Clinical Management of Cytotoxic Drug Overdoses in Companion Animals

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In general, companion animals tolerate chemotherapy exceptionally well, with far fewer side effects than their human counterparts. This is primarily due to the lower doses used in veterinary species (well below the maximum tolerated dose in people) and the less frequent use of multimodality therapies. Since most cytotoxic effects on bone marrow, heart, nervous system, and gastrointestinal tract are dose related, the moderate doses used in companion animals typically result in only mild side effects, including nausea, vomiting, diarrhea, and inappetence. It is estimated that less than 5% of animals require hospitalization for chemotherapy-related toxicities and that less than 1% may actually die as a result of chemotherapy-related toxicity.[1]

Typically most morbidity noted in veterinary patients following chemotherapy is related to poor tolerance to standard cytotoxic drug doses. In these patients, many factors may contribute to the increased incidence of side effects, including (1) reduced or delayed elimination of the drug because of limited liver metabolism or renal excretion, (2) geriatric alterations in drug pharmacodynamics, (3) pre-existing cardiac, pulmonary, or bone marrow disease, (4) prior chemotherapy and/or radiation exposure, or (5) breed differences in drug tolerance (MDR1 gene deletion mutation: reducing elimination of drugs such as vincristine, vinblastine, and doxorubicin).[2]

Unfortunately, accidental ingestion of owner's medications (e.g., fluorouracil ointment) has contributed significantly to the veterinary chemotherapy overdose literature. On rare occasion, inadvertent administration of large or inappropriate doses, the wrong drug, or an incorrect schedule of administration has also lead to significant morbidity or mortality in veterinary species as well as humans Many errors noted in the literature are frequently caused by drugs that are spelled similarly (carboplatin instead of cisplatin or vincristine in place of vinblastine). Errors are also due to poor handwriting skills or failure to place a leading zero before a decimal point (i.e., a volume of .1 ml should be written as 0.1 ml). Miscalculation of infusion rates (over hours rather than days) and provision of more than a cycle's worth of drug at one time has also lead to serious overdoses. Miscalculation of doses based on weight conversions between kilograms (kg), pounds (lb)lb, and square meters (M^2) contribute significantly to error rates. Client misinterpretation of directions on outpatient prescription labels has also resulted in overdoses. Clients frequently misinterpret "Take one tablet weekly" as "Take one tablet daily," or "Take one tablet every Monday" as "Take one tablet every morning."

In these cases, dose-related side effects should be anticipated to occur and prophylactic intervention may be required to limit the severity of morbidity incurred. Although chemotherapeutic accidents are believed extremely rare in veterinary medicine, it is difficult to assess the exact incidence since most incidences probably go unreported. Although chemotherapeutic "mishaps" are currently considered rare in veterinary medicine, as the practice of veterinary oncology grows, the number of patients undergoing chemotherapy increases, and the number of large clinics doing multiple chemotherapeutic treatments concurrently continues to expand, the incidence of misfilled cytotoxic drug orders and accidental overdoses is likely to increase in number.

Unfortunately, limited data are available even in the human literature on the prophylactic management of cytotoxic drug overdoses. Because of the unethical nature of conducting toxicologic studies in humans, most data on cytotoxic drug toxicities come

from original toxicologic studies in research animals or from published human case reports on inadvertent overdoses. Although many cases often go unreported, little to no information is often available on how to best manage drug overdoses when they occur. Drug Information and Poison Control frequently offer no more advice than what is available on the manufacturer's package insert or a Physicians Desk Reference. Advice is typically to provide "supportive care" rather than prophylactic intervention. In order to best treat patients following an overdose, defined treatment protocols should be readily available. The provision of aggressive prophylactic measures (hospitalization, decontamination, hydration, anecdotes, hematopoietic growth factors, prophylactic gastrointestinal protectants, and antibiotics) and prompt supportive care for serious adverse side effects following an overdose may lessen the likelihood of irreversible harm (Table 1).

In this chapter, the pharmacological management of accidental chemotherapeutic overdoses is discussed. Current data from the human literature are presented as well as the few case reports and anecdotal information found in the veterinary literature. Clinical management of accidental overdoses of the more common cytotoxic agents used in companion animals are proposed based on available clinical data and speculation in some instances, where no data are available.

Management of *l*-Asparaginase (Elspar) Overdoses

L-Asparaginase is very different than most other chemotherapeutic agents in that most of its fatal toxicities are not dose dependent, but are typically due to hypersensitivity reactions or rapid reduction of large tumor burdens. Currently, no documented clinical case reports of L-asparaginase overdoses were noted in the veterinary literature. Manufacturer animal toxicology data suggest that intravenous administration of L-asparaginase in dogs at doses of 250, 1000, and 2000 IU/Kg/day revealed only decreased serum albumin, protein, and body weight at the highest dose. Anorexia, emesis, and diarrhea occurred at all doses. In humans, only one case of L-asparaginase overdose (ten-fold) was located in the literature. A 3-year-old boy with acute lymphoblastic leukemia was administered chemotherapy consisting of L-asparaginase, vincristine, daunorubicin and dexamethasone. He inadvertently received a ten-fold overdose of L-asparaginase. Despite very high plasma ammonia levels, he remained well clinically, with normal laboratory parameters.[3]

Maximum Subcutaneous or Intramuscular Dosages*
Dogs
400 IU/kg to a maximum of 10,000 IU
Cats
400 IU/kg
*Dosage adjustments (reductions) may be required in geriatric animals who are more sensitive to this drug or when using in combination with other cytotoxic drugs.
Toxicities Associated with Overdoses
 Gastrointestinal Toxicity

Nausea and vomiting are common at standard doses of L-asparaginase and should be anticipated. Anorexia, weight loss, diarrhea, and ulcers (oral and intestinal) may also occur.

