REFERENCES

1. Hornfeldt CS, Jacobs MR. A poison information service for small animals offered by a regional poison center. *Vet Hum Toxicol* 33:339, 1991.
2. Hornfeldt CS, Murphy MJ. 1990 Report of the American Association of Poison Control Centers: Poisoning in animals. *J Am Vet Med Assoc* 200:1077, 1992.
3. Hornfeldt CS, Murphy MJ. Summary of small animal poison exposures in a major metropolitan area. In Bonagura JD, editor: *Current veterinary therapy: small animal practice XIII*. Philadelphia, 1999, WB Saunders.
4. Anonymous. Core content for veterinary toxicology. *Vet Hum Toxicol* October 38(5):[illegible] 1996.

14 Adverse Drug Reactions

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Adverse drug reactions are an ever-present threat when drugs are used in clinical practice. 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. Drug toxicity includes all toxicity associated with a drug, including that observed in overdose situations (e.g., poisonings with drugs). *Side effects* generally refers to nondeleterious effects that may occur during therapy, such as polydipsia and/or polyuria in dogs given 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. 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 ADRs are a significant contributor to patient morbidity and mortality.

When using any 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 th
is dependent on the relative risks and benefits of the drug compared
the risk of no treatment or the risk associated with alternative treat
such as surgery. A drug should not be used without a specific thera
goal so that efficacy and toxicity can be balanced appropriately.

When assessing risk, the veterinarian needs to look at the popul
risk (How frequent and severe is the ADR?) and the individual risk
this patient have any characteristics that increase or decrease
Assessing risks of an ADR may be frustrating because the inform
necessary to truly assess risk is not available. Veterinarians are often
drugs with limited published clinical data in veterinary species. There
an understanding of the mechanism or pathogenesis of ADRs is
helpful, as discussed in detail below. Finding information on the a
frequency and severity of ADRs is often difficult.

Although mechanisms are in place for reviewing and recording A
of licensed products, information for drugs used off-label is less rea
available. Many standard veterinary textbooks list adverse reactions
have been reported to drugs without incorporating information on spe
differences or indeed noting if the adverse reactions have been repo
in veterinary species. Further, information on the frequency and seve
of ADRs is often lacking. For licensed animal products, the company m
keting the product is a good source of information, either through in
mation on the package insert or through direct contact with the compa
The Center for Veterinary Medicine, U.S. Food and Drug Administrat
and the Veterinary Drugs Directorate, Health Canada maintain a rec
of adverse events that have been reported and use this information to r
ommend changes in drug labels when appropriate. The FDA's databas
available through its website (http://www.fda.gov/cvm/index/ade/AD
eport.htm) and is a good source of up-to-date information on poten
ADRs that have been reported.

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

In summary, to make the most use of the information available,
tailor our decisions to the individual patient, and to make rational clini
decisions, an understanding of the basic principles of ADRs is invaluab

fore this chapter will first present general principles that can be
d in many clinical situations to guide therapeutic decisions. This will
lowed by a brief overview of hepatic and renal ADRs.

SSIFICATION OF ADVERSE DRUG CTIONS

al different systems for classifying ADRs exist, based on either clini-
resentation or mechanism of toxicity. The clinical presentations of
Rs are dependent on the pharmacological and chemical properties of
drug and the target organ damaged. In many cases, the exact mecha-
of toxicity is not known or understood. This can make classification
ug toxicities difficult, but does not prevent us from employing a broad
anistic classification that will assist in making clinical decisions.

se-dependent adverse drug reactions

st ADRs are dose-dependent. That is, the larger the dose, the greater
number of patients affected and/or the more severe the reaction.
se types of ADRs or toxicities are generally predictable and can be
roduced in experimental models. The majority of patients will experi-
e a dose-dependent ADR if the drug is given at a sufficient dose or for
fficient period of time. In a clinical setting, the frequency of these
tions depends largely on the care with which the products are used
knowledge of specific dose adjustment that may be required. They
occur at therapeutic doses or plasma concentrations in some individ-
, but they are commonly associated with elevated drug plasma concen-
ions resulting from altered pharmacokinetics in the patient caused by
current disease, pregnancy, age, or a drug interaction. This is particu-
y true for drugs with a narrow therapeutic index, where changes in
rmacokinetics result in a functional overdose despite use of a normally
therapeutic dosage regimen.

Patients may be *hypersusceptible* to a dose-dependent ADR, so that they
e a reaction at doses (or plasma concentrations) lower than typically
served. Hypersusceptibility may result from altered pharmacokinetics,
ier through disease, genetic variation, or a drug interaction, that leads
higher than expected drug concentrations in the circulation or at spe-
ic sites for a given drug dose. The majority of dose-dependent toxicities
be avoided by careful and appropriate selection of the dose, taking
o consideration patient characteristics and concurrent drug use.

