

Drug Hypersensitivity Reactions Targeting the Skin in Dogs and Cats

K.L. Voie, K.L. Campbell, and S.N. Lavergne

Adverse drug reactions (ADRs) can be dose dependent or idiosyncratic. Most idiosyncratic reactions are believed to be immune-mediated; such drug hypersensitivities and allergies are unpredictable. Cutaneous reactions are the most common presentation of drug allergies. In veterinary medicine it can be difficult to assess the true prevalence of adverse drug reactions, although reports available suggest that they occur quite commonly. There are multiple theories that attempt to explain how drug allergies occur, because the pathogenesis is not yet well understood. These include the (pro)-haptens hypothesis, the Danger Theory, the pi concept, and the viral reactivation theory. Cutaneous drug allergies in veterinary medicine can have a variety of clinical manifestations, ranging from pruritus to often fatal toxic epidermal necrolysis. Diagnosis can be challenging, as the reactions are highly pleomorphic and may be mistaken for other dermatologic diseases. One must rely heavily on history and physical examination to rule out other possibilities. Dechallenge of the drug, histopathology, and other diagnostic tests can help to confirm the diagnosis. New diagnostic tools are beginning to be used, such as antibody or cellular testing, and may be used more in the future. There is much yet to learn about drug allergies, which makes future research vitally important. Treatment of drug allergies involves supportive care, and additional treatments, such as immunosuppressive medications, depend on the manifestation of the disease. Of utmost importance is to avoid the use of the incriminating drug in future treatment of the patient, as subsequent reactions can be worse, and ultimately can prove fatal.

Key words: Adverse drug reaction; Allergy; Cutaneous.

Adverse drug reactions (ADR) occur commonly, and in human patients account for up to 16.8% of all hospitalized cases.¹ Usually self-limiting, most adverse drug reactions resolve upon discontinuation of the offending drug. However, in some cases they can be quite severe, and can lead to fatality.² Although the risk of an adverse event with any given individual drug is relatively low, ADRs are seen commonly because of the increasing numbers of patients seen, the increasing number of drugs available, and the increasing use of drug combinations in a given patient.

Adverse drug reactions are divided into 2 categories: dose-dependent or idiosyncratic reactions (Fig 1). In dose-dependent reactions, the onset and the intensity of the clinical signs correlate with the size of the dose received by the patient. These clinical signs are typically known adverse effects of the drug in question or are related to the physical or chemical properties of the parent drug or one of its metabolites.³ Dose-dependent ADRs therefore are relatively common, predictable, and could in theory happen to any individual. Conversely, idiosyncratic drug reactions occur independently of the dose, and are not directly related to the pharmacologic, physical, or chemical properties of the drug.⁴ They are therefore relatively uncommon and unpredictable. The exact mechanisms of idiosyncratic reactions are not well understood, but in the case of

Abbreviations:

ADR	adverse drug reaction
BAT	basophil activation test
DRESS	drug rash with eosinophilia and systemic symptoms
IDT	intradermal testing
LTT	lymphocyte transformation test
MHC	major histocompatibility complex
MPE	maculopapular exanthema
SJS	Steven-Johnson Syndrome
TCR	T cell receptors
TEN	toxic epidermal necrolysis

drug allergies (or drug hypersensitivities), the immune system is thought to be involved. The remainder of this review will focus on such drug allergies. There are many different manifestations of drug hypersensitivities, including blood dyscrasias, hepatotoxicity, and cutaneous signs. Cutaneous adverse drug reactions are the most common form of hypersensitivity.^{3,5} The focus of this article will be the cutaneous manifestations of drug allergies in dogs and cats.

Incidence of Cutaneous Drug Hypersensitivity Reactions in Veterinary Medicine

It can be challenging to determine the incidence of ADRs, especially drug hypersensitivities. In human medicine, ADRs seem to occur in 10–20% of hospitalized patients and in 7% of the general population.³ They result in 300,000 hospitalizations annually.¹ These ADRs can be very serious, and are considered to be between the 4th and 6th cause of death in hospitalized patients.⁶ In addition, the expense of treatment of drug allergies can be astounding. In human medicine, treatment of adverse drug reactions can cost more than \$136 billion per year, adding approximately

From the University of Illinois-Urbana-Champaign, College of Veterinary Medicine, Urbana, IL.

Corresponding author: Sidonie N Lavergne, University of Illinois-Urbana-Champaign, College of Veterinary Medicine, 2001 South Lincoln Ave, Urbana, IL 61802; e-mail: sidolavergne@hotmail.com.

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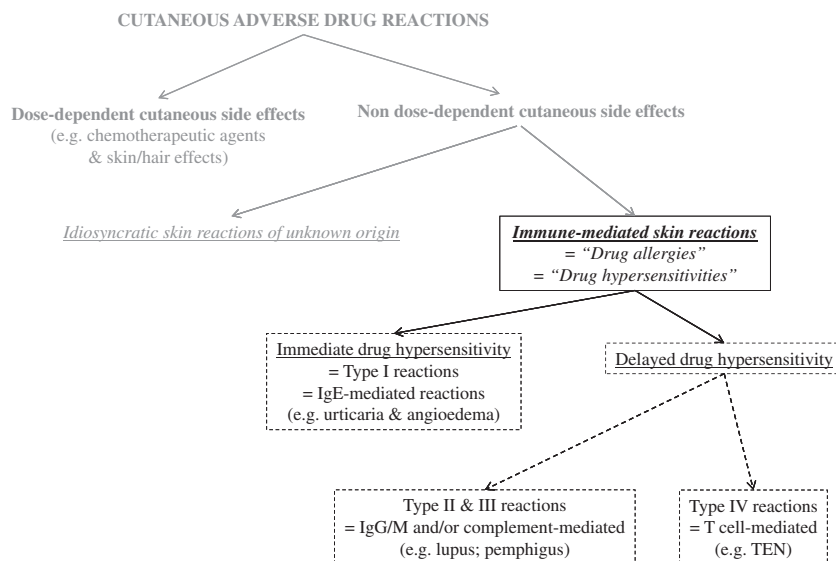


Fig 1. Classification of cutaneous adverse drug reactions.

