Idiosyncratic Drug Toxicity Affecting the Liver, Skin, and Bone Marrow in Dogs and Cats

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INTRODUCTION

Drug toxicities can be categorized generally as dose dependent or idiosyncratic. For dose-dependent reactions, toxicity increases reliably with dose in one or more species, and most members of a population are affected at high enough dosages. In contrast, idiosyncratic reactions occur in only a small proportion of patients at therapeutic dosages, and are more difficult to predict. Idiosyncratic toxicity does not increase with dose in the general population (therefore they are not considered dose dependent), but toxicity probably does increase with dose in susceptible individuals.

Idiosyncratic drug toxicity is often caused by reactive metabolites, which may be variably generated among individuals (Fig. 1). These reactive metabolites typically cause oxidative stress and/or lead to haptens that trigger a humoral or T cell–mediated immunologic response. Although idiosyncratic drug reactions are sometimes called drug hypersensitivity reactions, they may or may not involve an adaptive immune response.

KEYWORDS

- Adverse drug reaction
- Hepatotoxicity
- Skin eruption
- Blood dyscrasia

KEY POINTS

- Idiosyncratic drug toxicity reactions typically occur in the first 1 to 2 months of drug therapy.
- The presence of a new fever, skin eruption, blood dyscrasia, or hepatopathy (with either a cholestatic or hepatocellular pattern) should raise suspicion for idiosyncratic drug toxicity. Proteinuria, uveitis, arthropathy, or mucocutaneous ulceration can also be seen.
- Management involves early drug discontinuation and, depending on the drug involved, treatment with glutathione precursors, short courses of prednisolone, or intravenous immunoglobulin.

Disclosures: The author has nothing to disclose.
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http://dx.doi.org/10.1016/j.cvsm.2013.04.003
vetsmall.theclinics.com
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response. Idiosyncratic drug reactions usually require discontinuation of the suspect drug and avoidance of structurally related drugs because they may cause a similar reaction.

TARGETS OF IDIOSYNCRATIC DRUG TOXICITY

The liver, skin, bone marrow, and circulating blood cells are common targets of idiosyncratic drug toxicity. The liver is susceptible because of high blood flow and a high concentration of cytochrome P450s and other biotransformation enzymes that can generate reactive metabolites. Blood cells have a high tissue mass of circulating or dividing cells, which express cytochrome P450s, myeloperoxidases, and cyclooxygenases, each of which can bioactivate certain drugs. In addition, the skin has a large surface area, with a high number of antigen-presenting (Langerhans) cells, and some cytochrome P450 and cyclooxygenase activity in keratinocytes.

DRUGS IMPLICATED IN IDIOSYNCRATIC TOXICITY

This article focuses on the most common drugs associated with idiosyncratic toxicity; less commonly prescribed drugs or those with only single reports of idiosyncratic toxicity are listed in Table 1.

Potentiated Sulfonamides

Sulfonamide antibiotics are one of the oldest antimicrobial classes used in veterinary medicine, and are still important for the treatment of methicillin-resistant staphylococcus and fluoroquinolone-resistant gram-negative bacterial infections. However, potentiated sulfonamides can lead to hepatopathy, blood dyscrasias, and skin eruptions, typically after 5 to 14 days of treatment (also known as sulfonamide
## Clinical presentation of idiosyncratic sulfonamide toxicity

