Idiosyncratic Drug Toxicities

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Mechanisms of toxicity

A. Dose-dependent
   1. Increasing toxicity with increasing dose, in one or more species
   2. Virtually all members of a population or species will be affected at high enough dosages
   3. Relatively predictable
      a) Therapeutic drug monitoring helpful
   4. May be due to property of parent compound, or to a metabolite that is *reliably* generated in that species
   5. May or may not be related to the desired pharmacologic action of the drug
   6. Requires dose reduction but usually not drug discontinuation

B. "Idiosyncratic"
   1. Toxicity at therapeutic dosages, in a small proportion of the species or population
   2. Toxicity does not increase with dose in the general population (therefore not considered "dose-dependent"), but toxicity probably does increase with dose among susceptible individuals
   3. Relatively unpredictable
      a) Therapeutic drug monitoring generally not helpful
   4. May be due to property of parent compound or of a metabolite that is variably generated in that species
   5. Usually not related to desired pharmacologic action of the drug
   6. May or may not involve an immunologic response
   7. Usually requires discontinuation of the suspect drug

Idiosyncratic toxicity - Targets

A. Liver
   1. Susceptibility of liver
      a) Site of first-pass clearance of many orally administered drugs
      b) Site of P450-mediated bioactivation of some compounds to more reactive metabolites
   2. Types of adverse effects on hepatic function caused by drugs
      a) Acute:
         1) Cytotoxic
            i. Often due to reactive metabolite
            ii. May lead to haptenization with immune response
         2) Cholestatic
            i. Inhibition of transporters
         3) Mixed
            i. Cytotoxic and cholestatic
      b) Chronic:
         1) Many patterns could result from chronic drug injury: chronic hepatitis, steatosis, vacuolar degeneration, granulomatous change, or cirrhosis

B. Bone marrow
   1. Susceptibility
      a) Large tissue mass (including circulating cells)
      b) Rapidly dividing cells.
      c) Bone marrow precursors and peripheral blood cells are metabolically active
         1) Cytochrome P450
         2) Myeloperoxidases
         3) Cyclooxygenases
            i. Can bioactivate drugs to reactive intermediates
   2. Idiosyncratic drug-induced blood dyscrasias include
      a) Thrombocytopenia
      b) Neutropenia
         1) Agranulocytosis if severe
      c) Hemolytic anemia

d) Pure red cell aplasia
e) Aplastic anemia

3. Mechanisms of idiosyncratic bone marrow damage include
   a) Reactive drug metabolite leading to:
      1) Cytotoxic destruction of peripheral or stem cells
      2) Haptenization with immune response directed at peripheral or stem cells
      3) Genetic mutations in stem cells
   b) Suppression of hematopoiesis due to deranged cytokine production

C. Skin
1. Susceptibility
   a) Large tissue mass
   b) Keratinocytes can bioactivate some drugs
   c) Large number of antigen presenting cells in skin (Langerhans cells)
2. Idiosyncratic skin eruptions caused by drugs:
   a) Vasculitis
      1) Examples: Meloxicam, sulfadiazine
   b) Pemphigus foliaceus
      1) Example; potentiated sulfonamides
      2) Erythema multiforme
         i. Localized detachment of the epidermis
      3) Stevens-Johnson syndrome
         i. Widespread lesions but less than 10% of epidermis is detached
      4) Toxic epidermal necrolysis
         i. Widespread lesions with more than 30% of epidermis is detached
3. Mechanisms of skin lesions
   a) Haptenization of keratinocytes > targeting of altered "self" by antibodies and/or T cells
   b) Association with HLA genotypes (MHC I and MHC II) in humans

Drugs implicated in idiosyncratic drug toxicity

A. Phenobarbital
1. Toxicity in humans: idiosyncratic toxicity not a major side effect
2. Hepatotoxicity in dogs
   a) Probably better described as dose-dependent with individual modifiers
   b) Ranges from asymptomatic increases in bile acids, to overt cirrhosis
   c) Possible mechanism of toxicity
      1) Induction of P450 enzymes with secondary bioactivation and hepatotoxicity of other substances (drugs, dietary components, environmental toxins)
      2) Direct cytotoxic effect is unlikely, since hepatotoxicity has not been seen with loading doses of phenobarbital
   d) Risk factors
      1) Prolonged duration and high dose
      2) Prior therapy with primidone or phenytoin
   e) Management
      1) Phenobarbital discontinuation or dose reduction
      2) Maintenance dose of KBr at 40-60 mg/kg/day
         i. KBr loading dose of 400-600 mg/kg if brittle epilepsy and no hepatic encephalopathy
      3) Rapid taper of phenobarbital over 1-2 weeks
      4) Both felbamate and zonisamide are also associated with hepatotoxicity in dogs
         i. Not ideal rescue drugs for phenobarbital hepatotoxicity until more is known about mechanisms
   f) Prevention of phenobarbital hepatotoxicity
      1) Use combination antiepileptic therapy to avoid chronic high dosages of phenobarbital
      2) Screen patients on phenobarbital with serum bile acids every 6-12 months
      3) Monitor for
         i. Increases in ALT > SAP
         ii. Hypoalbuminemia