The occurrence of a dose-dependent toxicity in a patient is no
sarily an absolute contraindication to future use of the drug. If possi
reason for the occurrence of the ADR should be ascertained. For e
was a dosing error made or was the ADR the result of a drug inte

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

Pharmacological toxicity

Pharmacological toxicity (also referred to as mechanism-based, re
mediated, augmented, or Type A adverse reactions) is a form of
dependent ADR that arises through exaggerated or undes
pharmacological effects of a drug (Box 14-1). Pharmacological toxi
dependent on an interaction of the parent drug or a pharmacolo
active metabolite with a specific target or receptor. These effects m
related to the intended therapeutic target, or to additional, insepa
secondary pharmacological actions. In the latter instance, the ADR
often called "side effects." For example, a minor side effect woul
mydriasis associated with the use of atropine as a preanesthetic age

Intrinsic toxicity

Intrinsic toxicity is determined by the chemical properties of the drug
its pharmacological properties. That is, the toxicity is dependent o
intrinsic chemical properties of the drug—hence the term intrinsic t
ity. The drug or its metabolites do not bind to specific receptors to e
these toxicities, but instead bind nonspecifically to a variety of protei
nucleic acids, or disrupt membranes or organelle function (Box 1

Box 14–1

Examples of Pharmacological Toxicities

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

14–2

ples of Intrinsic Toxicities

glycoside nephrotoxicity and ototoxicity
inophen methemoglobinemia/hemolytic anemia
inophen hepatotoxicity
amide-induced hypothyroidism
ubicin cardiotoxicity

sic toxicity may have a short time course (e.g., acetaminophen
ity) or a longer time course (e.g., bone marrow suppression with chemo-
py). It is also referred to as Type A (augmented) or Type C (chronic
rse reactions, depending on the nature and time course of the
ion.

trinsic toxicity is frequently dependent on the metabolism of the
nt drug to toxic metabolites, a process referred to as bioactivation.
site of toxicity is therefore dependent on the sites of accumulation of
toxin, the localization of enzymes necessary for metabolism of the
pound, and the susceptibility of specific cells to the toxic effects. A
al intrinsic toxin is acetaminophen. Acetaminophen is metabolized to
tive metabolites that cause methemoglobinemia, hemolytic anemia,
ver damage, the primary clinical manifestations being dependent on
species of animal affected. Drugs or chemicals with carcinogenic
perties, which bind to DNA or damage DNA through other mecha-
ms, would be included in this category.

inical pharmacology of dose-dependent verse drug reactions

se-dependent ADRs have the potential to occur in all patients, but
y may be avoided in many instances by careful selection of the dose,
ing into account the patient characteristics. Patient evaluation becomes
y important in deciding whether an adjustment in the recommended
ndard dose is required. Susceptibility to dose-dependent ADRs can
enhanced through factors which lead to greater drug exposure (i.e.,
creased clearance and increased absorption) or that enhance the phar-
acological effect (e.g., concurrent medications; presence of epileptic foci
the brain). This hypersusceptibility may also be referred to as *patient
nsyncrasy*. For example, hypersusceptibility of collie dogs to ivermectin
urotoxicosis is related to an increased penetration of ivermectin into the
ntral nervous system resulting from a genetic variation in P-glycoprotein

responsible for pumping ivermectin out of the central nervous syst
Inhibition of metabolism or clearance of a drug can lead to accumul
to toxic levels. Glucocorticoids and nonsteroidal antiinflammatory
(NSAIDs) have synergistic effects on the occurrence of gastropathy.
case of intrinsic toxicities that are dependent on bioactivation to
metabolites (a process called bioactivation), factors which alter me
lism of the drug or affect cell defense mechanisms (e.g., deplete cel
glutathione) will also enhance susceptibility.

The target organ and clinical signs are dependent on a number of
tors. For pharmacological toxicity, the observed signs will be dependen
the pharmacological effects. For intrinsic toxicities, the clinical manif
tions will depend on the affected organ. The target organ will depen
accumulation of the drug, the cell defense mechanisms present in t
organs, and the presence of the enzymes required for bioactivation o
drug. For example, the nephrotoxicity of aminoglycosides is dependen
part on their accumulation in renal tubular cells. If this accumulatio
prevented by appropriate dosing regimens, then the risk of nephrotoxi
is decreased.

Treatment in dose-dependent toxicities should involve discontinua
of the drug and, if clinically indicated, removal of the drug from the b
through appropriate measures. When appropriate, therapy can be direc
at the specific pharmacological target to either treat or prevent the AD
Targeting to the appropriate pharmacological target is critical. For exam
misoprostol is the best and most effective therapy to prevent NSA
induced gastropathy.[3] Once ulcers or erosions have occurred, discontin
tion of the NSAID followed by appropriate therapy with sucralfate or
acid inhibitor such as ranitidine or omeprazole would be appropriate.
the other hand, since loss of prostaglandin is not the primary mechan
behind steroid-induced gastric bleeding, misoprostol is not effective
preventing steroid-induced gastropathy.[4,5]

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

In summary, dose-dependent ADRs are the most common class of AD
encountered clinically. They can be minimized by careful and judicio
use of the drug, taking into account the individual patient. The clini

station and treatment will be directed by the pharmacological
rties of the drug or the mechanism of the chemically based toxicity
e target organ. The previous occurrence of a dose-dependent ADR
animal is a clear indication for modification of the therapeutic
en, but does not necessarily contraindicate the use of the causative
lated drug in the patient.