- Fever (50% of cases)\(^2\)
- Hepatocellular necrosis, cholestasis, or both

### Table 1

Other drugs associated with idiosyncratic toxicity in dogs or cats

<table>
<thead>
<tr>
<th>Drugs in Dogs</th>
<th>Toxicity</th>
<th>Clinical Features, Mechanism(s)</th>
<th>Monitoring and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylbutazone</td>
<td>Aplastic anemia in dogs(^{49})</td>
<td>Oxidation of phenylbutazone to reactive metabolites by blood cell peroxidases(^{50})</td>
<td>Phenylbutazone not recommended for use in dogs or cats</td>
</tr>
<tr>
<td>Fenbendazole</td>
<td>Pancytopenia, bone marrow necrosis in dogs(^{29,51})</td>
<td>Not established; onset within 2 wk of starting fenbendazole</td>
<td>Very rare; routine monitoring of CBC not indicated</td>
</tr>
</tbody>
</table>
| Flucytosine       | Skin eruptions with depigmentation and ulceration\(^{52}\) | Median onset 2–6 wk after starting flucytosine  
Nasal planum, scrotum, and mucocutaneous junctions affected | Clinical vigilance, drug discontinuation, and supportive care   |
| Mitotane          | Hepatopathy (mixed hepatocellular and cholestatic pattern)\(^{53}\)  
Bone marrow necrosis\(^{29}\) | Hepatopathy seen after 1 mo of treatment (single case)\(^{53}\) | Hepatopathy and bone marrow lesions apparently rare            |
| Griseofulvin      | Neutropenia or pancytopenia in cats\(^{54,55}\)  
Pancytopenia in a dog\(^{56}\) | Neutropenia reported in FIV-positive cats; recurrent with rechallenge\(^{55}\)  
Toxicity not reproducible in cats given high dosages\(^{57}\) | Alternatives to griseofulvin recommended                       |
| Albendazole       | Bone marrow suppression in a cat\(^{58}\) | One case report, erythroid and megakaryocytic lines affected, mechanism unknown  
Reported in humans with underlying cirrhosis                  | Reversible with drug discontinuation and supportive care       |
| Meloxicam         | Vasculitis with ulcers, vesicles, and erosions in a dog\(^{30}\) | Noted within 2 d of starting drug, which is atypical for a drug hypersensitivity reaction with first exposure | Apparently rare                                                 |

Abbreviations: CBC, complete blood count; FIV, feline immunodeficiency virus.

hypersensitivity). Keratoconjunctivitis sicca may also be seen, but this occurs in about 15% of treated dogs,\(^1\) often after a month or more of administration, and does not fit a classic idiosyncratic pattern, although its pathogenesis is not entirely understood.
- Transient neutropenia
- Thrombocytopenia
- Hemolytic anemia (Coomb negative or positive)
- Skin eruptions
  - Vasculitis
  - Pemphigus foliaceus
  - Bullous skin eruptions (erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis)
- Polyarthropathy
- Proteinuria
- Uveitis

Sulfonamide hypersensitivity reactions are caused by an oxidized hydroxylamine metabolite that is generated by cytochrome P450s and myeloperoxidases. This hydroxylamine can circulate in the plasma, and spontaneously oxidizes to a reactive nitroso metabolite that covalently binds to proteins and acts as a hapten. Drug-specific T cells, some of which have been shown to mediate toxicity against keratinocytes, have been found in human patients, and drug-specific T cells may also occur in dogs. In addition, dogs with sulfonamide hypersensitivity develop antidrug antibodies that cross react with sulfamethoxazole, sulfadiazine, and sulfadimethoxine in about 30% of dogs. In dogs with thrombocytopenia following sulfonamide antimicrobials, antiplatelet antibodies are present, which recognize noncovalent drug-platelet complexes. Some of these antibodies require the continuous presence of sulfonamide drug to bind to platelets, which may explain why thrombocytopenia may resolve rapidly in some dogs after sulfonamide discontinuation.

Risk factors for sulfonamide hypersensitivity in dogs are not clear. Brand name and generic formulations have each been implicated. Doberman pinschers seem to be over-represented among dogs with the combination of polyarthropathy, thrombocytopenia, and proteinuria. Human patients with sulfonamide hypersensitivity may also cross react with structurally related arylamine drugs such as dapsone and sulfapyridine (found in sulfasalazine). However, there is no clear evidence of cross reactivity between sulfonamide antibiotics and nonarylamine drugs containing a sulfonamide group, such as furosemide, acetazolamide, and hydrochlorothiazide. Despite the term sulfonamide hypersensitivity, it is the arylamine moiety, and not the sulfonamide part of the drug, that is involved in hapten generation.

Management of suspected sulfonamide hypersensitivity
- Owner vigilance for adverse events
- Stop potentiated sulfonamide at first sign of illness
- Supportive care
- Consider treatment with antioxidants:
  - Ascorbate and glutathione decrease binding of sulfonamide metabolites to dog liver proteins in vitro (Lavergne and Trepanier, unpublished data, 2005)
    - Ascorbate 90 mg/kg/d intravenous (IV) (empiric dosage)
    - N-acetylcysteine 140 mg/kg loading IV, then 70 mg/kg every 6 hours for 7 treatments (as for acetaminophen toxicosis)
- Consider short course of prednisone (2–3 months)
  - If persistent thrombocytopenia or hemolytic anemia
- Consider IV immunoglobulin
  - Anecdotal success for sulfonamide-associated bullous skin eruptions in a dog (IV immunoglobulin G at 0.5 g/kg)
Methimazole

In cats, the antithyroid drug methimazole is also associated with idiosyncratic toxicity affecting the liver, skin, and blood cells. Similar reactions have also been reported for carbimazole, which is a prodrug of methimazole (see the carbimazole [Vidalta] label).