Hypersensitivity Reactions

Hypotension, bronchospasm, laryngeal edema, erythema, urticaria, wheals, hives, fever, and dyspnea occur rarely at normal doses (<10%–25%) and are not dose dependent. Hypersensitivity reactions typically are not observed until after the second dose. In humans, test doses are given before administration.

Hepatic Toxicity

Elevated liver enzymes (bilirubin, aspartate aminotransferase [AST], alkaline phosphatase), decreased albumin, edema, and fatty changes to the liver occur in humans following high doses. Liver toxicity may be fatal. Reduced serum albumin was noted in manufacturer toxicology studies in dogs with high-dose L-asparaginase (>1000 IU/kg).

Pancreatitis

Pancreatitis is reported in dogs following standard treatment and may be severe following high doses.[4,5] Pancreatitis may be hyperosmolar, with non-ketotic hyperglycemia, glycosuria, and polyuria. Inflammation and necrosis of the pancreas is reported in humans despite normal amylase concentrations. Fulminant and fatal pancreatitis may occur more frequently with overdoses.

Hematologic Toxicity

Bone marrow suppression is uncommon at normal doses but may increase in incidence with an overdose. Decreased fibrinogen, clotting factors, platelets, leukopenia and an increased prothrombin time have been reported in humans with high doses. Coagulopathies and thrombosis of large vessels may also occur.

Nervous System

Hyperexcitation, lethargy, agitation, convulsions, and seizures may occur with large doses. Hypocalcemia associated with necrosis of the parathyroid cells and seizures has been reported in rabbits receiving 1000 IU/kg/day (Merck-Preclinical toxicology data). Hypertriglyceridemia and hyperlipidemia-associated hyperviscosity syndrome have occurred in pediatric and adult human populations that may result in CNS syndrome.[6] It is unknown if this side effect is dose dependent.

Renal System

Azotemia (pre-renal) with increased calcium and phosphorus excretion may occur more frequently at high doses because of protein degradation. Proteinuria and acute renal shut down may also occur with high doses.

Miscellaneous

Increased plasma concentrations of ammonia are anticipated as a result of breakdown product from asparagine. Very high ammonia concentrations are reported following at least one ten-fold overdose in a human patient.[3]

Treatment of L-Asparaginase Overdoses
Gastrointestinal System

Both acute and delayed nausea, vomiting, and diarrhea are anticipated. Delayed gastrointestinal upset may be the result of hyperammonemia. Selective inhibitors of type 3 (5-HT-3) serotonergic receptors (granisetron, ondansetron, dolasetron) or substituted benzamides (metoclopramide) may be effective. For nausea and vomiting refractory to

these, a combination of both, with or without a corticosteroid (dexamethasone, methylprednisolone) should be considered. Give antiemetic therapy for at least 24 hours or longer if high ammonia levels persist.

Hypersensitivity Reactions

Anaphylaxis precautions should be observed. Hypersensitivity reactions are typically not seen on the first dose but may occur with subsequent doses. Although rare (<10%–25%), be prepared to treat hypersensitivity reactions with epinephrine, antihistamine, corticosteroids, and airway maintenance if necessary. The incidence should not be greater with overdoses but has caused significant morbidity and mortality following L-asparaginase administration.

Hepatotoxicity

Monitor LFTs, clotting factors, triglycerides, and cholesterol. Lipolytic therapy may be required to reduce serum lipid levels that may cause hyperviscosity, resulting in central nervous system (CNS) syndrome. In humans, the lipolytic agent atorvastatin (Lipitor) has been used to reduce cholesterol following L-asparaginase, but its efficacy and safety are not established in dogs. A low-fat diet may be helpful for continuous reduction in serum lipids.

Pancreatitis

Assess patient for hyperglycemia and pancreatitis. Monitor blood and urine glucose. Administer insulin and IV fluids to prevent diabetic ketoacidosis.

Hematologic System

Monitor for myelosuppression, which is rare following standard doses in companion animals but may increase with high doses. Patients' clotting function should be monitored because of the potential for decreased clotting factors.

Nervous System

Hypertriglyceridemia, hyperlipidemia, hyperammonemia, and hyperglycemia may all contribute to the CNS syndrome and should be monitored carefully. Hypocalcemia associated with necrosis of the parathyroid cells and seizures has been reported in rabbits receiving 1000 IU/kg/day of L-asparaginase. Supplementation with calcium gluconate was beneficial in this setting (manufacturer's data).

Renal Failure

For severe renal failure, dialysis should be considered. Hyperammonemia has also been managed with sodium benzoate. Sodium benzoate (206 mg/kg/day plus low protein diet for 2 days) for ammonia-trapping therapy has been effective in humans.[6,7]

Drug Removal

No reports were noted at this time for the use of dialysis in L-asparaginase overdoses. In general, overdoses may be managed without experiencing significant morbidity. Dialysis may be beneficial in the case of severe hyperammonemia or renal failure.