syncratic adverse drug reactions

ncratic ADRs are the second major class of ADRs. They are also
ed to as host-dependent, dose-independent, Type B (bizarre), Type II,
tient-related ADR. These terms are often used interchangeably (Box
). Unfortunately, because of our lack of understanding of the patho-
is of many idiosyncratic adverse drug reactions, there remains con-
able confusion regarding idiosyncratic reactions. Many clinicians use
erm "idiosyncratic" to denote "unknown mechanism." This, however,
inappropriate use of the term, particularly as the mechanisms of
idiosyncratic ADRs become elucidated. The defining characteristic
diosyncratic ADRs is that they occur in patients at serum concentra-
within the therapeutic range and will not occur in the majority of
nts despite increasing the dose to otherwise toxic levels. That is, a
fic interaction must occur between the patient and the drug to result
e adverse reaction. They are not classically dose-dependent and are
ly dependent on the characteristics of the individual patient (host-
ndent or patient-related). They usually cannot be reliably reproduced
n experimental setting. Thus both experimentally and in the clinical
ng, their occurrence is unpredictable. The incidence of idiosyncratic
Rs is usually much lower than dose-dependent ADRs, but in certain
ulations they may be relatively frequent. Idiosyncratic ADRs are

Box 14–3
amples of Idiosyncratic Adverse Drug Reactions in terinary Species

- ylthiouracil/methimazole toxicity in cats
- onamide polyarthritis, thrombocytopenia, hepatotoxicity in dogs
- zepam hepatotoxicity in cats
- endazole hepatotoxicity in dogs
- lignant hyperthermia triggered by halothane in pigs and dogs
- profen hepatitis

dependent on the chemical properties, not the pharmacological pro
ties, of the drug. They are distinguished from hypersusceptibility to p
macological or intrinsic toxicities in that they cannot be produced si
by elevating the dose or increasing the exposure in the target popula
or in experimental animals.

The clinical presentation of idiosyncratic drug reactions is variable
depends on the exact mechanism underlying the reaction. For exam
malignant hyperthermia from halothane exposure in pigs and hepatot
icity from sulfonamide antimicrobials are both idiosyncratic ADRs. T
have both distinct pathogenesis and distinct clinical signs. However,
majority of idiosyncratic ADRs have characteristics associated with
immunological pathogenesis and many people are referring to these ty
of reactions when they use the term idiosyncratic reactions.

Drug hypersensitivity syndrome reactions, drug-induced hemol
anemia or thrombocytopenia, drug-induced lupus, drug fever, and dr
induced immune-mediated hepatitis are all terms used to describe id
syncratic reactions that are thought to have an immunological bas
The clinical manifestations of "idiosyncratic hypersensitivity syndro
reactions" include such pathological states as fever, lymphadenopathy, d
matopathies, hepatitis, nephritis, leucopenia, agranulocytosis, eosinophil
thrombocytopenia, and aplastic anemia. This type of idiosyncratic reac
is relatively rare (frequency estimated to be <1/1000) and has a delay
onset, with clinical signs generally manifesting 7 to 14 days or longer aft
the start of therapy. They are distinct from the typical drug allergy cha
acterized by anaphylaxis and/or urticaria occurring immediately aft
drug administration, which is an IgE-mediated immediate hypersensitivi
reaction directed against the drug.

Idiosyncratic reactions are important in veterinary medicine from
patient treatment standpoint, but they also have an influence on vete
nary practice from another perspective. Fear of idiosyncratic toxicity
humans may be the reason for the banning of products for use in foo
animals (e.g., chloramphenicol causes aplastic anemia in rare individua
or may lead to the withdrawal of a drug from the market. Some prac
tioners are reluctant to prescribe drugs that have been associated wi
idiosyncratic ADR in humans for fear of precipitating an event in th
owner. In general, owners should be warned about the potential for dru
employed in veterinary practice to cause idiosyncratic reactions in human
(Box 14-4) and be instructed to wash their hands immediately after admi
istering the drug to their animals. It is wise to inquire if the client or an
immediate family members have drug allergies before dispensing a dru
so that they can take appropriate precautions, such as wearing gloves an
washing hands.

x 14-4

ne Drugs Used in Veterinary Practice That Have Been ociated with Idiosyncratic Reactions in Humans

- lcillins
- phalosporins
- thromycin
- lfonamides
- methoprim
- loramphenicol
- matic anticonvulsants, including phenobarbital, phenytoin, carbamazepine, and felbamate
- enylbutazone
- pyrone
- enothiazine derivatives (chlorpromazine)
- alothane, Isoflurane
- ethimazole, propylthiouracil
- ptopril
- ocainamide

athogenesis of idiosyncratic adverse rug reactions

he pathogenesis of idiosyncratic ADRs is complex and is dependent on e reaction under consideration. For example, malignant hyperthermia related primarily to mutations in the ryanodine receptor in the muscle rcoplasmic reticulum[8] so that muscle calcium homeostasis cannot be aintained in the face of challenge with certain muscle relaxants, caine, and halothane. It is an idiosyncratic reaction because it requires a ecific patient genotype and, although a mutated receptor is responsible r susceptibility, interaction of halothane with a specific receptor is not quired to trigger the clinical event. The most common types of idiosynatic reaction, however, involve cellular damage, leading to organ specific amage, such as nephropathies, hepatopathies, blood dyscrasias, and rmatopathies. These reactions are commonly dependent on bioactiation to a reactive intermediate that can either directly cause cellular amage or trigger a pathological immune response.

