i.e., decreased clearance and increased absorption) or that enhance the pharmacologic effect (e.g., concurrent medications; presence of epileptic foci in the brain). This hypersusceptibility may also be referred to as *patient idiosyncrasy.* For example, hypersusceptibility of collie dogs to ivermectin neurotoxicosis is related to an increased penetration of ivermectin into the central nervous system resulting from a genetic variation in P-glycoprotein responsible for pumping ivermectin out of the central nervous system.[1,2] Inhibition of metabolism or clearance of a drug can lead to accumulation to toxic levels. Glucocorticoids and nonsteroidal antiinflammatory drugs (NSAIDs) have synergistic effects on the occurrence of gastropathy. In the case of intrinsic toxicities that depend on bioactivation to toxic metabolites, factors that alter metabolism of the drug or affect cell defense mechanisms (e.g., deplete cellular glutathione) also enhance susceptibility.

The target organ and clinical signs depend on a number of factors. For pharmacologic toxicity, the observed signs depend on the pharmacologic effects. For intrinsic toxicities, the clinical manifestations depend on the affected organ. The target organ depends on accumulation of the drug, the cell defense mechanisms present in those organs, and the presence of the enzymes required for bioactivation of the drug. For example, the nephrotoxicity of aminoglycosides depends in part on their accumulation in renal tubular cells. If this accumulation is prevented by appropriate dosing regimens, then the risk of nephrotoxicity is decreased.

Treatment in dose-dependent toxicities should involve discontinuation of the drug and, if clinically indicated, removal of the drug from the body through appropriate measures. When appropriate, therapy can be directed at the specific pharmacologic target to either treat or prevent the ADR. Targeting to the appropriate pharmacologic target is critical. For example, misoprostol is the best and most effective therapy to prevent NSAID-induced gastropathy.[3] Once ulcers or erosions have occurred, discontinuation of the NSAID followed by appropriate therapy with sucralfate or an acid inhibitor such as omeprazole is appropriate. On the other hand, because loss of prostaglandin is not the primary mechanism behind steroid-induced gastric bleeding, misoprostol is not effective in preventing steroid-induced gastropathy.[4,5]

For intrinsic toxicities, drug withdrawal and supportive care are the most important steps. In certain cases, treatment directed at supporting specific cell-defense mechanisms may be appropriate. *N*-acetylcysteine can function both as an antioxidant to alleviate methemoglobinemia associated with acetaminophen toxicity and as a precursor for glutathione to scavenge reactive metabolites associated with hepatotoxicity.[6] Other antioxidants can also be employed to minimize the hematologic toxicity associated with acetaminophen.

In summary, dose-dependent ADRs are the most common class of ADRs encountered clinically. They can be minimized by careful and judicious use of the drug, taking into account the individual patient. The clinical manifestation and treatment is directed by the pharmacologic properties of the drug or the mechanism of the chemically based toxicity

and the target organ. The previous occurrence of a dose-dependent ADR in an animal is a clear indication for modification of the therapeutic regimen but does not necessarily contraindicate the use of the causative or a related drug in the patient.

Idiosyncratic Adverse Drug Reactions

Idiosyncratic ADRs are the second major class of ADRs. They are also referred to as *host-dependent, dose-independent, Type B (bizarre), Type II,* or *patient-related* ADR. These terms are often used interchangeably (Box 23-3). Unfortunately, because of our lack of understanding of the pathogenesis of many idiosyncratic ADRs, considerable confusion remains. Many clinicians use the term *idiosyncratic* to denote "unknown mechanism." This, however, is an inappropriate use of the term, particularly as the mechanisms of some idiosyncratic ADRs become elucidated. The defining characteristic of idiosyncratic ADRs is that they occur in patients at serum concentrations within the therapeutic range and will not occur in the majority of patients despite increasing the dose to otherwise toxic levels. That is, a specific interaction must occur between the patient and the drug to result in the adverse reaction. They are not classically dose-dependent and are highly dependent on the characteristics of the individual patient (host-dependent or patient-related). They usually cannot be reliably reproduced in an experimental setting. Thus both experimentally and in the clinical setting, their occurrence is unpredictable. The incidence of idiosyncratic ADRs is usually much lower than dose-dependent ADRs, but in certain populations they may be relatively frequent. Idiosyncratic ADRs depend on the chemical properties, not the pharmacologic properties, of the drug. They are distinguished from hypersusceptibility to pharmacologic or intrinsic toxicities in that they cannot be produced simply by elevating the dose or increasing the exposure in the target population or in experimental animals.

The clinical presentation of idiosyncratic drug reactions is variable and depends on the exact mechanism underlying the reaction. For example, malignant hyperthermia from halothane exposure in pigs and hepatotoxicity from sulfonamide antimicrobials are both idiosyncratic ADRs. They have a distinct pathogenesis and distinct clinical signs. However, the majority of idiosyncratic ADRs have characteristics associated with an immunologic pathogenesis and many people are referring to these types of reactions (hypersensitivity reactions, "drug allergies," immune-mediated drug reactions) when they use the term *idiosyncratic reactions.*

