Compendium

Drug-Associated Blood Cell Dyscrasias

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Abstract: *Many therapeutic drugs have been associated with hematologic adverse drug events (ADEs) in animals. Some drugs, notably chemotherapeutic agents and oxidant compounds, cause dose-dependent bone marrow suppression, while others induce idiosyncratic ADEs. Major mechanisms associated with ADEs include immune- or oxidant-mediated destruction of blood cells and toxic bone marrow injury. General classes of drugs that can cause idiosyncratic ADEs include estrogenic compounds, NSAIDs, antibiotics, antifungals, antithyroid drugs, anticonvulsants, antiparasitics, and cardiac drugs. ADEs associated with chemotherapeutic agents, phenylbutazone, phenobarbital, propylthiouracil (in cats), methimazole (in cats), and azathioprine occur frequently enough to warrant performing periodic complete blood counts during the course of treatment.*

Many therapeutic drugs have been associated with adverse drug events (ADEs) affecting the hematologic system in dogs and cats.[1–4] These ADEs have been categorized as type A or type B reactions.[5] Type A ADEs are dose-dependent responses that may be exaggerated in an individual patient.[5] Type B ADEs are idiosyncratic reactions that are unrelated to a drug's pharmacologic effects. Idiosyncratic drug reactions are the most challenging to define because of their unpredictability and may involve a variety of mechanisms.[5,6] A unique genetic or acquired susceptibility of the individual patient is usually involved. Genetic susceptibility frequently involves mutations that alter drug metabolism or induce immune responses to the drug or its metabolites.[7] Acquired susceptibility may occur because of hepatic or renal disease leading to altered metabolism or excretion of the drug or its metabolites.[7]

The site at and mechanism by which a drug acts are important in determining prognosis; however, some drugs act at multiple sites or by several mechanisms, making this determination difficult. Sites of action include the blood and various bone marrow components, including hematopoietic stem cells, proliferating hematopoietic cells, and bone marrow stromal tissue.[6,7] Erythrocytes are particularly sensitive to oxidative injury.[8] Blood cells also appear to be uniquely susceptible to immune-mediated destruction. This susceptibility may be related to the fact that antibodies bind to blood cells in healthy animals as a means of identifying aged cells for removal.[9] Therefore, immune-mediated ADEs could be seen as a normal immune mechanism gone awry. Bone marrow progenitor and proliferative cells are rapidly dividing cells and are, therefore, susceptible to chemotherapeutic agents. Capillaries and sinusoids within marrow are vulnerable to injury. Vascular injury can be seen in bone marrow core biopsy sections as interstitial edema, hemorrhage, necrosis, myelofibrosis, or inflammation.[4,10–12]

Evaluation of Suspected Hematologic Adverse Drug Events

The temporal association of a drug treatment with a hematologic disorder does not in itself provide proof of an ADE. Other potential causes of the hematologic condition should be eliminated by evaluation of the history, clinical, and clinicopathologic findings. An overall diagnostic approach to evaluation of hematologic disorders has been presented elsewhere.[13] Standard criteria for the definition of drug-induced cytopenias have not been defined for animals but have been proposed for humans.[14]

In humans, neutropenia has been defined as <1500 neutrophils/μL.[14] Neutropenia is defined as compatible with an ADE if it is discovered during treatment with a drug. Its relation to therapy is considered to be inconclusive if it is discovered within 1 month after stopping administration of a drug or more than 1 month after administration if no leukocyte counts have been obtained in the interim. An increase in the neutrophil

Key Facts

- Idiosyncratic ADEs are frequently associated with immune- or oxidant-mediated destruction of blood cells or toxic injury to bone marrow.
- Suspected ADEs should be reported to the US Food and Drug Administration.
- Drugs most frequently reported to induce ADEs include chemotherapeutic agents, estradiol (in dogs), phenylbutazone, acetaminophen, sulfadiazine, phenobarbital, azathioprine, propylthiouracil (in cats), and methimazole (in cats).
- Dogs and cats given drugs with a high probability of inducing hematologic dyscrasias, including chemotherapeutic agents, phenylbutazone, phenobarbital, azathioprine, propylthiouracil, and methimazole, should be monitored with periodic complete blood counts.