Clinical signs consistent with an immunological pathogenesis for many diosyncratic reactions include a delayed onset, typically 7 to 14 days after e start of therapy, fever, skin rash, and occasionally eosinophilia. The clinal signs are highly variable, depending on the patient and other clinical actors. Patients may display a clearly systemic disease with multiple rgans affected, or may have a single abnormality, such as thrombocyopenia, neutropenia, skin rash, or hepatitis. A previous exposure to the rug may have occurred, but is not necessary. If an animal has tolerated

a drug for more than 6 to 8 weeks, the likelihood of experien
idiosyncratic reaction drops. Despite the variable clinical presenta
appears that common pathogenic events underlie the clinical disea

The immunological responses that have been identified in c
idiosyncratic reactions in humans and animals have been directed
either drug-modified proteins or autoantigens. Drugs are then
generally too small to trigger an immunological response; however,
are metabolized to reactive metabolites, they may form drug-p
conjugates (Fig. 14-1) that are capable of triggering an immunol
response.[3,9] The immune response may be directed against the
protein conjugate or against the protein itself (autoantigen) tha
altered by the drug. The factors that determine which animals will
rience an idiosyncratic reaction remain obscure, although genet
environmental differences in metabolic capacity and immunol
responsiveness appear to play roles.

The general scheme of Gell and Coombs for the classificati
immunological reactions is frequently applied to drug-induced im
reactions but is of limited usefulness in classifying idiosyncratic reac
True drug allergies are typical Type I (IgE-mediated) immediate h
sensitivity type reactions, but idiosyncratic hypersensitivity syndr
reactions can have manifestations of Type II (antibody-directed
cytotoxicity), Type III (immune-complex disease), and Type IV (del
hypersensitivity—cell-mediated) reactions to varying degrees within
individual patient. The basis of the target-organ specificity of idio
cratic adverse reactions and the variable clinical presentations are
fully understood, but appear to depend on the sites of bioactivatio
the drug, the stability of the reactive metabolites formed, and the site

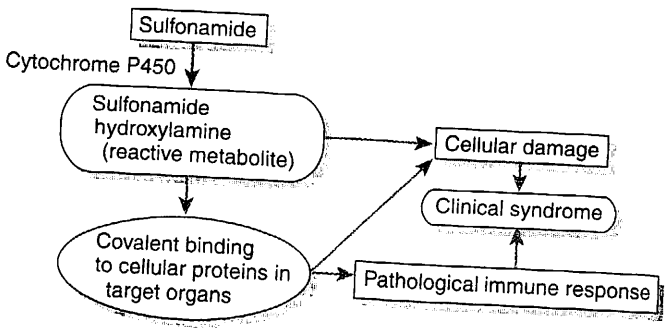

Figure 14–1. Simplified scheme of the pathogenesis of sulfonamide hypersen
tivity reactions.

binding of the reactive metabolites, and the nature of the
response in individual animals.

al pharmacology of idiosyncratic rse drug reactions

clinical perspective, the major difficulty with idiosyncratic ADRs unpredictability. They are not dose-dependent and so cannot be d by careful dose selection. Although they are usually rare, they are ally fatal. However, while their delayed onset means that a previous erm exposure does not guarantee safety, if an idiosyncratic reaction occurred during or after a prolonged exposure (e.g., 4 to 8 weeks), likely to occur on subsequent exposures. If a reaction is a true drug (e.g., IgE mediated), a previous exposure is required and reexpo- ay precipitate an acute anaphylactic response. The temporal rela- ip for immediate hypersensitivity reactions are thus very different he delayed-onset hypersensitivity reaction described above.

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

wners should be warned of the possibility of idiosyncratic adverse reactions. Drug withdrawal is the most important step and owners d be told to stop the drug immediately should any untoward events r. Clinical manifestations depend on the target cell or organ, but they usually systemic reactions. Often the first signs noted by the owner are rgy, depression, and anorexia. The treatment should be directed at linical manifestation of the ADR. The use of corticosteroids for yncratic hypersensitivity ADRs is poorly documented. However, dotal experience in humans and the documentation of an immuno- al component to the reactions suggests that animals not responding pportive care should be treated with high dose corticosteroids (e.g., unosuppressive doses, not antiinflammatory doses). Animals that ifest neutropenia as a clinical signs should be treated with an appro- te broad-spectrum prophylactic antibiotic to protect against second- bacterial infections.

f, an animal has experienced an idiosyncratic ADR, use of the sus- ted or a chemically related drug should be considered contraindicated ess no other alternative exists for a life-threatening illness. In that case, esensitization protocol should be considered as part of the reinitiation

of therapy. Unfortunately, there is essentially no published experience these protocols in veterinary patients.