Drug hypersensitivity syndrome reactions, drug-induced hemolytic anemia or *thrombocytopenia, drug-induced lupus, drug fever,* and *drug-induced immune-mediated hepatitis* are all terms used to describe idiosyncratic reactions that are thought to have an immunologic basis. The clinical manifestations of *idiosyncratic hypersensitivity syndrome reactions* include such pathologic states as fever, lymphadenopathy, dermatopathies, hepatitis, nephritis, leukopenia, agranulocytosis, eosinophilia, thrombocytopenia, and aplastic anemia. This type of idiosyncratic reaction is relatively rare (frequency estimated to be <1/1000) and has a delayed onset, with clinical signs generally manifesting 7 to 14 days or longer after the start of therapy.[7] They are distinct from the typical drug allergy characterized by anaphylaxis or urticaria occurring immediately after drug administration, which is

Box 23-3 Examples of Idiosyncratic Adverse Drug Reactions in Veterinary Species

Propylthiouracil and methimazole toxicity in cats
Sulfonamide polyarthritis, thrombocytopenia, hepatotoxicity in dogs
Diazepam hepatotoxicity in cats
Mebendazole hepatotoxicity in dogs
Malignant hyperthermia triggered by halothane in pigs and dogs
Carprofen hepatitis

an immunoglobulin (Ig) E–mediated immediate hypersensitivity reaction directed against the drug.

Idiosyncratic reactions are important in veterinary medicine from a patient treatment standpoint, but they also have an influence on veterinary practice from another perspective. Fear of idiosyncratic toxicity in humans may be the reason for the banning of products for use in food animals (e.g., chloramphenicol causes aplastic anemia in rare individuals) or may lead to the withdrawal of a drug from the market. Some practitioners are reluctant to prescribe drugs that have been associated with idiosyncratic ADR in humans for fear of precipitating an event in the owner. In general, owners should be warned about the potential for drugs employed in veterinary practice to cause idiosyncratic reactions in humans (Box 23-4) and be instructed to wash their hands immediately after administering the drug to their animals. It is wise to inquire if the client or any immediate family members have drug allergies before dispensing a drug so that they can take appropriate precautions, such as wearing gloves and washing hands.

Pathogenesis of Idiosyncratic Adverse Drug Reactions

The pathogenesis of idiosyncratic ADRs is complex and depends on the reaction under consideration. For example, malignant hyperthermia is related primarily to mutations in the ryanodine receptor in the muscle sarcoplasmic reticulum[8] so that muscle calcium homeostasis cannot be maintained in the face of challenge with certain muscle relaxants, caffeine, and halothane. It is an idiosyncratic reaction because it requires a specific patient genotype and, although a mutated receptor is responsible for susceptibility, interaction of halothane with a specific receptor is not required to trigger the clinical event. The most common types of idiosyncratic reactions, however, involve cellular damage, leading to organ-specific damage, such as nephropathies, hepatopathies, blood dyscrasias, and dermatopathies. These reactions commonly depend on bioactivation to a reactive intermediate that can either directly cause cellular damage or trigger a pathologic immune response.

Clinical signs consistent with an immunologic pathogenesis for many idiosyncratic reactions include a delayed onset, typically 7 to 14 days after the start of therapy, fever, skin rash, and occasionally eosinophilia. The clinical signs are highly variable, depending on the patient and other clinical factors. Patients may display a clearly systemic disease with multiple organs affected, or may have a single abnormality, such as thrombocytopenia, neutropenia, skin rash, or hepatitis. A previous exposure to the drug may have occurred, but is not necessary. If an animal has tolerated a drug for more than 6 to 8 weeks, the likelihood of experiencing an idiosyncratic reaction drops. Despite the variable clinical presentation, it appears that common pathogenic events underlie the clinical disease.

Box 23-4 Some Drugs Associated with Idiosyncratic Reactions in Humans

- Penicillins
- Cephalosporins
- Erythromycin
- Sulfonamides
- Trimethoprim
- Chloramphenicol
- Aromatic anticonvulsants, including phenobarbital, phenytoin, carbamazepine, and felbamate
- Phenylbutazone
- Dipyrone
- Phenothiazine derivatives (chlorpromazine)
- Halothane, isoflurane
- Methimazole, propylthiouracil
- Captopril
- Procainamide

The immunologic responses that have been identified in cases of idiosyncratic reactions in humans and animals have been directed against either drug-modified proteins or autoantigens. Drugs are themselves generally too small to trigger an immunologic response; however, if they are metabolized to reactive metabolites, they may form drug-protein conjugates (Figure 23-1) that are capable of triggering an immunologic response.[3,9] The immune response may be directed against the drug-protein conjugate or against the protein itself (autoantigen) that was altered by the drug. The factors that determine which animals will

experience an idiosyncratic reaction remain obscure, although genetic and environmental differences in metabolic capacity and immunologic responsiveness appear to play roles.

The general scheme of Gell and Coombs for the classification of immunologic reactions is frequently applied to drug-induced immune reactions but is of limited usefulness in classifying idiosyncratic reactions. True drug allergies are typical type I (IgE-mediated) immediate hypersensitivity–type reactions, but idiosyncratic hypersensitivity syndrome reactions can have manifestations of type II (antibody-directed cell cytotoxicity), type III (immune-complex disease), and type IV (delayed hypersensitivity—cell-mediated) reactions to varying degrees within an individual patient. The basis of the target-organ specificity of idiosyncratic adverse reactions and the variable clinical presentations are not fully understood but appear to depend on the sites of bioactivation of the drug, the stability of the reactive metabolites formed, and the sites of covalent binding of the reactive metabolites, and the nature of the immune response in individual animals.