Methimazole hepatotoxicity shows a mixed hepatocellular and cholestatic pattern in cats, and typically occurs in the first month of treatment, with a 1% to 2% incidence of jaundice. Drug-induced increases in liver enzymes resolve within several weeks of methimazole discontinuation, although clinical improvement is more rapid. Rechallenge has led to recrudescence of hepatotoxicity. These changes are distinct from innocent increases in alanine aminotransferase (ALT) and serum alkaline phosphatase (SAP) seen in cats with hyperthyroidism, which resolve with a return to the euthyroid state and do not worsen during antithyroid drug treatment.

Methimazole hepatotoxicity also occurs in about 9% of human patients, with a mean onset of 28 days after starting the drug. Hepatotoxicity has been observed in a rodent model, and is associated with an N-methylthiourea metabolite that is generated by flavin monooxygenases. Glutathione depletion is an experimental risk factor for methimazole hepatotoxicity, and either N-acetylcysteine or taurine attenuate hepatocyte toxicity in vitro. These findings may have relevance for methimazole hepatotoxicity in cats. Although we recently found no association between glutathione depletion and idiosyncratic methimazole toxicity in pet cats, cats were tested after their adverse reactions instead of before methimazole administration, and only blood, not hepatic, glutathione was measured.

Blood dyscrasias are seen in about 4% of cats treated with methimazole, and include thrombocytopenia and neutropenia or agranulocytosis. These reactions typically occur in the first 1 to 2 months of treatment, and rechallenge has led to recurrence. Monitoring for blood dyscrasias is important, because these reactions can progress to bleeding or secondary infections.

In humans, methimazole-induced and carbimazole-induced blood dyscrasias are well described, to include thrombocytopenia, hemolytic anemia, neutropenia, and agranulocytosis. These reactions seem to be immune mediated, but can occur after years of therapy. Drug-dependent antibodies targeting neutrophils (FcyRIIIb) and erythrocytes (Rh complex proteins) have been shown, as well as antibodies that bind to the adhesion molecule PECAM-1 in the presence of drug. PECAM-1 (also known as CD31) is expressed on platelets, neutrophils, and monocytes, and antibodies against this molecule may explain the involvement of multiple cell lineages in these blood dyscrasias. In addition, the requirement of drug for antibody binding in vitro is consistent with the development of transient protein-drug neoantigens. Such a scenario is also consistent with the clinical observation of rapid recovery of cell counts after drug discontinuation in cats, although methimazole-dependent or carbimazole-dependent antibodies in cats have yet to be evaluated.

Pruritus and facial excoriation develops in 2% to 3% of cats treated with methimazole, most commonly in the first 3 weeks of treatment. Lesions are typically caused by self-trauma of the neck and the face anterior to the pinnae, but have not been characterized histologically. Pruritus and urticaria are also seen in about 8% of pediatric patients and up to 20% of adults treated with methimazole, typically in the first 4 weeks of treatment. More severe bullous skin eruptions such as Stevens-Johnson syndrome have also been reported. The mechanisms for these reactions have not been explored.
Prevention and management of methimazole toxicity

- Counsel owners to monitor for lethargy, vomiting, inappetence, jaundice, or pruritus.
- Stop drug at first potential sign of adverse reaction.
- Evaluate cat as soon as possible:
  - Physical examination for skin excoriations
  - Rule out blood dyscrasia (complete blood count [CBC])
  - Rule out hepatotoxicity (ALT, bilirubin, SAP)
    - Compare with pretreatment liver enzymes (often reversibly increased in hyperthyroid cats)
  - Evaluate for renal decompensation (blood urea nitrogen [BUN], creatinine, serum T4)
- If simple gastrointestinal (GI) upset (normal blood work):
  - Plan dose reduction or switch to transdermal methimazole, which has a lower incidence of GI upset than oral methimazole
- If blood dyscrasia, hepatopathy, or facial excoriation:
  - Plan radioiodine, or, if not available, thyroidectomy with atenolol pretreatment
  - The efficacy of glutathione precursors or glucocorticoids has not been evaluated for methimazole in this setting.