Table 1. Myelosuppressive Potential of Chemotherapeutic Drugs Used in Dogs and Cats[15,16]

High	Moderate	Low to None
• Cyclophosphamide	• Chlorambucil	• L-Asparaginase
• Cytosine arabinoside	• 5-Fluorouracil	• Bleomycin
• Doxorubicin	• Melphalan	• Corticosteroids
• Hydroxyurea	• 6-Mercaptopurine	
• Vinblastine	• Methotrexate	
	• Vincristine	

count to >1500 cells/µL within 1 month after stopping drug treatment is also suggestive of an ADE.

Thrombocytopenia has been defined as <100,000 platelets/µL in humans.[14] Occurrence of thrombocytopenia within 1 month after initiation of drug treatment or remission within 3 weeks after stopping treatment is suggestive of an ADE.

The definition of drug-induced anemia depends on the species and breed of animal involved. Further, the rapidity of onset of anemia depends on the mechanism by which the drug induces anemia. Drugs that induce intravascular hemolysis frequently cause rapid and severe anemia with associated icterus and hemoglobinuria. Drug-induced extravascular hemolysis is associated with a somewhat less rapid onset of anemia, and hemoglobinuria and icterus are frequently lacking. Anemia associated with suppression of erythropoiesis has a slow, progressive onset. When an ADE is suspected, the US Food and Drug Administration database (http://www.fda.gov/cvm/adetoc.htm) can be reviewed to determine if others have reported similar toxicoses and used to report the suspected toxicosis.[5]

Type A Adverse Drug Events

Chemotherapeutic Agents

The myelosuppressive potential of chemotherapeutic agents varies (**TABLE 1**).[15,16] Because of their high mitotic rate, the progenitor and proliferative pools of cells in bone marrow are predisposed to toxic injury by chemotherapeutic drugs. Cytopenia due to myelosuppression is the most frequent chemotherapeutic toxicosis and often necessitates temporary or permanent discontinuation of treatment.

Bone marrow suppression by chemotherapeutic agents is dose dependent and follows a predictable course based on the half-life of cells in the blood. The half-life of neutrophils is 4 to 8 hours; however, neutropenia does not occur until 5 to 7 days after myelosuppression because there is a 5- to 7-day supply of mature neutrophils in the bone marrow storage pool.[15] Platelet half-life is 5 to 7 days; the nadir of thrombocytopenia occurs 7 to 9 days after myelosuppression.[15,16] Because of the comparatively long half-life of erythrocytes (120 days in dogs; 60 days in cats), anemia would be expected only with long-term administration of chemotherapeutic agents.[15] Neutrophil and platelet counts usually return to baseline values within 72 to 96 hours after therapy is discontinued.[15]

Beyond destruction of hematopoietic cells, chemotherapeutic drugs have few adverse effects on the hematopoietic system. Multifocal areas of coagulation-type necrosis have been reported in association with administration of cyclophosphamide and vincristine.[4] An increase in dysplastic hematopoietic cells and atypical mitotic figures (i.e., secondary dysmyelopoiesis) is a frequent finding and should not be confused with a myelodysplastic syndrome.[17,18] Doxorubicin administration has been association with poikilocytosis in dogs and cats, including the presence of ovalocytes, echinocytes, schistocytes, and keratocytes.[19] Doxorubicin is known to bind to cell membranes, but the exact mechanism by which it produces erythrocyte shape alterations is unknown.[19]