Clinical Pharmacology of Idiosyncratic Adverse Drug Reactions

From a clinical perspective, the major difficulty with idiosyncratic ADRs is their unpredictability. They are not dose-dependent and so cannot be avoided by careful dose selection. Although they are usually rare, they are potentially fatal. Although their delayed onset means that a previous short-term exposure does not guarantee safety, if an idiosyncratic reaction has not occurred during or after a prolonged exposure (e.g., 4-8 weeks), it is unlikely to occur on subsequent exposures. If a reaction is a true drug allergy (e.g., IgE mediated), a previous exposure is required and reexposure may precipitate an acute anaphylactic response. The temporal relationships for immediate hypersensitivity reactions are thus very different from the delayed-onset hypersensitivity reaction described previously.

A major dilemma with idiosyncratic reactions is diagnosis. Often the clinical signs may not be clearly distinguishable from those associated with the primary disease process. The clinician should consider idiosyncratic reactions on their differential diagnosis list when unexpected changes in clinical progress occur.

Owners should be warned of the possibility of idiosyncratic ADRs. Drug withdrawal is the most important step and owners should be told to stop the drug immediately should any untoward events occur. Clinical manifestations depend on the target cell or organ, but they are usually systemic reactions. Often the first signs noted by the owner are lethargy, depression, and anorexia. The treatment should be directed at the clinical manifestation of the ADR. The effectiveness of corticosteroids in treating idiosyncratic hypersensitivity ADRs is poorly documented. However, anecdotal experience in humans and the documentation of an immunologic component to the reactions suggests that animals not responding to supportive care should be treated with high-dose corticosteroids (e.g., immunosuppressive doses, not antiinflammatory doses). Animals that manifest neutropenia as a clinical sign

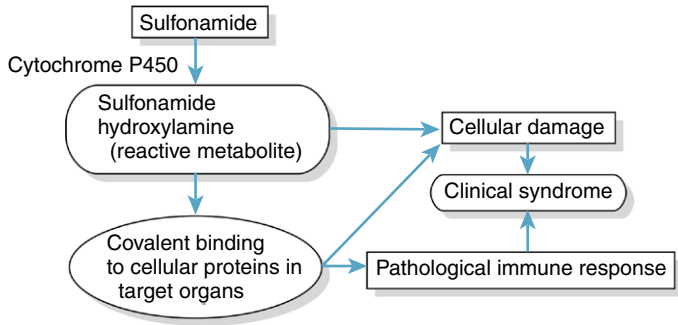

Figure 23-1 Simplified scheme of the pathogenesis of sulfonamide hypersensitivity reactions.

should be treated with an appropriate broad-spectrum prophylactic antibiotic to protect against secondary bacterial infections.

If an animal has experienced an idiosyncratic ADR, use of the suspected or a chemically related drug should be considered contraindicated unless no other alternative exists for a life-threatening illness. In that case, a desensitization protocol should be considered as part of the reinitiation of therapy. Unfortunately, there is essentially no published experience with these protocols in veterinary patients.

Incidence of Adverse Drug Reactions

The incidence of many ADRs in veterinary medicine is often unknown because of the difficulties in attributing clinical events to drug administration and the dependence on spontaneous reporting of ADRs. Many ADRs are not apparent until the drug has been used in a large number of genetically variant animals. The newest drug available is not necessarily the best or safest choice for therapy, particularly when considering drugs developed for use in humans. A drug relatively safe for use in humans is not necessarily safe in dogs and cats. Clinical studies demonstrating safety of drugs should also be evaluated carefully to determine if the patient population studied is representative of the population in which you wish to use the drug.

Small experimental studies at higher-than-normal clinical doses may indicate what dose-dependent toxicities to be aware of and give an indication of the therapeutic index, but they do not determine the incidence of dose-dependent or idiosyncratic reactions to expect at typical clinical doses in the general patient population. In general, the large clinical trials and postmarketing surveillance necessary to determine the incidence of ADRs are not available in veterinary medicine. Many times the impression of the incidence or importance of an ADR is colored by personal experience. Although this may be useful experience, it can often be misleading. In general, dose-dependent ADRs tend to be more common but less serious, whereas idiosyncratic ADRs tend to be relatively rare but more serious (e.g., the incidence of sulfonamide hypersensitivity reactions in dogs is probably less than 1/1000). The unpredictability and potential severity of idiosyncratic toxicities gives them an effect disproportionate with their incidence.

It is always important to remember that the likelihood of an ADR in the patient being treated is more important than the frequency of occurrence in the general population and the decision to use the drug should be based on an assessment of risk in the individual patient. Particular vigilance for adverse reactions in neonates, older animals, animals with a previous history of an ADR, and animals receiving multidrug therapy is required. Many factors contribute to the occurrence of an ADR in a given patient. Drug factors include dose, duration, vehicle, and drug interactions from concomitant therapy. Patient factors include species or breed, genetic and environmental variation in drug metabolism, age, sex, body composition (fat vs. lean weight), pregnancy status (teratogenicity), concurrent disease states, immunologic status, and concurrent drug or chemical exposures. How these factors contribute to the development of an ADR depends on the drug and the type of toxicity.