\$8,000 in hospital expenses per case.^{7,8} Most cutaneous drug reactions in human medicine are associated with antibiotics.^{5,9}

In veterinary medicine, ADR also occur fairly commonly, but their true prevalence is much more challenging to determine. The Veterinary Medicines Directorate (VMD) in the UK oversees ADR reports, based on the degree of suspicion (“Probable”, “Possible”, “Insufficient Information”, or “Unlikely” to be drug related). Australia uses a similar system.^{10,11} In 2009, the VMD received 3,151 reports of suspected ADR. Of these, 1,486 were classified as serious reactions (fatal, life-threatening, disabling, incapacitating, or those that result in permanent or prolonged signs).^{12,13} In 2003, over 24,000 ADR were reported to the FDA-CVM¹⁴; this number increased to over 35 000 reports in 2007.¹⁵ Nevertheless, despite the relatively large number of ADR reported, the number is probably an underestimation.¹⁶ This is likely because of lack of recognition of clinical signs, lack of reporting, and misdiagnosis.

Estimating the number of reactions targeting the skin among reported reactions is rendered further challenging because the report system does not always have enough information to distinguish which organ was involved. In addition, lack of recognition of cutaneous signs may be quite frequent, because lesions may be mild, and can easily be missed in a haired patient. Because they have a multitude of clinical presentations, cutaneous drug reactions may be misdiagnosed as a number of other more common skin diseases. Veterinarians likely encounter drug allergies far more frequently than recognized.

Immune-mediated ADR (drug allergies or hypersensitivities) can be especially challenging to diagnose. However, it is necessary to recognize the importance of drug allergies, and realize that potentially they could happen any time a medication is prescribed.

Indeed, although drug allergies can be self-resolving, they also can be very severe, and may even lead to fatalities. For example, toxic epidermal necrolysis (TEN), a severe skin disorder that frequently is associated with drug allergies, carries a greater than 30–40% mortality rate in human medicine,¹⁷ and close to a 0% survival rate in veterinary medicine.²

Different Types of Hypersensitivity Reactions

In immunology, Gell and Coombs described 4 main types of hypersensitivity reactions (Fig 1).¹ In the case of drug-induced hypersensitivities, the antigen is thought to be the drug itself, one of its metabolites, or a drug- or metabolite-protein complex.¹⁸ Some attempts have been made to adapt the Gell and Coombs classification to address the variety of lesions that have been associated with drug hypersensitivity reactions (Table 1). It is, however, important to note that it is often difficult to apply this hypersensitivity classification to a patient’s specific clinical signs because the manifestations may not fall neatly into a specific category.

Type I Hypersensitivity

This immediate type of hypersensitivity is primarily an IgE-mediated reaction, occurring within minutes to hours after antigen exposure. In Type I hypersensitivity, antigen-bound IgE interacts via Fc receptors on mast cells and basophils, causing cell degranulation and inflammation. The mast cells and basophils release leukotrienes, histamine, eosinophilic chemotactic factor, platelet activating factor, kinins, serotonin, and proteolytic enzymes, which cause an inflammatory response and tissue damage. Examples of Type I hypersensitivities include angioedema, urticaria, and anaphylaxis. This type of ADR is relatively common,

Table 1. Extended Coombs and Gell classification of immune hypersensitivity applied to cutaneous drug allergy.

Extended Coombs and Gell Classification	Immune Response	Pathologic Event	Typical Clinical Manifestations Involving the Skin
Type I	B cell (IgE)	Mast cell degranulation	Urticaria, angioedema
Type II	B cell (IgG)	FcR-dependent cell lysis	Pemphigus, pemphigoid reactions
Type III	B cells (IgG)	Immune complex deposition, complement-dependent cell lysis	Lupus, lupoid reactions, vasculitis
Type IV	T cells		
Type IVa	Th1 (IFN γ)	Monocyte activation	Eczema
Type IVb	Th2 (IL-4, IL-5)	Eosinophilic inflammation	Exanthema
Type IVc	Cytotoxic T cell (perforin, granzyme B)	T cell-mediated cytotoxicity (both CD4+ and CD8+)	Exanthema, TEN
Type IVd	T cells (IL-8)	Neutrophil (activation and recruitment)	Pustular exanthema

Modified from Pichler Ann Intern Med 2003.⁸⁶

and has been specifically reported multiple times in the veterinary literature.^{19–21}

True anaphylactic drug reactions should not be confused with anaphylactoid reactions where a drug directly induces the release of proinflammatory molecules (eg, histamine release by opioids) without the involvement of a drug-specific response from the immune system. Opioids, such as morphine, can induce severe pruritus and skin inflammation by triggering the release of histamine directly from mast cells.²² In this instance, no drug-specific IgE is present, but the clinical signs are similar to those observed during an anaphylactic reaction; these reactions therefore are called anaphylactoid.¹

Type II Hypersensitivity

This type of nonimmediate reaction is IgM- and IgG-mediated and is sometimes called “cytotoxic hypersensitivity”. In Type II hypersensitivity reactions, antibodies are thought to bind to the antigen present on the surface of a cell, resulting in cell damage or lysis, sometimes via the complement cascade. Examples of cytotoxic hypersensitivity include drug-induced and drug-triggered pemphigus,^{23–25} immune-mediated hemolytic anemias or thrombocytopenias.²⁶

Type III Hypersensitivity

These reactions are IgG mediated and nonimmediate. The presence of antigen and antibodies can lead to formation of immune complexes (antigen-antibody complexes), which are deposited on the endothelium of blood vessels inducing vasculitis, or nephritis when renal capillaries are involved. Examples of Type III hypersensitivity reaction are systemic lupus erythematosus and other lupoid reactions,²⁷ vasculitis,^{28,29} or nephritis.³⁰