Oxidants

Many drugs have oxidant properties or are metabolized to oxidants.[8] ADEs associated with these drugs are dose dependent because tissue injury largely depends on the degree of oxidative injury. Oxidative damage of cell membranes usually manifests as lipid peroxidation or protein cross-linking.[8] In the case of erythrocytes, iron in heme can become oxidized to form methemoglobin.[8] If methemoglobin exceeds 10% of total hemoglobin, mucous membranes appear cyanotic.[8] Cross-linking of sulfhydral groups between hemoglobin molecules results in the formation of Heinz bodies.[8] Feline hemoglobin is more susceptible to Heinz body formation because it has eight reactive sulfhydral groups per molecule; most other species have two.[8] The drugs most frequently associated with oxidative injury include acetaminophen, aspirin, phenacetin, menadione, and methylene blue.[8,20,21]

Acetaminophen/Aspirin

Acetaminophen and aspirin are infrequently used therapeutically but are frequently reported causes of toxicosis in dogs and cats.[3] The toxic effects of acetaminophen are caused by formation of toxic metabolites, most notably *N*-acetyl-*p*-benzoquinone imine, by the cytochrome P-450 oxidase system.[3] Cats are more sensitive to the toxic effects of acetaminophen because they lack the specific glucuronyl transferases needed to conjugate the aromatic rings of drugs like acetaminophen.[3] This leaves larger amounts of free drug to be degraded to the toxic metabolite. Rapid depletion of reduced glutathione in feline erythrocytes leads to formation of methemoglobin and Heinz bodies. Dogs most frequently have clinical signs referable to the gastrointestinal system but can have hematologic abnormalities as well.[20] Clinical signs associated with hematologic injury include extreme weakness, hypothermia, anemia, cyanosis, methemoglobinemia, Heinz bodies, hemoglobinemia, hemoglobinuria, and icterus.[3]

As with acetaminophen, cats have difficulty detoxifying aspirin.[3] Clinical signs are not usually seen until cats are given a 5-grain aspirin tablet daily for several days.[21] Hematologic signs include Heinz body anemia and bone marrow hypoplasia.[20,21]

Estrogenic Compounds

Unlike cats, dogs are highly susceptible to estrogen-induced bone marrow suppression.[2,22,23] In dogs, hematologic dyscrasias can result

from a single large dose or repeated therapeutic doses of estradiol cypionate or from elevated endogenous estrogen levels caused by cystic ovarian follicles, ovarian granulosa cell tumors, or Sertoli cell tumors. Therapeutic doses of estradiol cypionate have been used in treatment of mammary tumors, prostatic hyperplasia, and urinary incontinence.[24] Dogs given doses of 0.9 to 1.5 mg of estradiol consistently have bone marrow toxicosis.[25,26] Affected dogs have an initial leukocytosis followed by bone marrow suppression with resultant nonregenerative anemia, leukopenia, and thrombocytopenia.[24] Recovery usually occurs within approximately 1 month. Therefore, the clinical and toxic doses of estradiol appear to overlap for dogs. The mechanism of action of estrogen on hematopoiesis is unknown. Serum inhibitors of hematopoiesis produced by thymus-derived T cells have been identified.[26]

Type B Adverse Drug Events

TABLE 2 summarizes the major drugs associated with type B ADEs in dogs and cats.

Estrogenic Compounds

Individual dogs appear to be particularly sensitive to the effects of estrogen and develop severe aplastic anemia when treated with estrogenic compounds. In these dogs, pancytopenia is present and the bone marrow is aplastic.[2,22,23] This appears to be the result of hematopoietic stem cell destruction. The prognosis for these dogs is poor, but recovery after weeks to months of supportive care has been documented.[2] Myelofibrosis, bone marrow necrosis, and dysmyelopoiesis have been observed in dogs given a therapeutic dose of estradiol cypionate.[2,23] Diethylstilbestrol has been administered orally at 0.2 to 1.0 mg/d for 5 days for treatment of prostatic hyperplasia. Bone marrow toxicity has been observed as an idiosyncratic reaction at this dosage. Affected dogs have an initial leukocytosis followed by severe bone marrow suppression with resultant nonregenerative anemia, leukopenia, and thrombocytopenia.[24]