Management of Carboplatin (Paraplatin) Overdoses

Cisplatin and carboplatin have similar mechanisms of action but differ in their side effect profile. The dose-limiting side effects of carboplatin typically involve bone marrow suppression and hepatotoxicity. This is in contrast to cisplatin, which is associated with sometimes severe nephrotoxicity, ototoxicity, and neurotoxicity even at therapeutic doses. In general, carboplatin is better tolerated than cisplatin unless a patient has impaired renal function. The incidence of severe leukopenia, neutropenia, and

thrombocytopenia for both drugs is significantly increased in patients with renal failure. Toxicologic studies done with platinum-containing agents in dogs suggest that dogs are highly predictive of toxicities seen in humans.[16] Therefore, toxicologic data obtained from human overdoses may be predictive of those in animals. Human literature suggests that most platinum-related overdoses have involved the inadvertent substitution of cisplatin for carboplatin. Because carboplatin is substantially less toxic than cisplatin on a milligram-for-milligram basis, and higher doses are used for carboplatin, substitution with cisplatin has resulted in massive overdoses with significant morbidity and mortality.

Maximum Intravenous Dosages*
Cats
   150 mg/m^2 or 10 mg/kg
Dogs
   Small dogs (<15 kg): 10 mg/kg; large dogs (>15 Kg): 300 mg/m^2
   *Dose reduction is required with renal insufficiency

Toxicities Associated with Carboplatin Overdoses
 Hypersensitivity reactions
   Hypersensitivity reactions (anaphylactoid, edema, wheezing, dyspnea, tachycardia, hypotension) urticaria, rashes, dermatitis, or erythema may occur following carboplatin treatment, but they are not dose related. Hypersensitivity reactions are frequency delayed and may be seen after multiple doses. Patients with a history of cisplatin hypersensitivity reactions may cross react.
Hematologic
   Bone marrow suppression (thrombocytopenia, leukopenia, neutropenia, and/or anemia) is dose dependent and may be severe at high doses. This is typically the dose-limiting side effect in humans.
Gastrointestinal
   Nausea, vomiting, and anorexia—both acute and delayed—should be anticipated in overdoses. Symptoms may continue for days and are believed mediated via both local and central mechanisms involving serotonin.
Nervous System
   Peripheral neuropathies (paresthesias) are reported rarely with carboplatin at standard doses but may occur more frequently with overdoses. Ototoxicity has been reported at doses of $\geq$2 g/m^2 in adults and at higher than recommended doses in pediatric patients. A reversible loss of vision is also noted at high doses in humans, which may be complete for light and color.
Renal Toxicity
   Elevations of serum creatinine and BUN would be expected at high doses. Renal failure is not normally witnessed at the low doses used in animals but may be seen following overdoses, since this side effect is a result of cumulative or high total dose effects.
Electrolyte Effects
   Hyponatremia, hypokalemia, hypocalcemia, and hypomagnesemia have all been reported in humans with high doses and should be carefully monitored.
Hepatic System

Elevations in serum alkaline phosphatase, aspartate aminotransferase (AST), serum glutamic-oxaloacetic transaminase (SGOT), or bilirubin concentrations have been reported in human patients receiving high-dose carboplatin. This may be severe in large overdoses.

Treatment of Carboplatin Overdoses

There are no established guidelines for treating human or animal overdoses of carboplatin. Since many of the side effects of carboplatin are concentration dependent and hemodialysis and plasmapheresis have been shown to effectively remove the drug, these measures may be beneficial in a severe overdose, if available. Alternatively, intravenous hydration and diuresis may speed drug elimination and reduce overall morbidity. At normal doses in humans, plasma platinum terminal half-lives are on the order of 4 to 6 days so that even delayed measures in reduction of carboplatin plasma concentrations may be of some benefit.

Hematologic

Neupogen (G-CSF) should be started prophylactically in the case of an overdose to prevent potentially severe neutropenia. In humans, G-CSF reduces the incidence, severity, and duration of Grade IV neutropenia following high-dose carboplatin.[17] Blood transfusions may also be required. Antibiotics should be started prophylactically.

Gastrointestinal

Serotonergic receptor antagonists in combination with a metoclopramide CRI may be effective. For nausea and vomiting refractory to these, a combination of both, with or without a corticosteroid (dexamethasone, methylprednisolone), should be considered. Both acute and chronic treatment may be required.

Nervous/Hepatic System

Because these are concentration-dependent side effects, any reduction in carboplatin concentrations may be beneficial. Intravenous hydration and diuresis may assist in the elimination of carboplatin from the plasma.

Renal

Intravenous normal saline given at twice the maintenance rate and mannitol (0.25–0.5 g/kg IV q 4–6 hr) and/or furosemide (1–2 mg/kg IV q 6–12 hr) may help to maintain renal function and assist in drug elimination.

Electrolytes

Monitor closely and replace if necessary.

Drug Removal

Carboplatin is removed by hemodialysis and plasmapheresis, but the clinical efficacy of these procedures in carboplatin overdose has not been proven. Other platinum-containing products are removed by dialysis but cause secondary rebound spikes in plasma platinum concentrations as drug leaves the tissues. Plasmapheresis has been effective clinically following cisplatin overdoses as described below.