Diagnosis of an Adverse Drug Reaction

Attribution of a clinical event to a drug can be difficult. Perhaps the most important clues to link a clinical event with drug treatment are an appropriate temporal relationship, a previous report of a similar ADR associated with the drug, and a lack of another clinical explanation of the event. There are many algorithms or probability methods that have been developed for diagnosing potential ADRs. However, essentially they simplify down to the following questions, which reflect a rational approach to attributing a clinical event to an ADR:

1. Is the temporal association of the event with drug treatment appropriate for the type of ADR? If signs were present before drug administration or occur long (generally 1 month, but could be longer in some situations) after drug discontinuation, they are

unlikely to be related to the drug. The temporal association should be appropriate for the suspected ADR and not incompatible with the pathogenesis of the suspected reaction. For example, an anaphylactic reaction would not occur 7 days after drug administration.

2. Has the suspected ADR been previously reported? If the signs are consistent with a previously reported ADR, the probability is much higher that the signs are the result of an ADR. If the ADR has not been previously reported, the probability is lower but this does not necessarily eliminate the possibility of an ADR. The drug company, the drug insert (particularly the safety section), the FDA's Adverse Event Reporting System website and drug handbooks are good places to find drug-specific information.
3. Are there other possible explanations for the clinical signs? It is important to differentiate clinical signs attributable to the disease from those that may be related to the drug. Other drugs that the animal may have been receiving should also be considered.
4. Has the drug been administered previously to the patient and what was the outcome? This needs to be interpreted in a manner consistent with the suspected ADR. If a previous exposure produced a similar response, it is more likely to be drug related. On the other hand, a previous uneventful exposure, although decreasing the likelihood, does not rule out an ADR.
5. Do the signs disappear with drug withdrawal and recur with reexposure? It is generally not ethical to reexpose an animal to a drug suspected of causing an ADR, but this may occur inadvertently or in clinical situations in which alternative therapies are limited.
6. Is there evidence of dosing error or elevated plasma concentrations? When in doubt, the dose should always be recalculated. If available, therapeutic drug monitoring (TDM) can be a useful tool in deciding if toxic drug concentrations exist.
7. Are predisposing factors present in the patient? Is the animal receiving other drugs likely to have pharmacodynamic or pharmacokinetic interactions with the drug in question? For example, use of an NSAID and an aminoglycoside may increase the risk of nephrotoxicity, whereas concurrent use of an NSAID and a glucocorticoid will increase the likelihood of gastric ulceration. Does the animal have a concurrent disease, which may increase susceptibility to an adverse event (i.e., underlying hepatic or renal disease or diabetes)?

Drug Interactions

Drug interactions refer to in vivo interactions between drugs. Drug interactions may be relative or absolute contraindications to the concurrent use of drugs. Drug interactions may lead to a diminished or an enhanced effect of a drug or may lead to the occurrence of toxicity. In general, drug interactions have either a pharmacodynamic or a pharmacokinetic basis.

Pharmacodynamic interactions are the pharmacologic effects of two drugs that may be opposite to each other (e.g., metoclopramide and dopamine have opposite effects on renal blood flow), work at the same site (e.g., two NSAIDs), or enhance the effects through sequential or complementary effects (e.g., effects of glucocorticoids on β_2-receptors and use of a β_2-agonist, such as terbutaline; effects of corticosteroids and NSAIDs on gastric integrity). Drug combinations should be assessed carefully for drug interactions before their use. There are many possible pharmacodynamic interactions, some of which are listed in Table 23-1.

Pharmacokinetic interactions occur when drugs inhibit or enhance each other's metabolism or renal excretion (Table 23-2). One drug may also displace another from protein binding sites, leading to greater free drug concentrations and hence pharmacologic effect. Drug interactions can lead to the occurrence of ADRs at doses or plasma concentrations lower than typically expected, depending on the mechanism of the interaction.

Knowledge of pharmacokinetic drug interactions in small animals remains limited. Probably the most common mechanism for pharmacokinetic interactions is metabolic

Table 23-1 Some Pharmacodynamic Drug Interactions

Drugs	Interaction	Mechanism
Glucocorticoids and NSAIDs	Increased gastrointestinal toxicity	NSAIDs primarily inhibit prostaglandin production, whereas corticosteroids increase gastric acid secretion and decrease mucosal defenses.
Furosemide and ACE inhibitors	Increased diuretic effect	ACE inhibitors decrease aldosterone secretion, which subsequently increases the diuretic effect of furosemide.
Furosemide and thiazide diuretics	Increased diuretic effect	Work at different sites in diuretics the renal tubule, leading to a synergistic diuretic effect.
Glucocorticoids and β-2 agonists	Increased bronchodilatory effect	Glucocorticoids upregulate and increase the responsiveness of β-receptors.
Sucralfate and gastric acid secretion inhibitors	Decreased efficacy of sucralfate	Sucralfate requires an acid pH for maximal efficacy; if gastric acid secretion inhibitors (e.g., cimetidine, ranitidine, omeprazole) increase gastric pH, efficacy of sucralfate may be decreased.
NSAIDs and anticoagulants	Increased bleeding	Combination of inhibition of platelet aggregation (NSAIDs) with inhibition of other coagulation pathways (heparin, warfarin) will lead to increased bleeding tendency.
Opioids and general anesthetics	Enhanced respiratory depression by opioids	General anesthetics generally enhance the respiratory depressant effects of opioids.