Nonsteroidal Antiinflammatory Drugs

Phenylbutazone

Phenylbutazone-associated neutropenia or pancytopenia occurs sporadically in dogs.[1,2,21,27] Two types of ADEs have been observed. One is a transient agranulocytosis that usually occurs within 2 weeks after starting treatment.[1] Affected dogs have a cellular bone marrow and frequently recover promptly when the drug is discontinued. This condition is most likely immune-mediated, but inhibition of bone marrow cell division or DNA synthesis cannot be ruled out. Alternatively, some dogs develop aplastic anemia after months or years of treatment, presumably as a result of bone marrow toxicity.[2,28] In my experience, the prognosis for recovery is poor for these dogs. Additionally, phenylbutazone therapy has been associated with bone marrow necrosis and myelofibrosis.[2,22,28]

Carprofen

Hematologic dyscrasias were reported in three dogs treated with therapeutic doses of carprofen.[4] All dogs had evidence of coagulation-type necrosis in bone marrow. These dogs had multiple cytopenias but recovered after therapy was discontinued.

Azathioprine

Administration of azathioprine to dogs has been associated with bone marrow toxicity.[29–31] Neutropenia and thrombocytopenia or pancytopenia has been observed 1 to several months after initiation of treatment with immunosuppressive doses (2 mg/kg once daily) of azathioprine. In dogs with this ADE, bone marrow is aplastic, and some dogs have mild myelofibrosis. The peripheral blood cell numbers slowly return to normal once the drug is discontinued, but complete recovery may be delayed. Cats appear to be more sensitive to azathioprine-induced bone marrow suppression. Of five cats given 2.2 mg/kg of azathioprine on alternate days, four developed multiple cytopenias.[29]

Azathioprine-induced bone marrow suppression in humans has been associated with homozygosity for the gene for thiopurine methyltransferase.[29,30] This enzyme plays an important role in the catabolism of azathioprine. Erythrocyte thiopurine methyltransferase concentrations vary in dogs.[31] However an analysis of erythrocyte thiopurine methyltransferase enzyme activity in six dogs with azathioprine-associated myelotoxicity revealed intermediate to high enzyme activity in all dogs.[31] Therefore, thiopurine methyltransferase, as measured in erythrocytes, does not appear to be a good indicator of azathioprine-associated myelotoxicity.

Antibiotics/Antifungals

Sulfonamides

ADEs have been reported for sulfamethoxazole, sulfadimethoxine, and sulfadiazine.[2,32–35] These drugs appear to induce an idiosyncratic syndrome that consists of neutropenia, thrombocytopenia, hemolytic anemia, fever, polyarthropathy, or hepatopathy.[32,33] Doberman pinschers may be at increased risk of sulfonamide hypersensitivity.[33] Sulfadiazine-associated aplastic anemia has also been reported in dogs.[2,34,35] The mechanism appears to be immune-mediated and is not related to folate deficiency.[32,33] Evidence of an immune-mediated etiology includes demonstration of drug-dependent antiplatelet antibodies and a positive direct Coombs test.[32,33] In one study, recovery occurred in 90% of non-thrombocytopenic dogs but only 63% of thrombocytopenic dogs.[32] In dogs with sulfadiazine-induced aplastic anemia, pancytopenia usually occurs 10 to 14 days after initiation of treatment.[2,34,35] The bone marrow is replaced by adipose tissue. The hematologic dyscrasia usually resolves within 2 weeks after discontinuation of treatment.