Management of Chlorambucil (Leukeran) Overdoses

Chlorambucil is an alkylating agent similar to nitrogen mustard. It is available in tablet form for outpatient therapy, making it easier to overdose because of client confusion with directions for use or inadequate "animal/child proofing" of the household. As a result,

multiple reports are available in the human literature concerning chlorambucil overdoses. In one case, a 22-month-old child ingested 32 mg (3.2 mg/kg) of chlorambucil tablets prescribed for a family member. She was seen in the emergency room within 1 hour of ingestion. Treatment with gastric lavage, activated charcoal, and magnesium sulfate as a cathartic was initiated. The patient developed irritability, myoclonic-like muscle jerks, an exaggerated startle reflex, vomiting, and EEG changes (epileptiform) within a few hours. The patient was discharged 28 hours after ingestion. A mild bone marrow suppression (leukopenia) was noted on follow-up 7 days after ingestion, which normalized by 23 days. An EEG performed 33 weeks after ingestion was normal.[7] Ataxia, coma, grand mal seizures, lethargy, staring gaze, tonic movements, and vomiting have been reported in other human patients following overdoses.[8] In humans, the risk of seizures increases with dose, with prior seizure history, and in very young children.[9]

At least one case report exists in the veterinary literature that describes an inadvertent overdose of a cat given chlorambucil orally. The 9.5-year-old cat was given a prescription of chlorambucil (15 mg/m^2 or 4 mg total) every 24 hours for 4 days, followed by 17 days of rest. The owner gave the first evening dose and repeated the dose in the morning. Two days later the cat presented with neurologic signs consisting of twitching and agitation, which began a few hours after the second dose was administered. Severe facial twitching, myoclonus, tonic-clonic seizures, hyperesthesia, and extreme agitation continued until the second day of admission. The cat had mild alterations in its CBC (normocytic, normochromic, non-regenerative anemia), WBC (leukocytosis), and biochemistry (hypocalcemia, hypercholesterolemia), which was attributed to the cats underlying lymphoma and stress. The cat was anorexic, which may have also been a result of the underlying intestinal lymphoma. Treatment consisted of intravenous crystalloids, potassium chloride, vitamin B complex, diazepam, ranitidine, and cefazolin for a brief febrile episode. Nasogastric and PEG tube feedings were instituted for nutritional support. The cat continued to improve clinically and was neurologically normal by day 4. He was discharged on day 7.[10]

Experiments performed with high-dose, intravenous chlorambucil in cats demonstrated that neurologic toxicity was often the dose-limiting side effect. Following doses of 15 to 40 mg/kg, bilateral discharges similar to petite mal epilepsy were noted on EEG. EEG changes were reversed with phenobarbital sodium. Age-related CNS changes were also noted in the study and suggested that young kittens (25–30 days old) had massive myoclonic flexor spasms, whereas older kittens (3 months) had more typical grand mal seizures or pure tonic seizures. The threshold for chlorambucil-induced seizures also appeared to be higher in more mature animals.[11]

Maximum Oral Dosage*
Cats
   2 mg once q 4 days. Tabs should not be split, so an alternative is 2 mg PO twice.
weekly.
Dogs
   2 to 6 mg/m^2 q 24 hours (dependent on neoplasia type); may also be used as a substitute for cytoxan 40 mg/m^2.
   *Dose reduction required with renal insufficiency. Prior seizures or CNS disease may increase risk of chlorambucil neurologic toxicities.

Toxicities Associated with Chlorambucil Overdoses
 Hematologic

Leukopenia, neutropenia, progressive lymphopenia, thrombocytopenia, and anemia have all been reported in humans following high doses of chlorambucil. Hematologic side effects are dose limiting in humans and are dose dependent. Excessive doses and prolonged therapy may result in irreversible bone marrow damage. In most overdose cases, only mild bone marrow suppression was noted, but depressive effects were highly variable in time of onset (2 days to 41 days after ingestion). Following overdoses, pancytopenia nadirs may occur 1 to 6 weeks after ingestion and not recover for 3 to 7 weeks.

Gastrointestinal

The gastrointestinal side effects of chlorambucil are also dose dependent. Nausea, vomiting, abdominal pain, discomfort, anorexia, and diarrhea have all occurred in human overdose cases. Gastrointestinal effects may only last for 24 hours, but nausea can persist for up to 7 days.

Neurologic

Tremors, muscle twitching, myoclonia, confusion, agitation, ataxia, flaccid paralysis, peripheral neuropathy, and hallucinations have all been reported in human cases. Focal and/or generalized seizures occur commonly with high doses or overdoses of drug. Seizures may occur very early after ingestion (2 hours) or be delayed (6–90 days). Focal seizures may progress to become generalized. Seizures are typically reversible. EEG changes may occur within 1 to 6 hours after ingestion or can be delayed (90 days).[12-14] Younger animals may be more susceptible to neurologic toxicity.

Pulmonary

In rare cases, a syndrome of bronchopulmonary dysplasia, interstitial pneumonitis, and pulmonary fibrosis has been reported in humans with prolonged continuous chlorambucil dosing. Fever, cough, rales, dyspnea, respiratory distress, hypoxia, and death have resulted.

Miscellaneous

In humans, at least one case of acute renal failure was reported following an overdose.[15] Dermatologic reactions may occur but are not dose related. Hypersensitivity reactions including rashes, urticaria, toxic epidermal necrolysis, and periorbital edema have all been reported. Hyperuricemia, hepatoxicity, and drug fever may also occur.

Treatment of Chlorambucil Overdoses

Hematologic

Excessive doses may result in pancytopenia and irreversible bone marrow damage. The manufacturer suggests that this may occur when the total dose in humans approaches 6.5 mg/kg in one course of therapy. Following large overdoses, treatment initiated 24 hours after ingestion with Neupogen may help to prevent severe myelosuppression. Transfusions with blood components may also be required. Antibiotic prophylaxis should be initiated if myelosuppression becomes severe. Complete blood counts should be measured at least three times weekly for 3 to 4 weeks.

Gastrointestinal

The adverse gastrointestinal effects of chlorambucil are typically mild and last less than 24 hours. These effects can be treated with anti-emetics. Serotonergic receptor antagonists or metoclopramide should be sufficient to control nausea and vomiting.