Type IV Hypersensitivity

These reactions are cell-mediated, and also are usually the most delayed reactions, with a mean time of

onset of 2 weeks.¹ T cells bind to antigens and, along with cytokines, induce a cell-mediated tissue destruction involving macrophages, cytotoxic T lymphocytes, or both.¹⁸ Examples include erythema multiforme, TEN, contact dermatitis, and rheumatoid arthritis.³¹

Theories of Drug Hypersensitivity Pathogenesis

Despite over half a century of research, the exact pathogenesis of drug hypersensitivity reactions remains unclear. This is why some clinicians and researchers use different words to describe certain reactions: “drug-associated” when the drug is thought to be part of the pathogenesis, but the direct cause-effect with the detected biomarkers or the clinical signs is not established; “drug-induced” when the immune events leading to the clinical signs are thought to be directly related to the drug and therefore expected to disappear when the drug is discontinued; and “drug-triggered” when the immune events leading to the clinical signs are thought to be indirectly related to the drug and therefore expected to continue despite drug withdrawal.

There currently are 4 different theories to describe the mechanism of drug hypersensitivities.¹⁸ It is likely that all theories have some relevance, and that components of each occur in conjunction with one another, depending on the drug and the clinical signs.

(Pro-)Hapten Hypothesis

The hapten-prohaptent hypothesis is based on the thought that drugs that are too small themselves to elicit an immune response bind to tissue proteins, thereby making the protein-drug complexes immunogenic.³² Haptens are chemically reactive small molecules (eg, penicillins) that bind to proteins. Prohaptens are drugs that are inert, but become protein-reactive after undergoing metabolic bioactivation (eg, sulfonamides, acetaminophen). Hapten-protein complexes are taken up by antigen presenting cells (APCs), and presented by the major histocompatibility complex (MHCs) to T cells. This elicits an inflammatory immune response and T-cell proliferation.

A study by Lavergne et al investigated the presence of antidrug antibodies in 34 dogs with a history of hypersensitivity to sulfonamides.³³ Sulfonamide serum adducts and antisulfonamide IgG antibodies were found in 50% of the hypersensitive dogs, and the presence of antidrug antibodies correlated with the presence of drug protein adducts. This provided the first evidence in veterinary medicine for the (pro-)hapten hypothesis.

Danger Theory

The original theories of immunity were based on the idea of self versus nonself. The Danger Theory was developed because these theories failed to answer why autoimmunity or neoplasia was allowed to occur, or why the immune system failed to respond to many “foreign” molecules encountered in daily life, such as the intestinal microflora. The main concept is that the immune system is reactive not toward “foreignness” per se, but rather to “danger”, such as cell debris, oxidative stress, or inflammation.³⁴

This relatively new theory is thought to play an important role in drug allergies.^{4,35} The mechanisms by which a drug or its metabolites could trigger such a “danger cascade” are not yet well established. Many of the drugs that are associated with drug hypersensitivity, however, are known to cause cell damage via oxidative stress. It is therefore reasonable to assume that some drugs or their reactive metabolites could induce some “danger signals”. In any case, the disease treated by the drug also would be associated with various types of danger signals (eg, microbial pathogenic molecules in infections treated with antimicrobials, proinflammatory prostaglandins in inflammatory diseases treated with anti-inflammatory drugs).³⁶ Indeed, “danger” signals commonly encountered in infectious diseases have been shown to increase the formation of intracellular drug-protein adducts thought to be toxic or immunogenic or both.³⁶

PI Concept

The Pharmacological Interaction (*PI*) concept proposes that a drug itself can directly interact non-covalently with the major histocompatibility complex (MHC) or T cell receptors (TCR) or both to induce an immune response.³⁷ This was based on the observation that the T cells of certain patients with a history of hypersensitivity to certain drugs could proliferate in response to drugs, without apparent drug metabolism or protein binding. This phenomenon is similar to how microbial superantigens nonspecifically activate the immune system, but in the case of the PI concept, there appears to be a certain level of specificity because not all T cell subsets are stimulated.

Viral Reactivation

A newer theory is the viral reactivation theory, which postulates that a relationship exists between

viral diseases and drug allergies.³⁸ Underlying viral infections, such as Epstein-Barr virus or herpes virus, may increase susceptibility of patients to adverse drug reactions. Antiviral T cells may be implicated in stimulating an immune response that causes drug hypersensitivity.

Common Clinical Patterns Associated with Drug Allergies

There are some differences in nomenclature between human and veterinary dermatology. For the most part, this is likely attributable to increased knowledge in the human medical field, and therefore more detailed description of reactions seen in human medicine. In this section, we describe different cutaneous reaction patterns that are seen as a result of adverse drug reactions, but it is important to remember that cutaneous drug hypersensitivity reactions can look like any known dermatology lesions and affect any part of the body (Table 2). Specific clinical signs cannot be attributed to specific drugs because each drug can induce different clinical signs, both qualitatively and quantitatively, depending on the individual patient (eg, Fig 2B and C).

Urticaria and Angioedema

Seen both in animals and humans, these are edematous cutaneous reactions that result from mast cell or basophil degranulation² because of Type I hypersensitivity reactions. The characteristic lesion is a hive, or wheal. In the case of urticaria, the edema is confined to the dermis, whereas in angioedema the edema spreads to the subcutaneous tissue, which makes lesions less distinct. Wheals are most commonly seen on the glabrous skin, often the ventral abdomen, and lesions often persist for <24 hours after drug discontinuation. Angioedema typically is noted on the head and face, and pruritus is variable. Chronic urticaria has been reported in a case of diethylcarbamezine reaction in a dog.² Other drugs that have been reported to cause urticaria and angioedema in veterinary patients include penicillin, ampicillin, tetracycline, vitamin K, propylthiouracil, amitraz, ivermectin, moxidectin, radiocontrast agents, and HyLyt efa shampoo.² Urticaria seems to be extremely rare in cats.³⁹

Pruritus

Pruritus is a common manifestation of cutaneous drug reactions, and may be the only clinical sign. It is thought to be particularly intense in cases of drug allergies. It may be mediated by histamines in immediate reactions, and proinflammatory cytokines in delayed reactions.⁴⁰ Symmetric pruritus without lesions may be present; the severity of the pruritus can be variable.