INCIDENCE OF ADVERSE DRUG REACTIONS

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

Small experimental studies at higher than normal clinical doses m indicate what dose-dependent toxicities to be aware of and give an i cation of the therapeutic index, but they do not determine the incide of dose-dependent or idiosyncratic reactions to expect at typical clini doses in the general patient population. In general, the large clinical t and postmarketing surveillance necessary to determine the incidenc ADRs are not available in veterinary medicine. Many times the impr sion of the incidence or importance of an ADR is colored by perso experience. While this may be useful experience, it can often be misle ing. In general, dose-dependent ADRs tend to be more common but l serious, whereas idiosyncratic ADRs tend to be relatively rare but m serious (e.g., the incidence of sulfonamide hypersensitivity reactions dogs is probably less than 1/1000). The unpredictability and poten severity of idiosyncratic toxicities gives them an impact disproportion with their incidence.

It is always important to remember that the likelihood of an ADR the patient being treated is more important than the frequency of occ rence in the general population and the decision to use the drug should based on an assessment of risk in the individual patient. Particular vigila for adverse reactions in neonates, older animals, animals with a previ history of an ADR, and animals receiving multidrug therapy is requir Many factors contribute to the occurrence of an ADR in a given patie Drug factors include dose, duration, vehicle, and drug interactions fr concomitant therapy. Patient factors include species or breed, genetic a

onmental variation in drug metabolism, age, sex, body composition s, lean weight), pregnancy status (teratogenicity), concurrent disease s, immunological status, and concurrent drug or chemical exposures. these factors contribute to the development of an ADR will depend he drug and the type of toxicity.

AGNOSIS OF AN ADVERSE DRUG ACTION

ribution of a clinical event to a drug can be difficult. Perhaps the most portant clues to link a clinical event with drug treatment are an appro- te temporal relationship, a previous report of a similar ADR associ- d with the drug, and a lack of another clinical explanation of the event. ere are many algorithms or probability methods that have been devel- d for diagnosing potential adverse drug reactions. However, essentially simplify down to the following questions, which reflect a rational roach to attributing a clinical event to an ADR:

s the temporal association of the event with drug treat- ment 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. For example, an anaphylactic reaction would not occur 7 days after drug administration.

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.

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.

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, while 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 ani to a drug suspected of causing an ADR, but this may occur inadv tently or in clinical situations where alternative therapies are limit
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 can be a u tool in deciding if toxic drug concentrations exist.
7. **Are predisposing factors present in the patient?** Is the ani receiving other drugs which are likely to have pharmacodynamic o pharmacokinetic interactions with the drug in question? For exampl use of an NSAID and an aminoglycoside may increase the risk of nephrotoxicity, whereas concurrent use of an NSAID and a glucoc coid will increase the likelihood of gastric ulceration. Does the ani 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 int actions may be relative or absolute contraindications to the concurrent of drugs. Drug interactions may lead to a diminished or an enhan effect of a drug, or may lead to the occurrence of toxicity. In general, interactions have either a pharmacodynamic or a pharmacokinetic ba

Pharmacodynamic interactions are the pharmacological eff of two drugs that may be opposite to each other (e.g., metoclopramide a dopamine have opposite effects on renal blood flow), work at the same (e.g., two NSAIDs), or enhance the effects through sequential or com mentary effects (e.g., effects of glucocorticoids on β_2-receptors and us a β_2-agonist, such as terbutaline; effects of corticosteroids and NSAIDs gastric integrity). Drug combinations should be assessed carefully for d interactions before their use. There are many possible pharmacodyna interactions, some of which are listed in Table 14-1.

Pharmacokinetic interactions are when drugs inhibit or enha each other's metabolism or renal excretion (Table 14-2). One drug m also displace another from protein binding sites, leading to greater f drug concentrations and hence pharmacological effect. Drug interacti can lead to the occurrence of ADRs at doses or plasma concentrations lo than typically expected, depending on the mechanism of the interactio

Knowledge of pharmacokinetic drug interactions in small ani remains limited. Probably the most common mechanism for pharmacok

Table 14-1
Some Pharmacodynamic Drug Interactions

Drugs	Interaction	Mechanism
Glucocorticoids and NSAIDs	Increased gastrointestinal toxicity	NSAIDs primarily inhibit prostaglandin production, while corticosteroids increase gastric acid secretion and decrease mucosal defenses
Furosemide and angiotensin converting enzyme 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 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 anaesthetics generally enhance the respiratory depressant effects of opioids

teractions is metabolic interaction at the level of cytochrome P450 in e liver. The cytochrome P450 family of drug metabolizing enzymes is a nique system. It is composed of more than 20 different enzymes, of which or 5 are likely responsible for the majority of drug metabolism. There e significant species differences in the regulation and substrate specificity these enzymes. Thus, although there are many similarities between

Table 14-2
Some Pharmacokinetic Drug Interactions in Dogs

Drug	Interaction	Mechanism
Phenobarbital (PB)	Griseofulvin—decreased efficacy Propranolol—decreased efficacy Lidocaine—increased clearance Chloramphenicol—decreased efficacy Primidone/phenytoin—increased hepatotoxicity	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—pharmacological toxicity	Chloramphenicol inhibits phenobarbital metabolism
Enrofloxacin	Theophylline—pharmacological 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

species, cytochrome P450-based drug interactions in dogs or cats are not necessarily the same as those in humans. Hence, while 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 combining drugs whose clearance is heavily dependent on metabolism when possible and when interactions have been reported in other species unless they have been shown not to occur in veterinary species. Table 14-2 summarizes some of the possible drug interactions and their mechanisms in small animals, primarily dogs.