Neurologic

Seizures and other CNS side effects are seen frequently in human patients following overdoses. Seizures may occur early, within hours after ingestion, and generally disappear within 24 to 48 hours. No apparent residual neurologic damage has occurred in humans to date. Phenobarbital sodium was shown to be of benefit in controlling EEG changes after chlorambucil in experimental treatment of cats receiving high intravenous doses of chlorambucil.[11]

Miscellaneous

In humans, pulmonary side effects have resulted in a discontinuation of chlorambucil. Steroids may be of some benefit. Allergic reactions may require antihistamines and steroids if severe.

Drug Removal

Chlorambucil is not significantly removed by dialysis. Absorption from the gastrointestinal tract is rapid (1 hour) and complete. Emesis may be induced only if the patient just recently ingested chlorambucil and if the patient is not comatose, vomiting, having seizures, or has lost gag reflex.

Gastric lavage with activated charcoal may also be useful.

Management of Cisplatin (Platinol) Overdoses

Cisplatin, as discussed under carboplatin, is more frequently overdosed than carboplatin because of inadvertent name interchange with carboplatin. In general, the dose-limiting toxicities for cisplatin are typically non-hematologic and include nephrotoxicity, ototoxicity, neurotoxicity, and emesis. At high doses of cisplatin, bone marrow suppression is more common and has been noted in multiple cases of cisplatin overdose. As stated under carboplatin, human toxicologic data may be useful in determining toxicities witnessed in dogs. Multiple cases of cisplatin overdoses have been reported in the human literature. An accidental cisplatin overdose (300 mg/m^2) in a 59-year-old male induced severe emesis, myelosuppression, renal failure, mental deterioration with hallucinations, dim vision, and hepatotoxicity. The patient was successfully managed with plasmapheresis and G-CSF. The renal function was restored after 3 months.[18] Similar side effects were also reported in a 68-year-old woman with a massive cisplatin overdose. In this case, the patient also experienced deafness (non-reversible) and seizures. Plasmapheresis was effective and reduced platinum concentrations from 2900 to 200 ng/ml. Further hydration, even after the onset of renal failure, resulted in increased urinary excretion of platinum.[19]

Maximum Intravenous Dosages*
Cats
    Lethal
Dogs
    70 mg/m^2
    *Dose reduction required with renal insufficiency

Toxicities Associated with Cisplatin Overdoses

Hypersensitivity Reactions

Anaphylactoid reactions, edema, wheezing, dyspnea, tachycardia, hypotension, urticaria, rashes, dermatitis, or erythema may occur following cisplatin treatment at any dose.

Hematologic

Bone marrow suppression (thrombocytopenia, leukopenia, neutropenia, and/or anemia), which is typically rare with cisplatin, is expected at higher doses and has been reported in human overdose cases. Myelosuppression may be severe.

Gastrointestinal

Severe nausea, vomiting, and anorexia are reported in humans following overdoses.[18,19] Both acute and delayed gastrointestinal symptoms should be anticipated in overdoses. Symptoms may continue for weeks and are believed mediated via both local and central mechanisms involving serotonin.

Nervous System

Peripheral neuropathies (reversible and non-reversible) are a dose-dependent toxicity in humans and may occur acutely or may be delayed following high doses of drug. Dorsal column myelopathy and autonomic neuropathy may also occur. Both partial and tonic-clonic seizures, slurred speech, loss of taste, mental deterioration, hallucinations, and tremors have also been described. Ototoxicity (non-reversible), loss of vision (cortical blindness), optic neuritis, and papilledema is also noted following overdoses of cisplatin in humans.

Renal Toxicity

Cisplatin is an extremely nephrotoxic heavy metal. Nephrotoxicosis is characterized by reduced glomerular filtration and renal tubular damage. Patients with prior renal impairment, hypertension, or diabetes, or those on other nephrotoxic drugs may be at increased risk of renal failure, particularly when high doses of cisplatin are used. At high doses, nephrotoxicity may be severe and result in irreversible renal damage, which may be fatal. Focal acute tubular necrosis and degeneration have been described.

Electrolyte Effects

Severe and prolonged hypophosphatemia, hypokalemia, hypocalcemia, and hypomagnesemia have all been reported in humans and should be carefully monitored. Cisplatin has caused significant hypomagnesemia and hypocalcemia in children at high doses resulting in cramps, clonus, tremor, carpopedal spasm, and tetany.

Hepatic System

Hepatotoxicity has been described following human cisplatin overdoses. Elevated liver enzymes (serum alkaline phosphatase, AST, bilirubin) have been reported in human patients receiving high dose regimens as well as cisplatin overdoses.[18]

Treatment of Cisplatin Overdoses

Overdoses of cisplatin typically result in severe toxicities. Prior experience with human overdoses suggests a number of effective but costly treatments. Plasmapheresis is considered the therapy of choice in humans following platinum overdoses but is not readily available in veterinary medicine. In humans, amifostine (Ethyol or WR-2721) has been given to reduce the severity and incidence of cisplatin-induced side effects

(neurotoxicity, nephrotoxicity, hypomagnesemia, bone marrow toxicity). This agent works as a cytoprotective pro-drug that releases free thiol groups that can act to detoxify reactive nucleophiles generated by alkylating agents and platinum-containing agents. Amifostine has been shown to be effective in human cisplatin overdoses and appears to be well tolerated in dogs.[20,21] In humans, amifostine may contribute to cisplatin-induced nausea and hypotension.