In humans, pruritus has been reported with drugs such as NSAIDs, antibiotics, opiates, radiocontrast media, and Vitamin A derivatives.⁴⁰ Scott et al

Table 2. Notable histopathologic findings in reaction patterns of cutaneous drug allergies.

<i>Angioedema/Urticaria</i>	Angioedema/urticaria histopathologically is characterized by edema. Urticarial lesions will have edema of the dermis, whereas in angioedema there is severe edema that extends from the dermis into the subcutis.
<i>Superficial Pustular Dermatitis</i>	Superficial pustules without prominent acantholysis is found on histopathology. Variable apoptosis may be present.
<i>Lupoid Drug Reaction</i>	Histopathology of lupoid-drug reactions may be difficult to distinguish from SLE, and clinical presentation and immunologic differentiation is required. The classic histopathologic finding is interface dermatitis, and in most cases, there is basal cell vacuolation and apoptosis, dermal-epidermal separation, and ulceration. Vasculitis can also occur.
<i>Pemphigus Foliaceus-Like Drug Reaction</i>	The classic histopathologic lesion is subcorneal pustules with prominent acantholytic cells.
<i>Erythema Multiforme</i>	The characteristic feature of erythema multiforme is keratinocyte apoptosis with lymphocyte satellitosis. Interface dermatitis is also present; lymphocytes and macrophages obscure the dermal-epidermal junction.
<i>Toxic Epidermal Necrolysis</i>	Toxic epidermal necrolysis is characterized by full-thickness coagulative necrosis with minimal dermal inflammation.

Modified from Gross, et al. "Skin Diseases of the Dog and Cat: Clinical and Histopathologic Diagnosis," 2005.⁴⁶

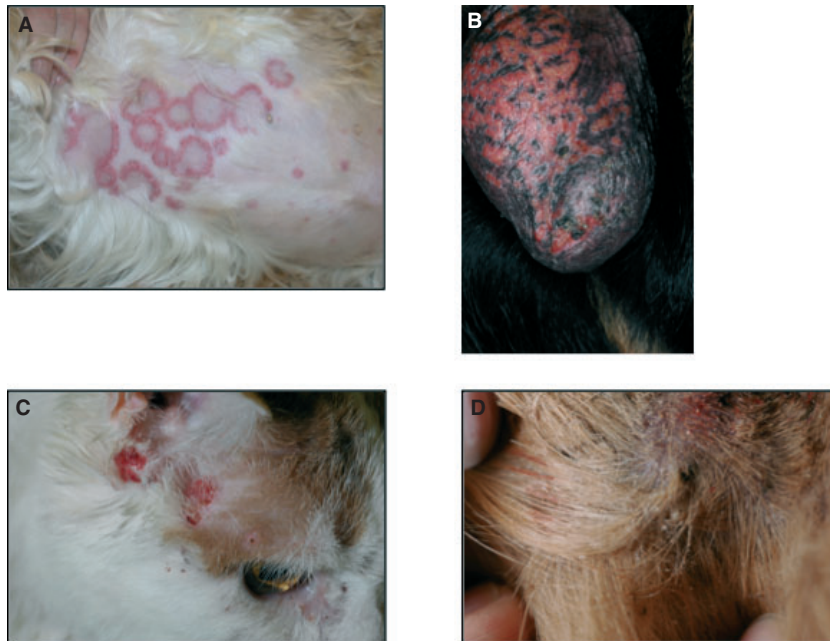


Fig 2. A dog featuring the classic target lesions of erythema multiforme, secondary to drug administration (Panel A). Erosions and ulcerations on the scrotum of a Doberman following administration of ampicillin/sulbactam (Panel B). A DSH cat is affected by ulcerations, crusting, and pruritus on the head following a course of amoxicillin/clavulanic acid (Panel C). Pemphigus-foliaceus was induced in this dog by application of the topical parasiticide Promeris Duo (metaflumizone/amitraz) (Panel D).

found that of 101 dogs with adverse drug reaction, 11.9% had allergic-like dermatoses that presented as pruritus.⁴¹ Pruritus and facial excoriations have been associated with methimazole administration in up to 15% of cats.^{42,43}

Sweet's Syndrome

Sweet's syndrome, or neutrophilic dermatosis in humans, is characterized by painful, erythematous plaques or nodules with an intense neutrophilic dermatitis, as well as concurrent systemic signs.³¹ Clinical

signs can include pyrexia, immune-mediated thrombocytopenia, leukocytosis, arthralgia, myalgia, and vasculitis. Although Sweet's syndrome often is idiopathic, adverse drug reactions have been known to cause this disease. In a case report described by Mellor et al, a 10-month-old Neapolitan Mastiff presented for a 7-day history of sudden-onset extensive skin eruptions, lethargy, weakness, and collapse.³¹ The dog had a history of carprofen, cephalexin, and amoxicillin-clavulanic acid administration after entropion surgery. Clinical features and skin biopsy results were consistent with Sweet's syndrome, but lymphocyte

transformation tests (LTT) for cephalexin and amoxicillin-clavulanic acid were negative. This indicated that the cause of the clinical signs could have been a result of hypersensitivity to carprofen, although this hypothesis was not tested by LTT. Carprofen also was associated with drug eruption resembling Sweet's syndrome and death in 2 additional dogs.⁴⁴ Firocoxib may have contributed to the development of Sweet's syndrome in an additional case report.⁴⁵