G INCOMPATIBILITIES

ncompatibilities are chemical interactions that occur between drugs ro. Drugs that are incompatible should not be mixed together in a e or fluid bag. As a general rule, do not mix drugs unless necessary hen only if you know they are compatible. Most standard reference contain information on drug incompatibilities and should be con- before mixing drugs.

UG-INDUCED HEPATOTOXICITY

g-induced liver damage remains one of the most important adverse drug tions. Because of its strategic location between the intestine and the sys- ic circulation, the liver can be exposed to relatively high drug concentra- s. When coupled with its high metabolic capacity, particularly through cytochrome P450 enzymes, the liver has the greatest exposure to reactive abolites. Intrinsic hepatotoxicity is often related to bioactivation to reac- metabolites that damage liver cells and cause hepatic necrosis (e.g., acet- inophen hepatotoxicity; see Chapter 28). It may also occur subsequent to ruption of mitochondrial function or disruption of bile transport, leading cholestatic injury. Idiosyncratic hepatotoxicity is nearly always related to activation to reactive intermediates. Dose-dependent hepatopathies are ially identified during the drug development process, but may still ribute to clinically important drug-induced toxicity. However, the major- of serious cases of hepatotoxicity are idiosyncratic in nature.

Box 14-5 provides a list of the most clinically important hepatotoxic drugs small animals. This is not a complete list of potential hepatotoxins, but her is a list of drugs that has been associated with hepatotoxicity in dogs d cats. There are other drugs that have been shown to be hepatotoxic other species (humans and rodents) but that have not been reported observed to cause clinically significant hepatotoxicity in veterinary cies. For example, many complementary or alternative health products g., certain kava products and germander) have been reported to cause patotoxicity in humans and conceivably may do so in animals, but no ecific reports exist.

henobarbital

he of the most commonly used hepatotoxin that remains a clinical allenge for veterinarians is phenobarbital. A small percentage of dogs

Box 14–5

Clinically Important Hepatotoxins

Intrinsic Hepatotoxins
Acetaminophen (dogs)
Phenobarbital/primidone/phenytoin
Glucocorticoids
Mitotane
Tetracycline
Cyclosporine
Griseofulvin
Thiacetarsemide
Ketoconazole

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

on chronic phenobarbital administration will develop hepatopathy a eventually hepatic cirrhosis.[10,11] Primidone and phenytoin may also ca hepatopathies in dogs. They are generally considered more hepatot than phenobarbital, particularly when used in combination therapy, a their use should be limited. Phenobarbital is known to cause elevation serum liver enzyme activities that are not directly correlated to the occ rence or degree of hepatotoxicity.[12,13] Although elevations in serum li enzyme activities have been attributed to enzyme induction, this is far fr clear.[12,13] Minor elevations in serum alanine aminotransferase (ALT) a alkaline phosphatase (AP) activities are generally not a cause for conce but elevations in ALT that are three to five times the upper limit normal should be monitored carefully. It should also be noted that d with significant hepatic cirrhosis may not have marked elevations in ser liver enzyme activities despite extensive liver damage. If elevations in and ALT activities are accompanied by decreases in albumin concent tion or serum urea nitrogen, they should be considered more seriou Additional diagnostic work-up, including a bile acid test, is indicat While hepatic biopsy may help to document actual liver damage, histopathological changes that are hallmarks of early phenobarbi hepatotoxicity have been identified.[12]

Dogs with high serum concentrations of phenobarbital (>30 40 μg/mL) are at increased risk of phenobarbital-associated li damage. While elevated serum phenobarbital concentrations are of observed in dogs that have developed hepatopathy,[11] it has been diffic to separate cause and effect. That is, loss of liver function may lead

eased clearance of phenobarbital and elevated serum concentrations. with low serum concentrations of phenobarbital may still lop liver disease (Cribb, unpublished observations). Yearly evaluation erum enzyme activities is often recommended, but has not been ly shown to prospectively identify dogs at risk of developing hepato- city. Unexpected increases in serum phenobarbital concentrations also be an indication of hepatic dysfunction. If dogs are removed phenobarbital early in the course of hepatic damage, recovery can ur. However, once the hepatic damage has proceeded to the stage of ificant cirrhosis, recovery appears less likely. Dogs should be carefully ned from phenobarbital and therapy with an alternative anticonvul- t, such as potassium bromide or levetiracetam, instituted if hepatopathy emonstrated or highly suspected.

iosyncratic hepatotoxicity

osyncratic hepatitis clearly occurs with sulfonamides, carprofen, methi- zole, diethylcarbamazine/oxibendazole, mebendazole, and diazepam companion animals. In all cases, the incidence is rare (probably less an 1/1000). The most common signs of idiosyncratic hepatotoxicity are ute onset of anorexia and malaise within the first 2 to 8 weeks of therapy. owever, hepatotoxicity can develop sooner or may have a delayed onset. hile periodic screening for elevations in serum liver enzyme activities sometimes recommended for idiosyncratic hepatotoxins, there is no idence that this is effective in predicting or preventing hepatotoxicity. he onset of liver damage is quick once it occurs so that dogs or cats can from normal serum activities to clinical liver damage in a few days me. When commencing drugs that are associated with idiosyncratic patotoxicity, it is useful to establish a baseline for serum activities before e start of therapy. It is also important to remember that fluctuations of rum enzyme activities out of the normal range are not uncommon and mple elevation is not necessarily an indication to stop the medication, hough it is a clear indication for enhanced clinical and biochemical onitoring of the patient.