iii. Increased bilirubin (even if mild)
iv. Clinical illness
v. Increased sedation (may indicate impaired hepatic clearance of phenobarbital)

3. Phenobarbital and superficial necrolytic dermatitis
   a) Phenobarbital is associated with almost 45% of cases of superficial necrolytic dermatitis
   b) Liver biopsies show steatosis with nodular regeneration and fibrosis
   c) Mechanism unknown
4. Phenobarbital has also been associated rarely with blood dyscrasias
   a) To include thrombocytopenia, neutropenia, anemia, or myelofibrosis (Jacobs 1998; Weiss 2002; Weiss 2005).
   b) Possible mechanisms include:
      1) Antibody or T cell responses to drug haptens
      2) Cumulative marrow toxicity from reactive metabolite
      3) Deranged folate metabolism
   c) Responds to drug discontinuation and supportive care unless advanced myelofibrosis has developed

B. Potentiated sulfonamide antibiotics
1. Idiosyncratic toxicity in humans and dogs
   a) Classically a delay in onset from 5-14 days post exposure
   b) Fever
      1) 50% of cases
   c) Hepatotoxicity
      1) Hepatocellular necrosis, cholestasis, or both
      2) 20% of FDA-reported drug hepatopathies in dogs were due to potentiated sulfonamides
   d) Thrombocytopenia, neutropenia, IMHA
      1) Neutropenia associated with sulfonamides is an early, transient finding and is usually modest
   e) Skin eruptions
      1) Vasculitis
      2) Pemphigus foliaceus (White 2002)
      3) Erythema multiforme, Stevens-Johnson syndrome toxic epidermal necrolysis
   f) Polyarthopathy, proteinuria
   g) Uveitis
2. Mechanisms of toxicity
   a) P450- or myeloperoxidase-generated oxidized metabolite (hydroxylamine), which is further converted to another oxidized metabolite (nitroso) that covalently binds to proteins and acts as a hapten
   b) T cell mediated cytotoxicity shown in humans
   c) Anti-drug antibodies documented in dogs and humans
      1) Anti-sulfonamide antibodies cross-react across sulfamethoxazole, sulfadiazine, and sulfadimethoxine in about 30% of dogs
      2) In humans and dogs, anti-platelet antibodies recognize non-covalent drug-platelet complexes
         i. Some of these antibodies require continuous presence of sulfonamide drug in order to bind to platelets
      3) Some dogs have antibodies to myeloperoxidase, which suggests that oxidative activation of the sulfonamide by myeloperoxidase contributes to hypersensitivity
   d) No clear evidence of cross-reactivity with other drugs containing sulfonamide moiety (e.g. furosemide, acetazolamide)
3. Risk factors
   a) Familial risk in humans
      1) Under investigation in our laboratory
   b) Breed risk in dogs
      1) Dobermans (arthropathy, thrombocytopenia, proteinuria)
      2) Schnauzers, Samoyeds over-represented in our series of 40 dogs with sulfonamide hypersensitivity
         i. May indicated dosing bias
   c) Tribrissen, Primor, and generic TMP-sulfamethoxazole all implicated in dogs
   d) AIDS in humans
      1) Glutathione and ascorbate depletion
      2) Down regulation of drug detoxification enzymes?

4. Management
    a) Stop potentiated sulfonamide at first sign of illness!!
    b) Ascorbic acid
        1) Ascorbate decreases haptenization of sulfonamides to dog liver proteins *in vitro*
        2) 90 mg/kg/day ascorbate IV (empirical dosage)
    c) N-acetylcysteine
        1) Glutathione also decreases haptenization of sulfonamides to dog liver proteins *in vitro*
        2) 140 mg/kg loading IV, then 70 mg/kg every 6 hours for 7 treatments
        3) Dilute 10 or 20% N-acetylcysteine sterile oral solution to 5% in D5W
        4) Give each IV dose over 30-60 minutes to minimize vomiting
    d) IV IgG
        1) Anecdotal success for sulfonamide-associated bullous skin eruptions in humans (Nuttall 2004)