Lupoid Drug Reactions or Lupus-like Drug Reactions

Allergic drug reactions may mimic the cutaneous lesions that are seen in systemic lupus erythematosus (SLE).⁴⁶ Dermatologic findings may include erythema, depigmentation, scaling, crusting, erosions, and ulceration of the skin, mucocutaneous junctions and mucous membranes, and alopecia. If vasculopathy is a factor, ear tip necrosis, foot pad ulceration, and pressure point ulceration also may be present.⁴⁷ As SLE is multisystemic, anemia, thrombocytopenia, polyarthropathy, and protein-losing nephropathy also may be present. In dogs, sulfonamides, hydralazine, primidone, and vaccines have been reported to cause SLE.²

Pemphigoid Reactions or Pemphigus-like Drug Reactions (Fig 2D)

These terms apply when the drug reaction mimics naturally occurring pemphigus foliaceus.⁴⁸ Pemphigus foliaceus-like drug reaction resolves once the offending drug is discontinued ("drug-induced pemphigus").⁴⁹ However, in cases of drug-triggered pemphigus foliaceus, the disease continues despite ceasing the offending drug. Further differentiation from naturally occurring pemphigus foliaceus includes unusually fast onset of clinical signs, unusually early age of onset, and unusual clinical features such as oral lesions ("drug-triggered pemphigus"). White et al presented 4 case reports of dogs with putative drug-related pemphigus foliaceus.⁵⁰ These cases involved trimethoprim-sulfamethoxypyridazine, trimethoprim-sulfamethoxazole, cephalexin, and oxacillin. Another puppy that was treated for juvenile cellulitis with amoxicillin-clavulanic acid and topical oxytetracycline developed clinical signs consistent with pemphigus foliaceus.⁴⁸ After discontinuation of all medications, the clinical signs resolved, and a diagnosis of pemphigus foliaceus-like drug reaction was made. A case of suspected drug-induced pemphigus vulgaris has been reported because of administration of polymyxin-B in a dog.⁵¹ Promeris, an ectoparasiticide containing amitraz and metaflumizone, has been associated with 22 published cases of pemphigus foliaceus-like drug reaction, as well as drug-triggered pemphigus.²⁵

Vasculitis

Neutrophilic immunologic vasculitis is a multifactorial disease, and is sometimes a result of drug allergy.^{46,52} Most often it is because of immune

complex deposition (Type III hypersensitivity) or may be related to autoantibodies produced against neutrophils.² The spectrum of severity can range from single organ vasculitis to multiple organ failure and death. Dermatologic findings include swelling because of subcutaneous edema, erythema, purpura, erythematous plaques, skin necrosis, and ulcerative lesions. Vasculitis often is evident in areas of the skin where there is poor collateral circulation, such as footpads, the tips of the pinnae and tail, and over bony prominences. Pain may be present, and often is seen in conjunction with tissue necrosis. Lavergne et al have identified some anti-neutrophil antibodies in dogs with a history of sulfonamide allergy; their presence correlated with a poorer prognosis.⁵³ Meloxicam was reported to have induced a neutrophilic vasculitis in a dog that had been treated for cranial cruciate ligament injury.⁵⁴

Fixed Drug Eruption

Fixed drug eruption lesions are well-circumscribed erythematous lesions that begin as edema and progress to bullae, and may ulcerate as a consequence of bullae rupture. Lesions may be solitary or multiple, and can appear on any site of the skin.⁴⁷ The classic feature of fixed drug eruptions is that repeated exposure to the drug results in lesions in identical locations. Satellitosis (lymphocytes adjacent to apoptotic keratinocytes) in histopathology samples indicates keratinocyte necrosis, which suggests a cell-mediated cytotoxic response.⁵⁵ Fixed drug eruptions have been noted in dogs with diethylcarbamazine reactions,⁵⁵ as well as with 5-fluorocytosine, aurothioglucose, and thiactetamide.⁴⁷ Scott et al reported 3 dogs with fixed drug eruptions, caused by levo-thyroxine, amoxicillin clavulanate, and cephalexin.⁴¹

Superficial Suppurative Necrolytic Dermatitis

Superficial suppurative necrolytic dermatitis (SSND) has been described only in Miniature Schnauzers and is associated with shampoos.^{2,41} Clinical signs begin 48–72 hours after topical application of shampoos, and the condition presents as erythematous papules and plaques, vesicles, and pustules. Most commonly, over-the-counter natural shampoos are implicated. Dogs may have concurrent systemic signs including pyrexia or lethargy. Scott et al reported 2 cases of SSND of 101 dogs with adverse drug reactions,⁴¹ and Murayama et al confirmed shampoo as an etiologic agent of SSND by patch testing in a Miniature Schnauzer.⁵⁶

Erythema Multiforme (Fig 2A)

Erythema multiforme is an uncommon cutaneous reaction pattern that can have variable manifestations and varied etiologies, including drug reaction, although this is controversial.^{46,55,57} It is believed to be a T cell-mediated hypersensitivity that is mounted against keratinocytes carrying drug-protein complexes, and

causing apoptosis.^{46,58,59} Ulceration may be substantial, and mucosal ulceration can be striking. Pruritus is not a common feature, but cutaneous pain may be evident. In animals, drugs that have been associated with EM include sulfonamides, cephalexin, chloramphenicol, aurothioglucose, diethylcarbamazine, gentamicin, penicillin, levamisole, and levo-thyroxine.⁴⁷ One study showed an increased frequency of EM in German Shepherd Dogs, Pembroke Welsh Corgis, Old English Sheepdogs, Chow Chows, Cairn Terriers, and Bearded Collies.⁵⁸

Toxic Epidermal Necrolysis and Steven–Johnson Syndrome (SJS)

Steven–Johnson syndrome and TEN both involve the detachment of the epidermis from the dermis over a significant surface of the skin. The SJS is less likely to be associated with systemic signs, and skin detachment (epidermolysis) occurs over less than 10% of the body area, whereas in TEN epidermal detachment encompasses greater than 30% of body surface area.⁶⁰ Both are relatively rare, but life-threatening, conditions because of rapid and extensive necrosis of the skin that predisposes the patient to sepsis and fluid loss. In humans, SJS and TEN are associated with drug reactions in 80–95% of cases, and survival rate when the patient can rapidly be admitted to a specialized intensive care unit remains lower than 30–50%. The pathomechanism of these severe skin reactions still remains unclear, but is thought to be caused by widespread, rapid apoptosis of keratinocytes mediated by CD8 T cells and mononuclear cells, with concurrent overexpression of toxic cytokines, such as TNF- α .^{2,60} Widespread erythema progresses to epidermal necrolysis that presents as sloughing of the skin with even gentle contact. Marked cutaneous pain is present.