Carprofen

Carprofen is commonly thought to have a higher risk of hepatotoxicity than other nonsteroidal antiinflammatory drugs (NSAIDs), but this has not been shown in a comparative study. The veterinary labels for meloxicam, etodolac, deracoxib, firocoxib, and robenacoxib also report liver toxicity in dogs. However, idiosyncratic carprofen hepatotoxicity has been described in the greatest detail.

Clinical presentation of carprofen hepatotoxicity

- Most dogs affected within 14 to 30 days
- Acute hepatic necrosis with marked increases in ALT
  - No reported cases of carprofen hepatotoxicity have had increases in SAP without large accompanying increases in ALT
- Labrador retrievers were over-represented in the initial report, but the manufacturer could not reproduce this syndrome in Labrador dogs (personal communication, Dr. Terry Clark, 2002). Therefore, this is unlikely to be a true breed risk.
- Manufacturer’s report rate: fewer than 5 cases per 10,000 dogs treated (<0.05%)
  - Hepatic dysfunction in less than 0.02% of treated dogs

Idiosyncratic NSAID hepatotoxicity also occurs in human patients, with diclofenac implicated most commonly. Threefold or higher increases in ALT occur in about 5% of patients, with hepatocellular necrosis in the first 6 months of diclofenac treatment seen much less commonly. Diclofenac metabolites cause mitochondrial injury in vitro, which could explain mild transaminase increases in some patients. The progression to hepatocellular necrosis could involve an amplification of this cytotoxicity by an immune response to drug haptens, in particular those formed by reactive acylglucuronide and quinone imine diclofenac metabolites. Carprofen shares some structural similarities with diclofenac, so a similar scenario could apply to carprofen as well. This topic requires further evaluation.

NSAID-associated blood dyscrasias and skin eruptions have been reported in isolated case reports in veterinary patients, to include thrombocytopenia and hemolytic anemia (1 case) and bone marrow necrosis (3 cases) during carprofen treatment, and vasculitis during meloxicam or carprofen treatment (1 case each).
Although hepatotoxicity, cytopenias, and vasculitis from NSAIDs can be severe, these idiosyncratic reactions are rare, and are not efficiently detected by routine biochemical monitoring. Clinical monitoring by owners is key, and every client should be advised to monitor for new vomiting, diarrhea, lethargy, skin lesions, or change in urine color. Dose-dependent gastric ulceration and new azotemia are more common, and deserve routine clinical monitoring. Middle-aged to older dogs are more likely to have preexisting organ dysfunction, and should have baseline blood work performed to evaluate hematocrit, BUN, creatinine, albumin, and ALT before starting NSAID treatment. Abnormal clinical signs during NSAID treatment in any dog should prompt drug discontinuation; a physical examination, CBC, and biochemical panel can distinguish between simple GI upset, gastric ulceration, renal compensation, or idiosyncratic reactions.

**Zonisamide**

Acute hepatotoxicity was recently reported in 2 dogs treated with the anticonvulsant drug zonisamide.\(^{31,32}\) In both dogs, clinical signs developed in the first 3 weeks of treatment, one with a hepatocellular pattern and one with a mixed hepatocellular and cholestatic pattern. Liver failure progressed in 1 dog; necropsy showed massive hepatic necrosis with marked periportal microvesicular steatosis. Further clinical experience is needed before the incidence of zonisamide hepatotoxicity is clear; however, dog owners should be informed of this potential adverse drug reaction when zonisamide is prescribed. Clients should be advised to watch for signs of lethargy, GI upset, change in mucous membrane color, or dark urine.

**Diazepam**

Oral diazepam has led to idiosyncratic acute hepatic necrosis in some cats.\(^{33,34}\) Affected cats have been otherwise healthy and treated for behavioral problems or urethrospasm; clinical signs were typically seen after 8 to 9 days of treatment. Both generic and brand name oral diazepam have been implicated, although injectable diazepam has not.\(^{33}\) The time frame for toxicity suggests an immune component (humoral or T-cell mediated), although this has not been explored. Reactions are fulminant and often fatal, but aggressive supportive care can be successful.\(^{35}\) Acute idiosyncratic liver injury from benzodiazepines is seen uncommonly in human patients,\(^{36,37}\) so potential mechanisms have not been explored.