ACE, Angiotensin-converting enzyme; *NSAID,* nonsteroidal antiinflammatory drug.

interaction at the level of cytochrome P450 in the liver. The cytochrome P450 family of drug-metabolizing enzymes is a unique system. It is composed of more than 20 different enzymes, of which 4 or 5 are likely responsible for the majority of drug metabolism. There are significant species differences in the regulation and substrate specificity of these enzymes. Thus although there are many similarities between species, cytochrome P450-based drug interactions in dogs or cats are not necessarily the same as those in humans. Hence, although we rely heavily on extrapolation of potential drug interactions in humans to drug interactions in dogs and cats, this may not always be reliable. Further work is required in companion animals to fully elucidate the extent of clinically significant metabolic drug interactions. Nevertheless, a reasonable rule of thumb is to avoid when possible combining drugs with a clearance that depends on metabolism and when interactions have been reported in other species unless they have been shown not to occur in veterinary species. Table 23-2 summarizes some of the possible drug interactions and their mechanisms in small animals, primarily dogs.

Drug Incompatibilities

Drug incompatibilities are chemical interactions that occur between drugs in vitro. Drugs that are incompatible should not be mixed together in a syringe or fluid bag. As a general rule, do not mix drugs unless necessary and then only if you know they are compatible.

Table 23-2 Some Pharmacokinetic Drug Interactions in Dogs

Drug	Interaction	Mechanism
PB	Propranolol—decreased efficacy Lidocaine—increased clearance Chloramphenicol—decreased efficacy	PB induces several cytochrome P450 enzymes, increasing the metabolism of several drugs. The increased hepatotoxicity when combinations of anticonvulsants are used is likely because of increased bioactivation.
Cimetidine	Theophylline—increased toxicity Metronidazole—increased toxicity Midazolam—increased effects Propranolol—increased effects	Cimetidine is a moderate inhibitor of several different P450 enzymes and so decreases metabolism of several drugs.
Chloramphenicol	Phenobarbital—pharmacologic toxicity	Chloramphenicol inhibits phenobarbital metabolism.
Enrofloxacin	Theophylline—pharmacologic toxicity	Enrofloxacin inhibits theophylline clearance.
Digoxin	Quinidine, verapamil, ketoconazole, itraconazole—decrease digoxin clearance leading to toxicity	These drugs inhibit P-glycoprotein–dependent renal clearance of digoxin.

PB, Phenobarbital.

Most standard drug handbooks contain information on drug incompatibilities and should be consulted before mixing drugs.

Drug-Induced Hepatotoxicity

Drug-induced liver damage remains one of the most important ADRs. Because of its strategic location between the intestine and the systemic circulation, the liver can be exposed to relatively high drug concentrations. When coupled with its high metabolic capacity, particularly through the cytochrome P450 enzymes, the liver has the greatest exposure to reactive metabolites. Intrinsic hepatotoxicity is often related to bioactivation to reactive metabolites that damage liver cells and cause hepatic necrosis (e.g., acetaminophen hepatotoxicity; see Chapter 30). It may also occur subsequent to disruption of mitochondrial function or disruption of bile transport, leading to cholestatic injury. Idiosyncratic hepatotoxicity is nearly always related to bioactivation to reactive intermediates. Dose-dependent hepatopathies are usually identified during the drug development process but may still contribute to clinically important drug-induced toxicity. However, the majority of serious cases of hepatotoxicity are idiosyncratic in nature.

Box 23-5 provides a list of the most clinically important hepatotoxic drugs in small animals. This is not a complete list of potential hepatotoxins but rather a list of drugs that have been associated with hepatotoxicity in dogs and cats. There are other drugs that have been shown to be hepatotoxic in other species (humans and rodents) but that have not been reported or observed to cause clinically significant hepatotoxicity in veterinary species. For example, many complementary or alternative health products (e.g., certain kava products and germander) have been reported to cause hepatotoxicity in humans and conceivably may do so in animals, but no specific reports exist.

Phenobarbital

One of the most commonly used hepatotoxins that remains a clinical challenge for veterinarians is phenobarbital. A small percentage of dogs on chronic phenobarbital administration will develop hepatopathy and eventually hepatic cirrhosis.[10,11] Phenobarbital is known to cause elevations in serum liver enzyme activities that are not directly correlated to the occurrence or degree of hepatotoxicity.[12,13] Although elevations in serum liver enzyme activities have been attributed to enzyme induction, this is far from clear.[12,13] Minor elevations in serum alanine aminotransferase (ALT) and alkaline phosphatase (AP) activities are generally not a cause for concern, but elevations in ALT that are three to five times the upper limit of normal should be monitored carefully. It should also be noted that dogs with significant hepatic cirrhosis may not have marked elevations in serum liver enzyme activities despite extensive liver damage. If elevations in AP and ALT activities are accompanied by decreases in albumin concentration or serum urea nitrogen, they should be considered more seriously. Additional diagnostic work-up, including a bile acid test, is indicated. Although hepatic biopsy may help to document actual liver damage, no histopathologic changes that are hallmarks of early phenobarbital hepatotoxicity have been identified.[12]

Dogs with high serum concentrations of phenobarbital (>30 to 40 mcg/mL) are thought to be at increased risk of phenobarbital-associated liver damage. Although elevated serum phenobarbital concentrations are often observed in dogs that have developed hepatopathy,[11] it has been difficult to separate cause and effect. That is, loss of liver function may lead to decreased clearance of phenobarbital and elevated serum concentrations. Dogs with low serum concentrations of phenobarbital may still develop liver disease (Cribb, unpublished observations). Yearly evaluation of serum enzyme activities is often recommended but has not been clearly shown to prospectively identify dogs at risk of developing hepatotoxicity. Unexpected increases in serum phenobarbital concentrations may also be an indication of hepatic dysfunction. If dogs are removed from phenobarbital early in the course of hepatic damage, recovery can occur. However, once the hepatic damage has proceeded to the stage of significant cirrhosis, recovery appears less likely. Dogs should be carefully weaned from phenobarbital and therapy with an alternative anticonvulsant, such as potassium bromide or levetiracetam, instituted if hepatopathy is demonstrated or highly suspected.