Hematologic

Neupogen (G-CSF) should be started prophylactically following severe overdoses. Blood transfusions may also be required. Amifostine has been shown to reduce cisplatin-induced bone marrow toxicity in humans. Antibiotics should also be started prophylactically.

Gastrointestinal

A selective serotonergic receptor antagonist in combination with a metoclopramide CRI may be effective. For nausea and vomiting refractory to these, a combination of both, with or without a corticosteroid, should be considered. Both acute and chronic treatment may be required.

Nervous/Hepatic

Because neurotoxicity and hepatic toxicity are concentration-dependent side effects, reduction in cisplatin tissue concentrations via plasmapheresis, hydration, and diuresis may be beneficial. Amifostine has also been shown to reduce cisplatin-induced neurotoxicity.

Renal

Cisplatin has been demonstrated to be less toxic in a high-chloride environment.[22] Intravenous normal saline given at twice the maintenance rate and mannitol (0.25–0.5 g/kg IV q 4–6 hr) and/or furosemide (1–2 mg/kg IV q 6–12 hr) may also be effective. Following cisplatin overdoses in humans, hydration, even after the onset of renal failure, has resulted in significant increased urinary excretion of platinum.[19] Ideally, hydration should be aimed at induction of a brisk diuresis, particularly after an overdose has occurred. Many substances have been evaluated in an attempt to minimize cisplatin=-induced nephrotoxicity, including sodium thiosulfate, glutathione, superoxide dismutase, MESNA, probenecid, and amifostine. Sodium thiosulfate (4 g/m^2) loading dose over 15 minutes to decrease hypotension, then 2.7 g/m^2 in three divided doses, has been administered to pediatric patients.[23] Amifostine has been administered to humans at a dose of 740 to 910 mg/m^2 (up to three doses in 24 hr) administered as a 15-minute intravenous infusion. Longer infusions may cause hypotension. Monitor for hypotension and give fluid boluses if needed. If blood pressure returns to normal within 5 minutes, infusion may be restarted (Micromedex Healthcare Services). Amifostine has had proven efficacy in human patients.[24]

Electrolyte Effects

Monitor closely and replace if necessary. Potassium chloride should be added to intravenous fluids to replace losses. Magnesium sulfate should be given intravenously if required.

Drug Removal

Hemodialysis is not effective because of rapid release of secondary platinum species from tissues causing a rebound effect.[23] Plasmapheresis is effective in reducing plasma

platinum concentrations following human overdoses. Concentrations have been reduced from 2979 ng/ml to 185 ng/ml following plasmapheresis in at least one human patient.[18]

Management of Cyclophosphamide (Cytoxan) Overdoses

The toxicity of high-dose cyclophosphamide is perhaps better known than any drug since it is a frequent drug of choice for bone marrow ablation, prior to bone marrow transplantation in humans. Acute toxicity from overdoses produces extensions of common adverse reactions such as leukopenia and thrombocytopenia. Cardiotoxic effects may occur and are dose dependent. Extreme overdoses in humans (4 g/m^2/day, four times per day) have resulted in fatal cardiotoxicity. The urinary system is also a target for toxicity because it is low in thiols (i.e., glutathione) that bind acrolein and other cytotoxic-active metabolites. Prolonged exposure of bladder mucosa to high concentrations of cytotoxic metabolites results in sometimes severe hemorrhagic cystitis.

Maximum Intravenous Dosages*
Cats
　10 mg/kg IV or PO
Dogs
　250 mg/m^2 IV or PO
　*Tablets should not be split!
　*Dose reduction (33%–50%) is required in patients with compromised bone marrow function.

Toxicities Associated with Cyclophosphamide Overdoses
 Hematologic
　One of the major dose-limiting side effects of cyclophosphamide is hematologic toxicity. Leukopenia, thrombocytopenia, hypothrombinemia, and anemia would be expected to be severe following an overdose.
Cardiac
　Cardiac toxicity is expected following extremely high doses. In humans, this has resulted in hemorrhagic myocardial necrosis, acute myocarditis, and fatal congestive heart failure within days of an overdose. Indicators may include sudden weight gain, ECG abnormalities, and dyspnea.
Gastrointestinal
　Nausea, vomiting, and anorexia are dose related and may be severe following an overdose. Nausea may be delayed for up to 12 to 24 hours. Although rare with smaller doses, diarrhea, hemorrhagic colitis, mucosal irritation, and oral ulceration may occur more frequently with overdoses.
Genitourinary
　Sterile hemorrhagic cystitis (hematuria, hemorrhagic cystitis) caused by chemical irritation of the bladder by active metabolites (acrolein) is noted at low doses, and its incidence may be increased in an overdose. Typically it is seen more frequently in dogs on chronic therapy but has been reported acutely with high doses and can also occur in cats.[25] Following standard oral doses, sterile hemorrhagic cystitis is reported to occur in 7% (14/203) of dogs and 3% (1/52) of cats.[26] Bladder fibrosis may occur with or without

cystitis and is also a dose-related side effect. Obstruction may occur from clots and cause significant pain on urination.

Metabolic

As a result of extensive purine catabolism, hyperuricemia may result and may be more prevalent at high doses with significant cellular destruction. Hyperkalemia resulting from rapid tumor lysis may also occur. In humans, hyponatremia resulting from impaired water excretion (SIADH) has also been reported and should be monitored. SIADH appears to be dose dependent in humans receiving cyclophosphamide.

Miscellaneous

At high doses over prolonged periods, human patients have developed interstitial pulmonary fibrosis, which has been fatal and non-responsive to corticosteroids. Other side effects may include hepatotoxicity, alopecia, anaphylactic reactions, skin pigmentation, and the development of secondary cancers (bladder, leukemia).