Chloramphenicol

Severe aplastic anemia has been reported as an idiosyncratic reaction in humans treated with chloramphenicol but has not been reported in dogs or cats.[6] However, when chloramphenicol is given to dogs or cats at several times the therapeutic dose, reversible bone marrow suppression and resultant cytopenias consistently occur.[36] An apparent idiosyncratic reaction to chloramphenicol was reported in one dog.[37] This dog had a moderate nonregenerative anemia with large

Table 2. Major Drugs Associated With Idiosyncratic (Type B) Hematologic Adverse Drug Events in Dogs and Cats

Drug	Species	Number of Animals Affected	Time to Onset[a]	Mechanism of Toxicity	Time to Recovery	Study or Studies
Estrogenic compounds	Dog	Many	2–4 weeks	Stem cell suppression	Prolonged, uncertain	Weiss and Klausner,[2] Christiansen,[21] Hoenig[23]
Phenylbutazone	Dog, cat	Many	1–2 weeks	Immune-mediated blood cell destruction	Days	Schalm,[1] Weiss and Klausner,[2] Christiansen,[21] Xavier et al,[27] Watson et al[28]
Phenylbutazone	Dog, cat	Many	Months	Stem cell suppression	Uncertain	Schalm,[1] Weiss and Klausner,[2] Christiansen,[21] Xavier et al,[27] Watson et al[28]
Carprofen	Dog	Few	Insufficient data	Necrosis, myelofibrosis	1–3 weeks	Weiss[4]
Sulfonamides	Dog	Many	1–2 weeks	Immune-mediated blood cell destruction	1–3 weeks	Weiss and Klausner,[2] Trepanier,[32] Giger et al,[33] Weiss and Adams,[34] Fox et al[35]
Sulfonamides	Dog	Many	1–2 weeks	Progenitor cell suppression	1–3 weeks	Weiss and Klausner,[2] Trepanier,[32] Giger et al,[33] Weiss and Adams,[34] Fox et al[35]
Griseofulvin	Cat	Many	2–4 weeks	Bone marrow suppression	1–2 weeks	Helton et al,[42] Rottman et al,[43] Shelly,[44] Weiss and Evanson[45]
Propylthiouracil	Cat	Many	0.5–2 months	Immune-mediated destruction of blood cells	1–2 weeks	Peterson et al[46]
Methimazole	Cat	Many	0.5–2 months	Immune-mediated blood cell destruction	2 weeks	Peterson et al[47]
Phenobarbital/ primidone	Dog	Many	Months to years	Destruction of mature granulocytes	1 week	Weiss,[4] Weiss and Smith,[12] Jacobs et al,[48] Thompson and Johnstone[49]
Phenobarbital/ primidone	Dog	Many	Months to years	Necrosis/myelofibrosis	3–8 weeks	Weiss,[4] Weiss and Smith,[12] Jacobs et al,[48] Thompson and Johnstone[49]
Azathioprine	Dog	Many	1–2 months	Bone marrow toxicity	4–8 weeks	Rinkardt and Kruth,[30] Rodriguez et al[31]
Metronidazole	Dog	Few	Insufficient data	Necrosis	Insufficient data	Weiss and Smith[12]
Levamisole	Dog	Few	1–4 weeks	Immune-mediated blood cell destruction	3–6 weeks	Atwell et al,[51] Atwell et al[52]
Albendazole	Dog, cat	Few	Insufficient data	Uncertain	1 week	Weiss and Evanson,[45] Stokol et al[53]
Amiodarone	Dog	Few	Insufficient data	Immune-mediated blood cell destruction	3–4 weeks	Calvert et al,[55] Jacobs et al[56]
Captopril	Dog	Few	Insufficient data	Bone marrow suppression	Insufficient data	Holland et al[57]
Human recombinant erythropoietin	Dog, cat	Many	2–6 months	Erythroid aplasia	Prolonged, uncertain	Randolph et al,[58] Cowgill et al[59]

[a]Immune-mediated adverse drug events can occur more quickly if the animal was previously exposed to the drug.

numbers of siderocytes (also called *Pappenheimer bodies*) and ringed sideroblasts consistent with drug-induced sideroblastic anemia.