The most important treatment for idiosyncratic hepatotoxicity is mediate cessation of therapy and diagnosis. The owners should be structed to immediately stop the drug and bring the animal in for eval- ation should it become anorexic or depressed. Serum liver enzyme activ- es should be determined and if elevated, a presumptive diagnosis of iosyncratic hepatotoxicity is made. Clinical experience suggests that ntinued treatment once the reaction has started is more likely to lead a fatal outcome. While hepatic biopsy may serve to confirm the hepatic

damage. this is rarely indicated and is probably not helpful in differ
ting idiosyncratic hepatotoxicity from other causes. There is no sp
therapy for idiosyncratic hepatotoxicity. In severe cases that contin
deteriorate. treatment with corticosteroids. on the assumption that th
an underlying immune-mediated pathogenesis. can be tried but ther
no good clinical studies to support this approach in human or veteri
medicine.

Drug-induced nephrotoxicity

Because of their large perfusion (approximately 25% of the car
output), their ability to concentrate and accumulate toxicants. and th
high metabolic activity. kidneys are highly vulnerable to drug-indu
toxic injury. The most common drugs associated with nephrotoxicity
small animals are presented in Box 14-6. It is important to note that
box and this section describe toxic events associated with drugs that
intrinsically nephrotoxic and do not address drugs, such as furosemide, t
can cause renal dysfunction through their pharmacological properties.
a general principle. two potentially nephrotoxic drugs should not be u
together and nephrotoxic drugs should be avoided in animals with kno
or suspected renal dysfunction. To minimize the risk of nephrotoxicity, i
important to maintain the hydration status of the animal and ensure a
quate urine output.

AMINOGLYCOSIDES. Nephrotoxicity is a major limiting factor f
aminoglycosides administration. Aminoglycoside toxicity results in re
failure with hypoosmotic polyuria. enzymuria. glucosuria. and proteinur
Serum creatinine can be increased after a few days of administration. Re
failure is usually reversible but can become irreversible if administration

Box 14–6

Drugs Associated with Nephrotoxicity

- Aminoglycosides
- Amphotericin B
- Cyclosporin A
- NSAIDs
- Sulfonamides
- Tetracyclines
- Radiocontrast agents
- Methoxyflurane

ged. Toxic mechanisms are not fully understood. but probably involve
uptake of the drug by tubular cells and accumulation in lysosomes.
apparatus. and endoplasmic reticulum. Histopathologically. aminogly
tubular cell toxicity is associated with formation of myeloid bodies that
from the accumulation of phospholipids in a concentric lamellar dis
on within enlarged and dysfunctional lysosomes. Rupture of over
med lysosomes is believed to be a major trigger for tubular cell death.
ired synthesis of protective prostaglandins and inhibition of mitochon
respiration and of protein synthesis have also been proposed as addi
toxic mechanisms.

s low trough levels of aminoglycosides have been associated with
ased nephrotoxicity in multiple human trials. single daily administra
s currently used in humans and horses.[14,15] However. multiple once
intramuscular administrations of gentamicin have been associated
signs of renal damage in dogs (increased serum creatinine and blood
nitrogen. renal tubular casts, and decreased specific urine gravity) and
re must still be exercised.[16] To minimize the risks associated with
oglycoside-induced nephrotoxicity. patient hydration should be
ntained. co-administration with other nephrotoxic or diuretic drugs
nflammatory drugs. furosemide should be avoided. and therapeutic
monitoring (TDM) should be used. TDM dose adjustment is related
e patient's pharmacokinetic parameters and minimal inhibitory con
ration (MIC) of the causative bacteria. The goal is to provide a dosage
imen that produces a peak concentration 8 to 10 times above the MIC
a trough concentration of less than 2 μg/mL. and and preferably less
n 1 μg/mL. Prostaglandin analogue supplementation (misoprostol) does
seem to be effective for the prevention or treatment of gentamicin-
ced renal injury.

ACTAMS. Cephalosporins have been commonly cited as being poten
y nephrotoxic drugs. The early cephalosporins (i.e., cephalordine) had
r nephrotoxic properties and a number of analogues were also shown
ause renal damage. The damage related to cephalosporins was selec
to the S2 segment of the proximal tubule as a result of active uptake
ough the organic anion transport system. However. none of the cur
ly used cephalosporins appear to be associated with a significant risk
ephrotoxicity.