Box 23-5 Clinically Important Hepatotoxins

Intrinsic Hepatotoxins
Acetaminophen (dogs)
Phenobarbital, primidone, phenytoin
Glucocorticoids
Mitotane
Tetracycline
Cyclosporine
Griseofulvin
Thiacetarsamide
Ketoconazole

Idiosyncratic Hepatotoxins
Diazepam in cats
Propylthiouracil and methimazole in cats
Trimethoprim and sulfonamide antimicrobials in dogs
Mebendazole
Carprofen
Diethylcarbamazine and oxibendazole

Idiosyncratic Hepatotoxicity

Idiosyncratic hepatitis clearly occurs with sulfonamides, carprofen, methimazole, diethylcarbamazine-oxibendazole, mebendazole, and diazepam in companion animals. In all cases, the incidence is rare (probably less than 1/1000). The most common signs of idiosyncratic hepatotoxicity are acute onset of anorexia and malaise within the first 2 to 8 weeks of therapy. However, hepatotoxicity can develop sooner or may have a delayed onset. Although periodic screening for elevations in serum liver enzyme activities is sometimes recommended for idiosyncratic hepatotoxins, there is no evidence that this is effective in predicting or preventing hepatotoxicity. The onset of liver damage is quick once it occurs so that dogs or cats can go from normal serum activities to clinical liver damage in a few days' time. When commencing drugs that are associated with idiosyncratic hepatotoxicity, it is useful to establish a baseline

for serum activities before the start of therapy. It is also important to remember that fluctuations of serum enzyme activities out of the normal range are not uncommon and simple elevation is not necessarily an indication to stop the medication, although it is a clear indication for enhanced clinical and biochemical monitoring of the patient.

The most important treatment for idiosyncratic hepatotoxicity is immediate cessation of therapy and diagnosis. The owners should be instructed to immediately stop the drug and bring the animal in for evaluation should it become anorexic or depressed. Serum liver enzyme activities should be determined and, if elevated, a presumptive diagnosis of idiosyncratic hepatotoxicity is made. Clinical experience suggests that continued treatment once the reaction has started is more likely to lead to a fatal outcome. Although hepatic biopsy may serve to confirm the hepatic damage, this is rarely indicated and is probably not helpful in differentiating idiosyncratic hepatotoxicity from other causes. There is no specific therapy for idiosyncratic hepatotoxicity. In severe cases that continue to deteriorate, treatment with corticosteroids, on the assumption that there is an underlying immune-mediated pathogenesis, can be tried, but there are no good clinical studies to support this approach in human or veterinary medicine.

Drug-Induced Nephrotoxicity

Because of their large perfusion (approximately 25% of the cardiac output), their ability to concentrate and accumulate toxicants, and their high metabolic activity, kidneys are highly vulnerable to drug-induced toxic injury. The most common drugs associated with nephrotoxicity in small animals are presented in Box 23-6. It is important to note that Box 23-6 and this section describe toxic events associated with drugs that are intrinsically nephrotoxic and do not address drugs, such as furosemide, that can cause renal dysfunction through their pharmacologic properties. As a general principle, two potentially nephrotoxic drugs should not be used together and nephrotoxic drugs should be avoided in animals with known or suspected renal dysfunction. To minimize the risk of nephrotoxicity, it is important to maintain the hydration status of the animal and ensure adequate urine output.

Aminoglycosides

Nephrotoxicity is a major limiting factor for aminoglycoside administration. Aminoglycoside toxicity results in renal failure with hypoosmotic polyuria, enzymuria, glucosuria, and proteinuria. Serum creatinine can be increased after a few days of administration. Renal failure is usually reversible but can become irreversible if administration is prolonged. Toxic mechanisms are not fully understood but probably involve active uptake of the drug by tubular cells and accumulation in lysosomes, Golgi apparatus, and endoplasmic reticulum. Histopathologically, aminoglycoside tubular cell toxicity is associated with formation of myeloid bodies that result from the accumulation of phospholipids in a concentric lamellar disposition within enlarged and dysfunctional lysosomes. Rupture of overwhelmed lysosomes is believed to be a major trigger for tubular cell death. Impaired synthesis of protective prostaglandins and inhibition of mitochondrial respiration and of protein synthesis have also been proposed as additional toxic mechanisms.