C. Methimazole
1. Toxicity in humans
    a) Chlolestasis or hepatic necrosis
    b) Neutropenia or agranulocytosis
2. Toxicity in cats
    a) Hepatocellular necrosis (increased ALT) or cholestasis (increased SAP)
    b) Blood dyscrasias (thrombocytopenia, neutropenia)
    c) Skin eruptions (facial excoriations)
        1) Biopsies typically not performed
3. Mechanisms of toxicity
    a) Hepatotoxicity is due to N-methylthiourea metabolite
        1) Glutathione depletion is risk factor experimentally
    b) In humans, methimazole-induced neutropenia is associated with an arrest in myeloid progenitors in the bone marrow
        1) May be due to humoral suppression of granulocyte-macrophage CFU's
            i. Anti-neutrophil antibodies documented
            ii. Association of certain HLA haplotypes
        2) Some studies have shown an increased risk of these reactions at higher methimazole doses
4. Management
    a) Evaluate cat at first sign of illness
        1) Rule out blood dyscrasia (CBC)
        2) Rule out renal decompensation
        3) Rule out hepatotoxicity (ALT, bilirubin, SAP)
            i. Make sure to compare to liver enzymes pre-treatment (often reversibly increased in hyperthyroid cats)
    b) If simple GI upset (normal blood work), reduce dose or switch to transdermal methimazole
    c) If idiosyncratic hepatopathy, blood dyscrasias, or facial excoriation, discontinue methimazole
        1) Transdermal route *not* beneficial in reducing risk of idiosyncratic toxicity from methimazole

D. Diazepam
1. Toxicity in humans
    a) Hepatotoxicity not a recognized side effect of diazepam in humans (or in dogs)
2. Toxicity in cats
    a) Fulminant hepatic necrosis with marked increases in ALT
3. Mechanism of toxicity
    a) Not known
    b) Delay of 8-9 days from exposure to onset of signs (reported initially) suggests immune component, but some cats have been affected within 96 hours of first exposure
4. Risk factors
    a) No known breed predilection; has affected healthy cats treated for behavioral problems
    b) Not reported with use of diazepam as IM pre-medicant or IV sedative
5. Management
    a) Stop diazepam
    b) Aggressive supportive care for liver failure
        1) Plasma, vitamin K

2) H_2 blockers
3) Antimicrobial coverage for bacterial translocation
4) Lactulose if encephalopathic

E. Carprofen
1. Toxicity in humans
a) Hepatotoxicity not reported in humans
2. Toxicity in dogs
a) Acute hepatic necrosis
b) Marked increases in ALT
c) More rarely (one case)
1) Neutrophilic dermatitis (vasculitis), thrombocytopenia, and IMHA
3. Mechanisms of toxicity
a) Not yet characterized
b) Most dogs affected 14 to 30 days after drug initiation
c) One dog affected by 5 days, others after 2 months
4. Risk factors
a) Labrador retrievers were over-represented in initial report
1) Manufacturer cannot reproduce syndrome in Labradors
2) Unlikely a true breed risk
b) Incidence: <5 cases per 10,000 dogs treated (0.05%)
5. Management
a) Stop carprofen at first sign of illness
1) Check ALT
2) Note: No reported cases of carprofen hepatotoxicity have had an increase in SAP without a large accompanying increase in ALT
3) Rule out GI bleeding
4) Rule out renal decompensation
b) Aggressive supportive care for liver failure
1) As for diazepam

F. Zonisamide
1. Acute hepatotoxicity recently reported in two dogs treated with the anticonvulsant zonisamide.
a) In one dog, clinical signs began three weeks after drug initiation, with a mixed biochemical pattern. Abnormalities resolved with drug discontinuation.
b) In a second dog, marked increases in ALT with hyperbilirubinemia were noted 10 days after zonisamide was started. This dog was euthanized due to hepatic failure; histopathology showed massive panlobular hepatic necrosis with marked periportal microvesicular steatosis.
c) Further clinical experience is needed before the incidence of zonisamide hepatotoxicity is clear
d) Dog owners and veterinary colleagues should be informed of this potential adverse drug reaction when zonisamide is prescribed.
1) Clients should be alerted to watch for acute signs of illness; if noted, zonisamide should be discontinued and serum ALT should be evaluated.