Cases in humans have improved success if treated extensively in burn units, yet have a mortality rate of >35% for SJS and 50% for TEN.⁶⁰ In veterinary medicine where such specific intensive care is unavailable, the disease usually is rapidly fatal, often within 2 days.⁵⁵ Flea dip preparations, both organophosphate dips and d-limonene dips, have been implicated in TEN in both dogs and cats.⁶¹ Other medications reported to have caused TEN in veterinary patients include sulfonamides, penicillin, ampicillin, aurothioglucose, cephalexin, griseofulvin, levamisole, and 5-fluorocytosine. In humans, sulfonamides, aminopenicillins, quinolones, cephalosporins, chlormezanone, nevirapine, lamotrigine, sertraline, aromatic epileptics, NSAID, allopurinol, and corticosteroids most often are implicated.²

Maculopapular Eruptions and Maculopapular Exanthema (MPE)

Maculopapular exanthema (“skin eruption” or “rash”) is the most commonly seen nonimmediate reaction in humans.⁴⁰ Clinical signs include maculopapular erythematous lesions that are variably pruritic.

Vesicles and angioedema also may be present.³⁹ In nonpruritic patients, mild eruptions could go unnoticed, whereas the reactions that are noticed may be mistaken for a more common inflammatory dermatosis. The MPE has been reported in cats treated with ampicillin, cephalexin, penicillin, sulfonamides, and griseofulvin,³⁹ resulting in miliary dermatitis, or suppurative papules and crusts.⁴⁶

Wells’ Syndrome (Eosinophilic Dermatitis)

Wells’ syndrome was first described in the 1970s as a cutaneous eosinophilic disorder. Its pathogenesis remains unknown, but cases often have been related to drugs.⁶² Eosinophilic dermatitis with erythematous, edematous, coalescing macules and plaques, resembling human Wells’ syndrome have been reported in dogs, and some cases were suspected to be adverse drug reactions.^{63,64}

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

DRESS also is known as drug-induced hypersensitivity syndrome (DIHS) and is a reaction seen in humans.^{40,65} It includes some combination of clinical signs such as severe cutaneous eruption, lymphadenopathy, hyperthermia, hepatitis, atypical lymphocytes, and characteristic eosinophilia, which can be severely delayed (weeks to months) after institution of the drug.^{17,65} The most common drugs associated with this manifestation of drug allergy are phenytoin, carbamazepine, sulfonamides, allopurinol, gold salts, and dapsone.¹⁷

DRESS has not been reported in veterinary medicine thus far. This could be because of the fact that veterinarians usually are not familiar with the existence of this syndrome.

The clinical pattern of a drug hypersensitivity reaction is probably dependent on both the patient and the drug. There may be a range of clinical signs seen in a particular patient. In addition, the clinical manifestations will vary from patient to patient, and among drugs. Because of scant published reports of drug allergies in veterinary medicine, it remains unknown how frequently each of these manifestations of drug allergies occur, and which drugs are most often responsible. The pleomorphic nature of the condition furthermore makes diagnosis and categorization more challenging.

How To Recognize and Diagnose ADR

History and Physical Examination

The history and physical examination are very important in diagnosing ADRs or eliminating them from the differential diagnosis. In veterinary medicine, the client should be questioned about any previous drug reactions, any past drug history, and any current medications that the animal may be taking (including

nutraceuticals). In particular, the timing between initiating drug treatment and the start of clinical signs should be investigated. Drug allergies may not be immediate, so even drugs that have been used chronically for months may be considered as potential culprits. Furthermore, the client should be questioned about the previous use of the same drug in question, because prior sensitization to the drug may make allergy more likely if the timing between initiating the drug and clinical signs is very rapid.

Another problem confounding the diagnosis of drug allergies is certain biases that clinicians may have. Sulfonamide and penicillin antibiotics, for example, are considered notorious for causing drug allergies. As a result, signs of allergic reactions observed with these drugs are more likely to be noted than with a drug that the clinician does not commonly associate with drug allergy.

Physical examination should include a complete evaluation, with a strong focus on the skin, including haired skin, the mucocutaneous junctions (oral, nasal, ocular, anus, and genital), and oral mucosa. The pleomorphism of cutaneous reaction patterns with drug allergies complicates diagnosis because these drug-related cutaneous signs can mimic any other cutaneous disease.⁴¹ Ruling out other possible causes is important for diagnosis of drug hypersensitivity.

The combination of a thorough history and a thorough physical examination may by themselves give a strong suspicion of drug hypersensitivity. Other diagnostic tests then can be performed to help make a definitive diagnosis.

Complete Blood Count and Serum Biochemistry

Complete blood work should be performed as part of the diagnostic evaluation. In many cases of ADRs, these laboratory findings will not be instrumental in the diagnosis of cutaneous drug hypersensitivity. However, it will be helpful when the drug allergic reaction is associated with hemolytic anemia, thrombocytopenia, nephritis, or hepatotoxicity. Furthermore, eosinophilia is a common marker of drug allergies in general. In cases of type I reactions, total IgE concentrations can also be increased. In addition, depending on the extent of cutaneous lesions, hypoproteinemia may be present as a result of cutaneous losses.