**Phenobarbital**

Phenobarbital hepatotoxicity typically occurs in dogs after a year or more of phenobarbital treatment, and can present with asymptomatic increases in bile acids, clinical signs of hepatic disease, or overt liver failure.\(^{38}\) The clinical presentation does not follow a classic idiosyncratic or dose-dependent pattern; it is seen late in the course of treatment, and can resolve with dose reduction; however, it has not been reported with loading doses or been reproduced in experimental studies.\(^{39,40}\)

Phenobarbital hepatotoxicity is probably best described as dose/duration dependent with individual modifiers, but individual risk factors are not clear. Hepatotoxicity could be related to cytochrome P450 induction by phenobarbital, with secondary bioactivation of dietary or environmental compounds. Primidone and phenytoin, which are also cytochrome P450 inducers, lead to a similar pattern of delayed hepatotoxicity.\(^{41}\) In contrast, phenobarbital in cats leads to neither cytochrome P450 induction nor hepatotoxicity. Given the popularity of phenobarbital as an anticonvulsant in dogs, this adverse reaction deserves further study.
Prevention and management of phenobarbital hepatotoxicity

- Use the minimal effective dosage of phenobarbital; consider combination therapy with bromide or other anticonvulsants.
- Evaluate serum bile acids every 6 months during phenobarbital treatment.
- Monitor for inappetence, vomiting, diarrhea, or increased sedation (which can signal decreased hepatic clearance of phenobarbital).
- Screen liver function tests if clinically ill (albumin, bilirubin, BUN, cholesterol, glucose, bile acids, and coagulation profile).
- If hepatopathy develops, plan phenobarbital discontinuation or substantial dose reduction.
- Consider transitioning to KBr monotherapy (40–60 mg/kg/d).
  - Rapid taper of phenobarbital over 1 to 2 weeks
  - KBr loading dose of 400 to 600 mg/kg if brittle epilepsy and no hepatic encephalopathy

In addition to liver toxicity, phenobarbital has rarely been associated with blood dyscrasias in dogs. Abnormalities have included thrombocytopenia, neutropenia, and anemia, with bone marrow necrosis or myelofibrosis noted on bone marrow evaluation. These reactions respond to drug discontinuation and supportive care unless advanced myelofibrosis has developed.

In human patients, anticonvulsant hypersensitivity syndrome, which can include thrombocytopenia, leukopenia, anemia, and hepatopathy, has also been associated with phenobarbital, with a different clinical presentation than in dogs. This syndrome typically occurs within the first 3 weeks of starting treatment, with a delay of 6 days or more. Reactions may be accompanied by fever, eosinophilia, lymphadenopathy, and skin eruptions, and share many clinical features with sulfonamide hypersensitivity. Patients are managed with drug discontinuation, along with weeks to months of antiinflammatory to immunosuppressive dosages of glucocorticoids in some cases, and IV immunoglobulin in severely affected patients. If hepatopathy is also present, patients are treated with N-acetylcysteine. These reactions may be caused by reactive arene oxide metabolites that form protein-drug haptens and elicit a secondary immune response. Drug-specific T cells have been shown in human patients with hypersensitivity reactions to anticonvulsants that are structurally related to phenobarbital.

In addition, phenobarbital has been associated with skin lesions in dogs; in particular, superficial necrolytic dermatitis. About 45% of cases of superficial necrolytic dermatitis (also called necrolytic migratory erythema or hepatocutaneous syndrome) in dogs are associated with phenobarbital administration. Skin lesions are characterized by hyperkeratosis, crusting, and erythema of the footpads, mucocutaneous junctions, and nasal planum. These lesions develop only after prolonged treatment (a median of 7 years) and are associated with hepatopathy; therefore, the pattern is not consistent with idiosyncratic drug toxicity. The presentation is distinct from the skin eruptions seen in human patients treated with phenobarbital, which occur early in treatment (within the first 2 months) and are not related to any accompanying liver toxicity.

SUMMARY: MONITORING FOR DRUG-INDUCED IDIOSYNCRATIC TOXICITIES

- Obtain a current drug history at every visit
- Always consider a possible adverse drug reaction in your differential list
  - Higher index of suspicion for an idiosyncratic reaction when clinical signs develop within 4 weeks of starting a new drug
● If clinical signs develop:
  ○ Evaluate for new 3-fold or higher increases in ALT, or cholestasis with jaundice
  ○ Screen for regenerative or nonregenerative cytopenias
  ○ Perform careful examination of skin and mucocutaneous junctions
  ○ Also evaluate for uveitis, joint effusion, or proteinuria

● When in doubt, discontinue all suspect drugs and reintroduce essential drugs one at a time, with careful clinical and biochemical monitoring after each drug addition. Allow 1 to 2 weeks between each drug addition.

REFERENCES