G. Phenylbutazone
1. Aplastic anemia in humans and dogs
2. Risk factors in humans
a) Older females
b) Treatment for longer than one month
c) This was the reason that this drug was removed from the market for humans
3. Mechanism of toxicity
a) Oxidation of phenylbutazone to reactive metabolites by peroxidases in bone marrow and peripheral blood cells
4. An herbal supplement subsequently found to also contain phenylbutazone was associated recently with aplastic anemia in a young boy

Monitoring for drug-induced idiosyncratic toxicities

A. The most important step is to always keep a possible adverse drug reaction in your differential list
1. Drug history for every patient

2. High index of suspicion when patient develops new clinical signs within 4 weeks of starting a drug
3. CBC, biochemical panel, and UA if clinical signs noted
    a) Phenobarbital: ALT, albumin, bilirubin, bile acids, CBC
    b) Sulfonamides: ALT, bilirubin, platelets, neutrophils
    c) Methimazole: ALT, SAP, bilirubin, CBC
    d) Diazepam: ALT, bilirubin
    e) Carprofen: ALT, bilirubin
4. Check for proteinuria, uveitis, and mucocutaneous lesions
5. Check for joint swelling and KCS (potentiated sulfonamides)
6. Skin biopsy if indicated

Common drugs associated with idiosyncratic (or unclassified) toxicity in dogs

Drugs in dogs	Toxicity	Mechanism(s)	Monitoring and management
Phenobarbital	Hepatotoxicity –probably actually dose-dependent with individual modifying factors (e.g. concurrent environmental exposures) Hepatocutaneous syndrome (relatively rare) Thrombocytopenia, neutropenia, anemia, or myelofibrosis (rare)	May result from P450 induction with secondary bioactivation of environmental toxins May be related to altered glucagon metabolism Unknown	Monitoring for hepatotoxicity (which has dose and duration-dependent component) most important – bile acids every 6 months Clinical monitoring for crusted foot pads Since blood dyscrasias are quite rare, serial CBCs probably not indicated
Potentiated sulfonamides	One or more of the following signs: polyarthropathy, skin eruption, immune thrombocytopenia, hemolytic anemia, transient neutropenia, uveitis, hepatic necrosis or cholestasis, proteinuria (presumptive glomerulonephritis) (KCS is also seen, but appears to be dose- and duration-dependent)	Likely immune reaction to sulfonamide after bioactivation by cytochrome P450 or myeloperoxidase Activated metabolite forms haptens with proteins in target tissues Anti-drug, anti-platelet, and anti-myeloperoxidase antibodies demonstrated in dogs	Vigilance by owner for vomiting, anorexia, diarrhea, fever, dark urine (bilirubinuria or hematuria), jaundice, petechiae, new or worsening skin lesions, or lameness with joint swelling Discontinue drug; provide aggressive support; consider N-acetylcysteine or SAMe, and vitamin C therapy to possibly reduce hapten formation
Carprofen	Acute hepatic necrosis	Unknown	Vigilance by owner for signs of lethargy, vomiting, or inappetance. Stop drug and evaluate biochemical panel if signs observed. Serial ALT measurements unlikely to be reliable due to rarity and acute onset. Perform baseline biochemical panel in older dogs. Increased SAP without increased ALT unlikely to be due to carprofen
Zonisamide	Acute hepatic necrosis Periportal steatosis	Not known	Vigilance by owner for signs of lethargy, vomiting, or inappetance. Stop drug and evaluate biochemical panel if signs observed.

Phenylbutazone	Aplastic anemia	Oxidation of phenylbutazone to reactive metabolites by peroxidases in bone marrow and peripheral blood cells	Phenylbutazone not recommended for use in dogs or cats

Common drugs associated with idiosyncratic (or unclassified) toxicity in cats

Drugs in cats	Toxicity	Mechanism(s)	Monitoring and management
Methimazole	Thrombocytopenia, neutropenia; hemolytic anemia less common	Blood dyscrasias due to arrest of bone marrow myeloid progenitors in humans Antibody or cytokine-mediated suppression of GM-CFU's suspected in humans. Positive ANA and direct Coombs tests reported in cats. Mechanisms for other reactions not known.	Routine CBC at 2 and 4 week rechecks while on methimazole
	Hepatic necrosis or cholestasis		Biochemical panel at 2 and 4 week rechecks
	Facial excoriation		Clinical monitoring
	Myasthenia gravis		Acetylcholine receptor antibody test if neuromuscular weakness noted
Diazepam	Acute hepatic necrosis	Unknown Not seen with injectable diazepam or with midazolam	Alternatives to oral diazepam recommended in cats.
Griseofulvin	Neutropenia Hepatotoxicity	Neutropenia reported in FIV positive cats; recurs with rechallenge Toxicity not reproducible in cats given high dosages	Alternatives to griseofulvin recommended in all cats
Albendazole	Pancytopenia	One case report, mechanism unknown Reported in humans with underlying cirrhosis	Reversible with drug discontinuation