β-Lactam Antibiotics

Cephalosporins have been associated with hematologic ADEs.[38–40] High-dose or prolonged administration of cephalosporins has the potential to cause agranulocytosis and thrombocytosis; affected animals have a positive result on a direct Coombs test.[40] Approximately half of dogs given high IV doses of cefonicid or cefazedone developed pancytopenia within 6 to 10 weeks after initiation of treatment in two studies.[38,39] The mechanism of the hematologic dyscrasia appears to be complex. In one study,[39] antierythrocyte, antiplatelet, and antineutrophil antibodies were detected, consistent with immune-mediated destruction. Cephalosporins also induce alteration in bone marrow. In the other study,[38] although bone marrow remained cellular, maturation arrest was observed in granulocyte and erythroid cell lines, and the number of macrophages increased. The most prominent ultrastructural change in bone marrow was mitochrondrial damage in hematopoietic and nonhematopoietic cells.[38] The hematologic dyscrasia resolved rapidly after the drug was discontinued.

Penicillin has been associated with acute allergic reactions.[41] Allergic reactions are most common in humans and horses and consist of acute anaphylaxis, collapse, shaking, urticaria, fever, leukopenia, eosinophilia, thrombocytopenia, and anemia.[41]

Griseofulvin

Griseofulvin is a fungistatic antibiotic used for treatment of mycotic diseases.[42] Hematologic ADEs occur in cats as an idiosyncratic reaction.[42–45] In most cases, neutropenia or panleukopenia occur several weeks after initiation of griseofulvin treatment.[42] The bone marrow is hypoplastic in most affected cats. Most cats recover after treatment is discontinued.

Antithyroid Drugs

Propylthiouracil/Methimazole

Severe immune-mediated hematologic ADEs consisting of agranulocytosis and severe thrombocytopenia have been reported in 8.6% of hyperthyroid cats treated with propylthiouracil and 3.8% of cats treated with methimazole.[46,47] Mild hematologic alterations, including eosinophilia, lymphocytosis, and mild leukopenia, were reported in 16.4% of cats treated with methimazole.[47] Clinical signs developed within 1 to 2 months after initiation of treatment and included weakness, lethargy, anorexia, and bleeding diathesis. Many affected cats tested positive on a fluorescent antinuclear antibody test and a direct Coombs test, indicating that the hematologic dyscrasia may have been immune-mediated. These hematologic abnormalities resolved within 2 weeks after methimazole treatment was discontinued.

Anticonvulsants

Phenobarbital/Primidone

Phenobarbital and primidone have been associated with several types of hematologic ADEs in dogs. Because primidone is metabolized to phenobarbital, the mechanism of toxicity may be similar for both drugs. The mildest hematologic disorder is neutropenia and thrombocytopenia.[4,48,49] Granulocyte hyperplasia in bone marrow indicates that the neutropenia may be due to destruction of mature granulocytes. However, more common ADEs are myelofibrosis and bone marrow necrosis.[4,12] Dogs with bone marrow necrosis are frequently bicytopenic or pancytopenic. The bone marrow is characterized by multifocal areas of coagulation-type necrosis and variable degrees of myelofibrosis.[4] Dogs with myelofibrosis without concurrent necrosis frequently have a severe nonregenerative anemia.

Phenytoin

Experimental studies have shown that long-term administration of phenytoin to dogs resulted in erythrocyte macrocytosis, neutropenia, thrombocytopenia, and neutrophil hypersegmentation.[50] These changes were thought to be due to folate deficiency. However, administration of phenytoin to dogs on a folate-restricted diet for 54 weeks reduced erythrocyte folate but did not induce a macrocytic anemia.[50] One dog undergoing long-term phenytoin therapy developed severe myelofibrosis and a severe normocytic nonregenerative anemia.[12]

Antiparasitic Drugs

Metronidazole

Three dogs treated with metronidazole had coagulation-type bone marrow necrosis.[12] All three dogs had pancytopenia; the two dogs for which follow-up data were available recovered after discontinuation of treatment.

Levamisole

Levamisole-induced thrombocytopenia and hemolytic anemia with a positive direct Coombs test have been reported in several dogs.[51,52] All dogs had hyperplastic bone marrow and recovered after levamisole treatment was discontinued.