Histopathology

Histopathology can be performed when drug allergic reactions seem to target a specific organ (eg, bone marrow histology for blood dyscrasias, skin biopsy for cutaneous manifestations). This is of particular importance with severe cutaneous reactions. Skin punch biopsies can be performed on representative lesions. If there are different stages of a particular lesion (eg, erythema, pustule, crust, ulceration), and finances are limited, obtaining newer lesions is more likely to yield a diagnosis. Ideally, several biopsies should be taken with inclusion of samples of different stages of lesions

and also clinically normal skin adjacent to the lesions. Because drug allergies can present in many different ways, histopathology can be useful to differentiate them from other possible differential diagnoses. However, diagnosis cannot be based on histopathology alone, because the reaction patterns seen with drug allergies also can be seen with other etiologies. *Skin Diseases of the Dog and Cat: Clinical and Histopathologic Diagnosis* by Gross et al is a useful textbook for histopathologic lesions of adverse drug reactions. See Table 2 for a concise table of histopathologic findings.

Dechallenge and Rechallenge

The most common test performed is withdrawal of the suspected offending drug (dechallenge). If resolution occurs after withdrawal, then most clinicians presume that their suspicion was correct. In veterinary medicine, especially where other diagnostic tests are less frequently available, this test is the most cost-effective and easiest to perform. If polypharmacy was used on the patient, this can complicate the process. In this case, there are 2 alternatives of how to make a diagnosis. All drugs can be discontinued, and once there is clinical resolution, the medications least likely to have caused a reaction can be reintroduced, one at a time. Alternatively, the clinician may discontinue medications most likely to have incited a reaction 1 at a time. This step-wise approach is useful if the patient is on medications necessary for survival, but is not advised if the clinical signs related to the drug allergy are life-threatening. Drug provocation tests are considered the gold standard to confirm a drug hypersensitivity reaction and identify the specific culprit drug.⁶⁶ However, ethical considerations come into play when the issue of drug provocation testing (rechallenge) is explored. Re-exposing a patient to a drug that previously caused a hypersensitivity reaction can lead to exacerbated clinical signs, and may be life threatening. Anaphylactic reactions and even death are possible. Therefore, this approach is not recommended. Provocation testing (rechallenge) should only be performed in instances where it is absolutely necessary to determine if the drug was indeed responsible for the clinical signs or which drug was the offending culprit because the patient's outcome or long-term survival depends on the suspected drug. This is generally performed under strict hospital surveillance by trained personnel in an environment with CPR capabilities, and the drug is administered at increasing doses (starting from a very low dose) every 30–60 minutes.⁶⁷ This test is always contraindicated in patients that have had near-fatal drug reactions, such as anaphylaxis, TEN, or DRESS.

Skin Tests

Skin testing (prick testing, patch testing, or intradermal testing) has been used in human patients to diagnose various allergic responses in sensitized patients.⁶⁷ There are a limited number of reports of patch testing being performed in veterinary medicine.⁵⁶ Prick testing

and intradermal testing are used to evaluate immediate reactions caused by IgE allergic reaction, and are evaluated within 24 hours, whereas for delayed reactions both intradermal testing (IDT) or patch testing are options, and require readings up to 72 hours. Anaphylaxis is a possible adverse effect of this test. Skin tests for drug allergy have been used mainly in human medicine where they remain relatively unreliable, especially in delayed type reactions.^{68,69} One explanation is that tests that are conducted with the parent drug are likely to be falsely negative if the immune system is sensitized against a drug metabolite or a drug-protein hapten. These tests are more useful in cases in which the suspicion of drug allergy has been built on strong evidence from the case history and clinical signs, and when specific protocols have been validated for the drug of interest.

Antibody Testing

For Type I Reactions. *IgE concentrations:* Increased total IgE concentrations might indicate a type I hypersensitivity reaction, but they are not specific for drug allergy.⁷⁰ Some laboratories have the capacity of measuring drug-specific IgE concentrations for certain specific drug allergies, but these assays often can give false-positive results because of technical artifacts, such as nonspecific binding or cross-reactivity.⁷¹

The basophil activation test (BAT): The BAT is an in vitro test that measures the capacity of basophils to release histamine or upregulate activation markers, such as CD63 and CD203c in the presence of the allergen, the drug itself or one of its metabolites in cases of drug hypersensitivity.⁶⁵ This type of assay appears to be helpful, but is not readily available for veterinary practitioners at this time.

For Delayed Reactions. Antidrug IgG has been detected in multiple drug allergies in both human and veterinary medicine.^{18,33,72} Autoantibodies against specific tissues (eg, liver, platelets, neutrophils) also have been identified in human and veterinary patients with a history of delayed drug hypersensitivity.^{53,73–75} There is very little evidence of antibodies specifically targeting cutaneous proteins in skin drug allergies to date.

Antidrug and antitissue antibodies that have been identified in patients with a history of delayed drug hypersensitivity sometimes have also been detected in patients who tolerated the drug normally. It is therefore difficult to consider them as more than diagnostic biomarkers. However, some of these antibodies have been shown to correlate with the prognosis of the drug reaction or its clinical signs.^{18,53} Trying to look for these antibodies more systematically in the future could help researchers characterize their potential diagnostic and clinical roles.

Cellular Testing

The lymphocyte transformation test (LTT) is used to evaluate delayed hypersensitivity, because T cells are more likely to be involved in those ADRs. It

measures ex vivo T cell proliferation in response to a specific drug antigen.⁷⁶ The lymphocytes are obtained from the patient, and cultured with the offending drug. The proliferative response can be measured by radiolabeled thymidine incorporation. This test has been used in veterinary patients with drug allergies on rare occasions,³¹ but is more commonly reported in the human literature.