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

AMPHOTERICIN B. In its conventional colloidal dispersion (Fungizone), amphotericin B is associated with high risks of renal t in humans and in veterinary species. It induces an intense renal art vasoconstriction and is directly cytotoxic in relation with its ability t cholesterol and form membrane pores, leading to tubular necrosis. S protocols have been developed for the administration of amphoteri to minimize nephrotoxicity. New lipid-based formulations have lo the toxic events related to amphotericin B administration in human icine. Clinical trials have not been performed in veterinary medici date and therefore use of safer azole antifungals is preferred to am tericin B wherever possible.

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

CYCLOSPORINE A. As cyclosporine A renal toxicity is a common p lem in human medicine, its increased use in veterinary medicine, cially for dermatological diseases, has raised the question of nephro risks in veterinary species. In contrast to humans, dog and cat kidney not seem to be a major target of cyclosporine toxicity. Very few cas renal impairment have been reported in the literature.[18]

NSAIDs. Renal synthesis of prostaglandins by cyclooxygenase consti a regulatory mechanism to cope with diminished renal perfusion that occur in volume-contracted states (i.e., dehydration, diuretics) or red cardiac output (i.e., congestive heart failure).[19] Because NSAIDs inhibit prostaglandin synthesis, they may impair renal function in h risk patients, culminating with acute renal failure. The nephrotoxic po tial of selective COX-2 inhibitors is unclear in human medicine[20] and not been addressed in veterinary species. NSAIDs can also damage kidney by direct toxicity, usually after massive administration. Both m anisms may be involved in acute renal papillary necrosis, which has reported in dogs and cats.[21,22]

RADIOCONTRAST AGENTS. Hyperosmolar radiocontrast agents been associated with renal damage and decreased renal clearance, cially in dogs with heart failure. Transient renal ischemia, direct tub

ity, and changes in glomerular capillary permeability have been pro- d to explain these alterations. New non-ionic agents with lower olarity (i.e., iopamidol) have decreased risks of toxicity.

LFONAMIDES. Idiosyncratic toxicity of sulfonamides in dogs has n associated with proteinuria, which may result from drug-induced merulonephritis.[3,4] However, renal toxicity is less common than some er signs (i.e., fever, arthropathy, and blood dyscrasias). Sulfonamides may cause crystalluria if high doses are administered to animals or if they dehydrated.

ETRACYCLINES. In dogs, high doses of oxytetracycline (25 mg/kg IV) ve been associ-ated with tubular nephropathy. Clinical signs include miting, diarrhea, dehydration, and isosthenuria with azotemia, hyper- atininemia, and hyperphosphatemia.[23] Renal damage has also been scribed with the use of outdated or degraded tetracycline.

ONCLUSION

taking a rational approach to adverse drug reactions based on an derstanding of the general principles of mechanisms of toxicity, the erinary clinician can go beyond the consultation of a list of adverse actions to a thoughtful assessment of risk and causality in our patients. is will lead to the safer, more appropriate use of drugs and better ient care. Although every veterinarian will experience the occurrence ADRs in their patients, careful use of drugs will minimize the quency and consequences.

FERENCES

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.
Paul AJ, Tranquilli WJ, Seward RL et al: Clinical observations in collies given ivermectin orally, *Am J Vet Res* 48:684-685, 1987.
Cribb AE: Adverse effects of non-steroidal anti-inflammatory drugs. In Ka W, editor. *Clinical pharmacology: Principles and practice*. Western Veterinary Conference, Las Vegas, 1998.
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.
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* 60:982-986, 1999.
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* 253:448-51, 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. Giger U, Werner LL, Millichamp NJ et al: Sulfadiazine-induced allergy in six Doberman pinschers. *J Am Vet Med Assoc* 186:479-484, 1985.
24. 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.
25. 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.
26. Margulies K, Schirger J, and Burnett J Jr: Radiocontrast-induced nephropathy: current status and future prospects. *Int Angiol* 11:20-25, 1992.

15

iscellaneous
ndoor Toxicants

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Hundreds of household and commercial products are available in nes and businesses. Although many household products are not highly ic, cleaning substances, cosmetics, and personal care products are a mon source of exposure for pets.

Household products are often complex chemical mixtures of organic inorganic compounds designed for specific applications. When an mal has been exposed to a household product, it is important for the rinarian to obtain the following information if possible: full trade me of the product, ingredients in the product (both active and inert), their concentrations, amount and dilution of the product the animal me in contact with, clinical signs and their progression in relation to the e of exposure, and any treatments given by the owner before coming with the animal. It is helpful to instruct the owner to bring in the original tainer of the product in question.

Even when this information is obtained, it may still be difficult for the ician to assess the situation because the toxicity of many household ducts is not always predictable on the basis of the chemical and physproperties of the individual ingredients. Interactions between ingrediwithin a single product and between different products when present combination further complicate the toxicological risk assessment. This dicament may be alleviated in part by appropriate consultations. formation on the ingredients and clinical toxicology of a particular oduct may be obtained from human and animal poison control centers, ergency medical centers, and manufacturers' product safety and infortion hotlines. Many commercial products have specific manufacturer's formation and telephone numbers as part of their labels; poison control ter numbers are available in local telephone directories, or dial the tional toll-free poison center telephone number (1-800-222-1222).

This chapter updates an earlier review of the clinical toxicology of mmon indoor toxicants, such as cleaning agents, corrosive and caustic