Box 23-6 Drugs Associated with Nephrotoxicity

- Aminoglycosides
- Amphotericin B
- Cyclosporin A
- Nonsteroidal antiinflammatory drugs
- Sulfonamides
- Tetracyclines
- Radiocontrast agents
- Methoxyflurane

As low trough levels of aminoglycosides have been associated with decreased nephrotoxicity in multiple human trials, single daily administration is currently used in humans and horses.[14,15] However, multiple once-daily intramuscular administrations of gentamicin have been associated with signs of renal damage in dogs (increased serum creatinine and blood urea nitrogen, renal tubular casts, and decreased specific urine gravity) and so care must still be exercised.[16]

To minimize the risks associated with aminoglycoside-induced nephrotoxicity, patient hydration should be maintained, co-administration with other nephrotoxic or diuretic drugs (antiinflammatory drugs, furosemide) should be avoided, and TDM should be used. TDM dose adjustment is related to the patient's pharmacokinetic parameters and minimal inhibitory concentration (MIC) of the causative bacteria. The goal is to provide a dosage regimen that produces a peak concentration 8 to 10 times more than the MIC and a trough concentration of less than 2 mcg/mL, and preferably less than 1 mcg/mL. Prostaglandin analogue supplementation (misoprostol) does not seem to be effective for the prevention or treatment of gentamicin-induced renal injury.

β-Lactams

Cephalosporins have been commonly cited as being potentially nephrotoxic drugs. The early cephalosporins (i.e., cephaloridine) had clear nephrotoxic properties and a number of analogues were also shown to cause renal damage. The damage related to cephalosporins was selective to the S2 segment of the proximal tubule as a result of active uptake through the organic anion transport system. However, none of the currently used cephalosporins appears to be associated with a significant risk of nephrotoxicity.

Among other β-lactams, only imipenem is significantly nephrotoxic. Therefore it is administered in combination with cilastatin to inhibit its metabolism by dehydropeptidase I on the brush borders of renal tubular cells to minimize its uptake into renal tubular cells and subsequent nephrotoxicity.

Amphotericin B

In its conventional colloidal dispersion form (Fungizone), amphotericin B is associated with high risks of renal toxicity in humans and in veterinary species. It induces an intense renal arteriolar vasoconstriction and is directly cytotoxic in relation with its ability to bind cholesterol and form membrane pores, leading to tubular necrosis. Several protocols have been developed for the administration of amphotericin B to minimize nephrotoxicity. New lipid-based formulations have lowered the toxic events related to amphotericin B administration in human medicine.[17] Clinical trials have not been performed in veterinary medicine to date and therefore use of safer azole antifungals is preferred to amphotericin B wherever possible.

Cisplatin

Nephrotoxicity is the major limiting factor of cisplatin administration in humans and is associated with acute renal failure and chronic renal failure. Although not fully documented in veterinary clinical settings, renal toxicity of cisplatin should be carefully monitored. Toxicity results from bioactivation of cisplatin to more toxic metabolites in the renal tubular cells, oxidative stress, and direct cytotoxicity of cisplatin through the inhibition of DNA and protein synthesis.

Cyclosporine A

As cyclosporine A renal toxicity is a common problem in human medicine, its increased use in veterinary medicine, especially for dermatologic diseases, has raised the question of nephrotoxic risks in veterinary species. In contrast to humans, dog and cat kidneys do not seem to be a major target of cyclosporine toxicity. Very few cases of renal impairment have been reported in the literature.[18]

Nonsteroidal Antiinflammatory Drugs

Renal synthesis of prostaglandins by cyclooxygenase constitutes a regulatory mechanism to cope with diminished renal perfusion that may occur in volume-contracted states (i.e., dehydration, diuretics) or reduced cardiac output (i.e., congestive heart failure).[19] Because NSAIDs can inhibit prostaglandin synthesis, they may impair renal function in high-risk patients, culminating with acute renal failure. The nephrotoxic potential of selective COX-2 inhibitors is unclear in human medicine[20] and has not been addressed thoroughly

in veterinary species. It is clear, however, that relatively selective COX-2 inhibitors can cause nephrotoxicity under the right circumstances. NSAIDs can also damage the kidney by direct toxicity, usually after massive administration. Both mechanisms may be involved in acute renal papillary necrosis, which has been reported in dogs and cats.[21,22]

Radiocontrast Agents

Hyperosmolar radiocontrast agents have been associated with renal damage and decreased renal clearance, especially in dogs with heart failure. Transient renal ischemia, direct tubular toxicity, and changes in glomerular capillary permeability have been proposed to explain these alterations.[23] New nonionic agents with lower osmolarity (i.e., iopamidol) have decreased risks of toxicity.

Sulfonamides

Idiosyncratic toxicity of sulfonamides in dogs has been associated with proteinuria, which may result from drug-induced glomerulonephritis.[24,25] However, renal toxicity is less common than some other signs (i.e., fever, arthropathy, and blood dyscrasias). Sulfonamides may also cause crystalluria if high doses are administered to animals or if they are dehydrated.

Tetracyclines

In dogs, high doses of oxytetracycline (25 mg/kg intravenously) have been associated with tubular nephropathy. Clinical signs include vomiting, diarrhea, dehydration, and isosthenuria with azotemia, hypercreatininemia, and hyperphosphatemia.[26] Renal damage has also been described with the use of outdated or degraded tetracycline.

Conclusion

By taking a rational approach to ADRs based on an understanding of the general principles of mechanisms of toxicity, the veterinary clinician can go beyond the consultation of a list of adverse reactions to a thoughtful assessment of risk and causality in our patients. This will lead to the safer, more appropriate use of drugs and better patient care. Although all veterinarians will experience the occurrence of ADRs in their patients, careful use of drugs will minimize the frequency and consequences.