Albendazole

Albendazole toxicity has been documented in one dog and two cats.[45,53] All three animals were pancytopenic; however, the dog had aplastic bone marrow, whereas the cats had hypercellular bone marrow. All animals had rapid hematologic recovery within 1 week after discontinuation of treatment.

Fenbendazole

Fenbendazole has been associated with bone marrow coagulation-type necrosis in a dog.[4] This dog was neutropenic and thrombocytopenic.

Thiacetarsamide

One dog had pancytopenia after repeated weekly administration of thiacetarsamide for treatment of demodectic mange.[54] The bone marrow was hypercellular, and the dog recovered after discontinuation of treatment. However, the dog subsequently developed severe nonregenerative anemia associated with bone marrow erythroid aplasia and died.

Cardiac Drugs

Amiodarone

Amiodarone is an antiarrhythmic drug that has been associated with hemolytic anemias and hepatopathies in dogs.[55,56] Hematologic alterations are characterized by thrombocytopenia and a positive result on a direct Coombs test with or without the presence of anemia. Affected dogs recover when treatment is discontinued.

Captopril

One dog developed pancytopenia after 18 months of continuous administration of captopril for treatment of a heart murmur.[57] The bone marrow was aplastic. Withdrawal of the drug and treatment of the dog with human granulocyte-colony stimulating factor and erythropoietin resulted in prompt hematologic recovery.

Quinidine

One dog developed anemia and neutropenia after prolonged administration of quinidine gluconate for treatment of premature ventricular contractions.[2] Three days after discontinuation of the drug, the neutrophil count had returned to the reference range and the bone marrow had normal cellularity.

Other Drugs

Human Recombinant Erythropoietin

Many dogs given human erythropoietin develop antibodies to the recombinant protein because of the 18.7% difference in the primary amino acid sequences of human and canine erythropoietin.[58,59] In addition to blocking the effects of the human erythropoietin, the antibody cross-neutralizes endogenous canine erythropoietin, resulting in profound erythroid hypoplasia.[58,59] The onset of the immune response is typically 2 to 3 months after initiation of treatment. Administration of recombinant canine erythropoietin to dogs suffering from recombinant human erythropoietin-associated red cell aplasia does not appear to be effective in resolving the anemia.[58] Use of species-specific erythropoietin prevents recombinant erythropoietin-induced red cell aplasia.

Heparin

Unfractionated heparin has been reported to cause marked thrombocytopenia as an idiosyncratic reaction in human patients within 4 to 14 days after initiation of treatment.[60] In these patients, heparin appears to exert a direct effect on platelets, causing platelet activation and aggregation, as well as to induce antiplatelet antibodies. Heparin-induced thrombocytopenia and erythrocyte agglutination have been described in horses, but the role of heparin in inducing thrombocytopenia in dogs and cats has not been well documented.[61]

Colchicine

Myelofibrosis and coagulation-type necrosis consistent with drug-induced bone marrow toxicity has been reported in a few dogs treated with colchicine.[4,12] Withdrawal of treatment resulted in hematologic recovery.

Mitotane

Two dogs given mitotane for treatment of Cushing disease developed coagulation-type bone marrow necrosis.[4] One dog had a nonregenerative anemia, and the other was thrombocytopenic. Withdrawal of drug treatment resulted in hematologic recovery.

Conclusion

Many therapeutic drugs have been associated with hematologic ADEs. Some drugs, such as chemotherapeutic agents and oxidants, produce ADEs in a dose-dependent manner, while others produce idiosyncratic ADEs. Because chemotherapeutic agents consistently suppress hematopoiesis, their administration should be monitored with periodic complete blood counts. Additionally, hematologic monitoring is warranted for idiosyncratic ADEs that occur relatively frequently. I recommend that patients receiving phenylbutazone, phenobarbital, propylthiouracil (in cats), methimazole (in cats), or azathioprine be periodically monitored for hematologic ADEs with complete blood counts. I further recommend that estradiol not be used as a therapeutic drug in dogs because the therapeutic and toxic doses overlap and because some dogs develop terminal aplastic anemia when given therapeutic doses. It is important to report suspected ADEs so that the true incidence of these events can be established.