ADR Algorithms

In an attempt to better assign causality to adverse drug events, different algorithms have been used in both human⁷⁷ and veterinary medicine.^{25,57,78} They include multiple factors, such as temporal relationships, dechallenge and rechallenge results, anatomical site, previous ADRs, type of ADRs, drug-drug interactions, or drug dosages. Each factor is given a score. These scores are added up, and the total is compared with a pre-established scale of likelihood of a drug allergic reaction. Because diagnosing a drug hypersensitivity reaction can be such a challenge, some authors recently have suggested that creating computer-based algorithms might be required to improve results.⁷⁹

Overview of Treatment Options

Supportive Care

The majority of drug allergies are not life threatening and will resolve once the offending medication is discontinued. In these cases, treatment is largely symptomatic. For cases in which the hypersensitivity has caused severe disease, additional treatment may be warranted according to the clinical signs and the clinical pathology results. Supportive care such as IV fluids may be necessary to account for fluid loss through the skin if there are large areas of ulceration. Similarly, cutaneous protein loss may necessitate oncotic support. In diseases, such as pemphigus vulgaris and TEN, where cutaneous pain is a prominent feature, analgesics are warranted.² When the integrity of the skin is compromised over a large surface, antibiotic therapy is advised. Depending on the extent of systemic signs associated with the drug allergy, additional therapies also may be implemented (eg, blood products if there is concurrent IMHA, or S-adenosyl methionine in cases of hepatotoxicity).

Anti-inflammatory and Immunosuppressive Treatment

Antihistamines also may prove beneficial in cases of Type I reactions in which clinical signs are caused by the release of powerful inflammatory mediators such as histamine. Interestingly, reports in the human literature note that the use of histamine H1 and H2 receptor antagonists is more beneficial than H1 receptor antagonist therapy alone.⁸⁰ Antihistamines also might help relieve some of the intense pruritus that some drugs can induce during allergic reactions.

The use of glucocorticoids in drug allergies is controversial. At immunosuppressive dosages (ie, 2–4 mg/kg of prednisone daily) they are expected to have a major effect on both the humoral and cellular immune system.⁷⁰ In human patients with anaphylaxis, their benefit remains unclear. They affect the late phase of anaphylaxis, which could be crucial for the outcome of the drug reaction.⁸⁰ In drug-induced pemphigus, treatment with corticosteroids may be necessary to manage the disease until the clinical signs resolve after the discontinuation of the drug. Drug-triggered pemphigus may necessitate chronic treatment with immunosuppressive drugs to manage the disease, because remission will not occur upon discontinuation of the drug.^{48,49} For other types of drug allergies, glucocorticoids have been used with mixed results depending on the patients. If indicated, both systemic and topical corticosteroids can be used to control the immunologic reaction. Dosages, treatment duration and how swiftly corticosteroids can be tapered will depend on many factors, including the disease present, the systemic health of the patient, response to treatment, and the potential for adverse effects from the corticosteroids themselves. Their use also could increase the risk of sepsis encountered in cases of severe skin detachment.²

Other immunosuppressive drugs, such as cyclosporine or azathioprine may be warranted, more so in severe cases of skin reactions, such as pemphigus, EM or TEN. However, these cases might also be those with the highest risk of secondary bacterial infection. Human IV immunoglobulins (IVIG) have been used in cases of EM and TEN, with some success.^{2,81,82} There are also reports of human IVIG being used in severe cases of pemphigus foliaceus.⁸³ One team successfully treated 2 dogs with suspected drug-induced skin lesions with human IVIG.⁸⁴

These immunosuppressive therapies have been used only in isolated cases of drug hypersensitivity in veterinary medicine, and randomized blinded clinical trials in human medicine are not available to provide true evidence of their efficacy in drug allergic reactions.

Future Management

If drug hypersensitivity has been documented, the drug should be avoided for the rest of the patient's life. Re-exposure to the offending drug, even in minute amounts, can cause similar or substantially worse clinical signs, and these signs can become life-threatening even if the reaction in the 1st episode was relatively benign.

In rare instances, desensitization may be performed, if future use of the drug is deemed imperative.⁸⁰ This is used occasionally in cases of drug allergy in human medicine, although the protocols can be cumbersome and are not always successful. Furthermore, the potential risks associated with these protocols are great, and may outweigh the indications for use of the drug.

In addition, drugs with related structures should be identified and avoided, as there is potential for cross-

reactivity. For example, cephalosporins and other β -lactam antibiotics often are thought to present a high risk of cross-reactivity because of the presence of the β -lactam ring in all of these antibiotics.⁶⁷ However, the risk of cross-reactivity in practice among these antibiotics is low; the rate of cross-reaction between penicillins or among penicillins and cephalosporins has been reported as 5% or less in humans.⁸⁵

Reporting

When ADRs have been diagnosed or are strongly suspected, they should be reported to the pharmaceutical company, which is legally obligated to transfer the report to the FDA, and which is likely to have up-to-date information regarding ADRs to the drug of interest. A monitoring and reporting program can provide benefits to clinicians, patients, and pharmacists. Especially in veterinary medicine, where case reports of ADRs are not commonly published in the literature, reporting will be an invaluable means of collecting more information and extending our knowledge about the mechanisms and treatments of these diseases.

In an era of translational research in which clinicians and researchers work side-by-side to improve patient care and scientific knowledge, contacting a researcher specialized in veterinary ADRs also could help the clinician establish a diagnosis and manage the clinical signs. Ex vivo experiments on the patient's samples (eg, blood, skin biopsies) could further advance knowledge of cutaneous drug allergies in veterinary medicine where evidence-based information is very limited.

Conclusion

Drug hypersensitivity reactions are idiosyncratic and immune-mediated. Cutaneous reactions are common manifestations that are easily mistaken for other cutaneous diseases. Very little is known about the pathogenesis of drug hypersensitivity reactions in veterinary medicine, limiting diagnostic and treatment options. Most information is derived from human medicine where knowledge about the pathogenesis of drug hypersensitivity also is relatively limited despite over half a century of research. Increasing awareness among veterinarians and better reporting hopefully will improve this frustrating situation.

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