References

1. Mealey KL, Bentjen SA, Gay JM, et al: Ivermectin sensitivity in collies is associated with a deletion mutation of the mdr1 gene, *Pharmacogenetics* 11:727–733, 2001.
2. Paul AJ, Tranquilli WJ, Seward RL, et al: Clinical observations in collies given ivermectin orally, *Am J Vet Res* 48:684–685, 1987.
3. Cribb AE: Adverse effects of non-steroidal anti-inflammatory drugs. In Ka W, editor: *Clinical pharmacology: principles and practice*, Las Vegas, 1998, Western Veterinary Conference.
4. Hanson SM, Bostwick DR, Twedt DC, et al: Clinical evaluation of cimetidine, sucralfate, and misoprostol for prevention of gastrointestinal tract bleeding in dogs undergoing spinal surgery, *Am J Vet Res* 58:1320–1323, 1997.
5. Rohrer CR, Hill RC, Fischer A, et al: Efficacy of misoprostol in prevention of gastric hemorrhage in dogs treated with high doses of methylprednisolone sodium succinate, *Am J Vet Res* 60:982–985, 1999.
6. St Omer VV, McKnight ED III: Acetylcysteine for treatment of acetaminophen toxicosis in the cat, *J Am Vet Med Assoc* 176:911–913, 1980.
7. Cribb AE, Lee BL, Trepanier LA, et al: Adverse reactions to sulphonamide and sulphonamide-trimethoprim antimicrobials: clinical syndromes and pathogenesis, *Adverse Drug React Toxicol Rev* 15:9–50, 1996.
8. Fujii J, Otsu K, Zorzato F, et al: Identification of a mutation in porcine ryanodine receptor associated with malignant hyperthermia, *Science* 253:448–451, 1991.
9. Park BK, Coleman JW, Kitteringham NR, et al: Drug disposition and drug hypersensitivity, *Biochem Pharmacol* 36:581–589, 1987.
10. Bunch SE: Hepatotoxicity associated with pharmacologic agents in dogs and cats, *Vet Clin North Am Small Anim Pract* 23:659–670, 1993.

11. Dayrell-Hart B, Steinberg SA, VanWinkle TJ, et al: Hepatotoxicity of phenobarbital in dogs: 18 cases (1985-1989), *J Am Vet Med Assoc* 199:1060–1066, 1991.
12. Gaskill C, Miller LM, Mattoon JS, et al: Liver histopathology and serum alanine aminotransferase and alkaline phosphatase activities in epileptic dogs receiving phenobarbital, *Vet Pathol* 42:147–160, 2005.
13. Muller PB, Taboada J, Hosgood G, et al: Effects of long-term phenobarbital treatment on the liver in dogs, *J Vet Intern Med* 14:165–171, 2000.
14. Godber LM, Walker RD, Stein GE, et al: Pharmacokinetics, nephrotoxicosis, and in vitro antibacterial activity associated with single versus multiple (three times) daily gentamicin treatments in horses, *Am J Vet Res* 56:613–618, 1995.
15. Tudor RA, Papich MG, Redding WR, et al: Drug disposition and dosage determination of once daily administration of gentamicin sulfate in horses after abdominal surgery, *J Am Vet Med Assoc* 215:503–506, 1999.
16. Albarellos G, Montoya L, Ambros L, et al: Multiple once-daily dose pharmacokinetics and renal safety of gentamicin in dogs, *J Vet Pharmacol Ther* 27:21–25, 2004.
17. Fukui H, Koike T, Saheki A, et al: Evaluation of the efficacy and toxicity of amphotericin B incorporated in lipid nano-sphere (LNS), *Int J Pharm* 263:51–60, 2003.
18. Robson D: Review of the pharmacokinetics, interactions and adverse reactions of cyclosporine in people, dogs and cats, *Vet Rec* 152:739–748, 2003.
19. Whelton A: Nephrotoxicity of nonsteroidal anti-inflammatory drugs: physiologic foundations and clinical implications, *Am J Med* 106:13S–24S, 1999.
20. Sandhu GK, Heyneman CA: Nephrotoxic potential of selective cyclooxygenase-2 inhibitors, *Ann Pharmacother* 38:700–704, 2004.
21. Silverman LR, Khan KN: "Have you seen this?" Nonsteroidal anti-inflammatory drug-induced renal papillary necrosis in a dog, *Toxicol Pathol* 27:244–245, 1999.
22. Wolf DC, Lenz SD, Carlton WW, et al: Renal papillary necrosis in two domestic cats and a tiger, *Vet Pathol* 28:84–87, 1991.
23. Margulies K, Schirger J, Burnett J Jr: Radiocontrast-induced nephropathy: current status and future prospects, *Int Angiol* 11:20–25, 1992.
24. Giger U, Werner LL, Millichamp NJ, et al: Sulfadiazine-induced allergy in six Doberman pinschers, *J Am Vet Med Assoc* 186:479–484, 1985.
25. Trepanier LA, Danhof R, Toll J, et al: Clinical findings in 40 dogs with hypersensitivity associated with administration of potentiated sulfonamides, *J Vet Intern Med* 17:647–652, 2003.
26. Moalli MR, Dysko RC, Rush HG, et al: Oxytetracycline-induced nephrotoxicosis in dogs after intravenous administration for experimental bone labeling, *Lab Anim Sci* 46:497–502, 1996.