Treatment of Cyclophosphamide Overdoses

Hematologic

Neupogen (G-CSF) should be started prophylactically (24 hr after chemotherapy overdose) in the case of a severe overdose. Blood transfusions may also be required. Anti-infectives should be started prophylactically. Drugs that interact with the P-450 enzyme system should be avoided. P-450 inducers (barbiturates) may increase formation of cyclophosphamide toxic metabolites, and P-450 inhibitors (cimetidine) may delay drug accumulation, leading to increased bone marrow suppression.

Cardiac

Cardiac toxicity is dose and concentration related so that any process to expedite drug clearance may reduce the potential for toxicity. Hemodialysis, if available, should be performed after extremely large overdoses. Hydration with forced diuresis may be of some help. Assess patient frequently for signs and symptoms of cardiac dysfunction.

Gastrointestinal

Emesis should be minimal following cyclophosphamide, even when administered to cats.[27] If vomiting and nausea are severe, a selective serotonergic receptor antagonist or metoclopramide may be effective. If gastrointestinal irritation or mucositis is evident, a proton pump inhibitor with or without sucralfate may be useful.

Genitourinary

In veterinary medicine, a variety of treatments have been tried to minimize bladder toxicity. Prednisone (0.5–1.0 mg/kg) PO once daily has been given to reduce bladder inflammation and promote diuresis.[4] Intravesicular administration of formulin (1%) or DMSO (25%–50%) has also been given with some success in dogs.[28,29] In humans, the mainstay of treatment is diuresis, bladder irrigation with aluminum sulfate (alum), and MESNA. In general, hyper-hydration with bladder irrigation may be equivalent to MESNA at reducing bladder toxicity. Therefore, patients with asymptomatic hematuria and/or minimal symptoms can be managed with fluid diuresis. Hydration is key to the prevention of cystitis, particularly in the first 72 hours. Frequent voiding of urine to eliminate accumulation of toxic metabolites in the bladder may also be helpful in reduction of hemorrhagic cystitis. More aggressive therapy may be necessary for symptomatic patients. In pediatric patients, MESNA (12 mg/kg IV at hours 0, 3, 6, 9, and 12)[30] and fluids (1.5–2.0 maintenance rate) are suggested if there is evidence of

hemorrhagic cystitis.[31] In dogs, the recommended dose of MESNA is based on the dose of cyclophosphamide used (20%). MESNA is given as an IV bolus followed by a 0.9% NaCl diuresis. Two additional doses can be given at 2 and 5 hours during the diuresis period.[32,33] Benzyl alcohol is used as a preservative in MESNA, which may be toxic to animals. However, cats have been given MESNA apparently without problems.[34]

Metabolic

If hyperuricemia is present, fluid therapy should be initiated. In pediatric patients, D_5W (3000 ml/m^2/day with 40 mEq/L NaHCO$_3$) is used in combination with allopurinol. If SIADH is present, treatment should involve fluid restriction and furosemide. Hypertonic crystalloids may be given to increase sodium solutes. Hyponatremia can lead to seizures or coma and should be frequently monitored. Slowly increase the sodium concentration at a rate of 0.5 to 1.0 mmol/L/hr, so that central pontine myelinolysis is not induced. Aggressive intravenous potassium supplementation may also be required.

Miscellaneous

Pulmonary fibrosis from cyclophosphamide is not reversed by corticosteroids.

Drug Removal

Hemodialysis is effective at reducing cyclophosphamide plasma concentrations and is suggested following large overdoses if available.[35,36] For orally administered overdoses, emesis may be suggested if noted early after ingestion. Activated charcoal may also be effective.

Management of Cytarabine (Cytosar) Overdoses

High-dose regimens of cytarabine are associated with many severe toxicities not frequently seen with standard doses. Severe and sometimes fatal CNS, gastrointestinal, cardiac, and pulmonary toxicity may occur. Toxicity studies in dogs have shown that toxicity is influenced by the schedule of administration. Total doses given to beagle dogs of 1920 mg/m^2 every 6 hours for 12 doses was lethal (causing bone marrow hypoplasia, liver, and kidney damage), but the same dose (1920 mg/m^2) every 6 hours for 8 doses produced only minimal toxicity (elevated transaminases). In general, the dose-limiting side effects in dogs are bone marrow suppression with leukopenia and reversible cerebellar dysfunction (manufacturer's toxicologic data).

Maximum Intravenous Dosages*

Cats

300 mg/m^2 or CRI: 100 mg/m^2 6- to 8-hour infusions.

Dogs

400 mg/m^2 or CRI: 100 mg/m^2 6- to 8-hour infusions.

*Dose reductions should be made in the case of severe hepatic or renal dysfunction or if severe myelosuppression is present.

Toxicities Associated with Cytarabine Overdoses

1. Hematologic

Bone marrow suppression is frequently seen at standard doses of cytarabine and would be expected to be severe following overdoses. Myelosuppression is manifested by reticulocytopenia, leukopenia, thrombocytopenia, anemia, and megaloblastosis.

Generally there is a biphasic drop in white blood cell count regardless of the dose or schedule. This may begin within 24 hours, followed by another nadir after 2 weeks.

Gastrointestinal

Whereas nausea and vomiting are encountered at standard doses, severe ulceration, bowel necrosis, and necrotizing colitis have been reported in humans following high doses. Diarrhea, ileus, abdominal pain, hematemesis, melena, hypokalemia, hypocalcemia, protein-losing enteropathy, and intestinal infections have also been reported.