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1. **Which is not a mechanism by which drugs can produce idiosyncratic hematologic dyscrasias?**
   - **a.** immune-mediated destruction of blood cells
   - **b.** altered drug metabolism due to individual genetic factors
   - **c.** bone marrow necrosis
   - **d.** genetic mutation of segmented neutrophils leading to decreased proliferation
   - **e.** myelofibrosis

2. **Which of the following drugs induces a type A ADE?**
   - **a.** acetaminophen
   - **b.** sulfadiazine
   - **c.** phenobarbital
   - **d.** albendazole
   - **e.** colchicine

3. **When giving drugs that have a relatively high incidence of type B ADEs, which of the following would be an appropriate course of action?**
   - **a.** give the drug at half the therapeutic dose
   - **b.** give the drug at the therapeutic dose but less frequently
   - **c.** monitor the hematologic system by performing periodic complete blood counts
   - **d.** give the drug by a different route
   - **e.** monitor therapeutic drug levels in the plasma

4. **Changes in blood cell counts follow a predictable course after administration of chemotherapeutic drugs. Which of the following is typical of these changes?**
   - **a.** neutropenia at 10 days and thrombocytopenia at 14 days
   - **b.** neutropenia at 5 days and thrombocytopenia at 9 days
   - **c.** neutropenia at 2 days and thrombocytopenia at 4 days
   - **d.** anemia at 10 days and thrombocytopenia at 14 days
   - **e.** anemia at 2 days and thrombocytopenia at 4 days

5. **Chemotherapeutic drugs induce blood dyscrasias by**
   - **a.** immune-mediated destruction of blood cells.
   - **b.** oxidant-mediated destruction of blood cells.
   - **c.** destruction of the proliferating pool of precursor cells in bone marrow.
   - **d.** destruction of nonproliferating cells in bone marrow.
   - **e.** shortened neutrophil and platelet survival in the blood.

6. **Which is not an expected finding in animals with severe acetaminophen toxicosis?**
   - **a.** cyanosis
   - **b.** methemoglobinemia
   - **c.** icterus
   - **d.** Heinz bodies
   - **e.** aplastic bone marrow

7. **Dogs treated with phenylbutazone can develop all of the following hematologic ADEs except**
   - **a.** transient agranulocytosis.
   - **b.** pancytopenia.
   - **c.** aplastic anemia.
   - **d.** pyogranulomatous inflammation.
   - **e.** bone marrow necrosis and myelofibrosis.

8. **Some dogs treated with phenylbutazone develop transient agranulocytosis with a cellular bone marrow within 2 weeks after starting treatment. Other dogs develop aplastic anemia after months or years of treatment. Which of the following most likely explains this discrepancy?**
   - **a.** The conditions are probably caused by different mechanisms.
   - **b.** Both conditions are caused by immune-mediated destruction of peripheral blood cells.
   - **c.** Both conditions are caused by destruction of bone marrow progenitor cells.
   - **d.** The first condition is a milder form of the second condition.
   - **e.** The second condition is a milder form of the first condition.

9. **In cats with hematologic dyscrasias associated with propylthiouracil or methimazole treatment, positive direct Coombs and antinuclear antibody test results suggest that the mechanism of injury is**
   - **a.** oxidant-mediated destruction of blood cells.
   - **b.** immune-mediated destruction of blood cells.
   - **c.** myelofibrosis.
   - **d.** stem cell suppression.
   - **e.** necrosis.

10. **Dogs with hematologic dyscrasias associated with _____ tend to have a poor prognosis.**
    - **a.** sulfonamides or chloramphenicol
    - **b.** propylthiouracil or methimazole
    - **c.** levamisole or albendazole
    - **d.** estrogenic compounds
    - **e.** metronidazole