Hepatic

Liver damage with increased hyperbilirubinemia, elevated transaminases, and alkaline phosphatases has been reported in humans. Liver abscesses and veno-occlusive disease have also been reported.

Nervous System

High doses of cytarabine are associated with sometimes very severe neurotoxicity, including cerebral and cerebellar dysfunction (ataxia, dysarthria, nystagmus, tremor). This is typically reversible. Peripheral motor and sensory neuropathies may also occur. The drug is a direct neurotoxin and reduced renal clearance may further increase neurotoxicity.

Pulmonary/Cardiac

Pericarditis with tamponade, cardiomyopathy, pulmonary edema, and sudden respiratory distress has been reported following high doses in humans.

Ophthalmic

Hemorrhagic conjunctivitis and keratitis may occur with very large doses. The drug is excreted into tears and may block corneal DNA synthesis.

Hyperuricemia

Extensive purine catabolism may occur at high doses and result in hyperuricemia. Serum uric acid concentrations should be monitored. Rapid cell kill with large tumor burden may also result in tumor lysis syndrome.

Treatment of Cytarabine Overdoses

Hematologic

Neupogen (G-CSF) should be started prophylactically in the case of a severe overdose (approximately 24 hours after chemotherapy, until counts return to normal). Blood transfusions may also be required. Antibacterials should also be started prophylactically.

Gastrointestinal

Selective serotonergic receptor inhibitors in combination with a metoclopramide CRI may be effective. For nausea and vomiting refractory to these, a combination of both, with or without a corticosteroid, should be considered. Both acute and chronic treatment may be required. Proton pump inhibitors may be useful in the prevention of severe ulceration. Prophylactic antibiotics should also be prescribed.

Hepatic/Nervous System

There is no known effective treatment for hepatic and nervous system side effects. Since the parent drug and its active metabolite (ara-CTP) are primarily cleared via renal elimination, intravenous hydration and diuresis may assist in the elimination of drug from the plasma. The efficacy of hepatoprotective agents such as milk thistle and SAM-E has not been evaluated. Frequent neurologic examinations should be performed. Concurrent

use of renal toxic drugs (aminoglycosides) should be avoided to prevent drug accumulation.

Pulmonary/Cardiac

Supportive care, for non-cardiac pulmonary edema (pressors and positive-pressure ventilation) may be required. Corticosteroids may be useful for chronic or hypersensitivity pneumonitis (should not be used if gastrointestinal ulceration is present).

Ophthalmic

This may be prevented by prophylaxis with ophthalmic corticosteroids. Steroid eye drops with dexamethasone or prednisolone should be given for at least 72 hours to prevent conjunctivitis.

Hyperuricemia

Hydration and alkalinization of urine may minimize or prevent hyperuricemia.

Drug Removal

Hemodialysis does not remove cytarabine from plasma.[35]

Management of Dacarbazine (DTIC) Overdoses

Manufacturer toxicology studies in dogs, rats, and mice suggest that the primary toxicities seen in all species at the maximum tolerated dose were bone marrow suppression, lymphoid, and gastrointestinal toxicity. No published dacarbazine overdoses were noted in the veterinary literature. Multiple reports suggest that its use in combination with other cytotoxic agents significantly increases the toxicity of dacarbazine. No antidote exists for most of the side effects associated with dacarbazine. The severity of hematologic and hepatic effects noted even at standard doses in humans suggests that overdoses may result in extreme morbidity and mortality. Although there is no confirmed treatment of dacarbazine overdoses, any process that increases drug elimination may be of benefit. In vitro studies suggest that it may be effective.[35] Approximately 46% to 52% of the parent drug is eliminated in the urine as well as 9% to 18% of its active metabolite (5-aminoimidazole-4-carboxamide (AIC).[37] Early hydration and forced diuresis to expedite renal clearance may be beneficial.

Maximum Intravenous Dosages*
Dogs

1000 mg/m^2 as a 4-hour infusion or 200 mg/m^2 given once daily for 5 days.

Cats

Not used

*Dose reduction should be considered in animals with limited hepatic function and renal function.

Toxicities Associated with Dacarbazine Overdoses
Gastrointestinal

Acute nausea, vomiting, loss of appetite, and anorexia occur in most patients treated with dacarbazine and would be expected to be severe with overdoses. Vomiting is believed to be due to a centrally mediated mechanism. At high doses, stomatitis and diarrhea may also occur.

Hematologic

   Both leukopenia and thrombocytopenia are frequently seen at standard doses and would be expected in dogs at high doses.

Hepatic
   Hepatic toxicity is rare but may be severe with standard doses of dacarbazine and is seen more frequently at high doses or with combination therapy. Severe hepatotoxicity, including hepatic vein thrombosis and fatal hepatocellular necrosis, has been reported.

Flu-Like Syndrome
   Fever, malaise, and myalgia are reported in humans after large single doses of dacarbazine and may occur in dogs following high doses.

Miscellaneous Effects
   Flushing, rashes, renal failure (elevated BUN, renal impairment), anaphylactic reactions, paresthesia, blurred vision, seizures, and photosensitivity have also been reported.

Treatment of Dacarbazine Overdoses

Gastrointestinal
   Patients may have severe and protracted vomiting and diarrhea. Hydration, gut rest, and TPN or PPN may be required. Selective serotonergic receptor inhibitors with a metoclopramide CRI and potentially a corticosteroid may be required to inhibit the severe nausea and vomiting expected acutely. Metoclopramide may be effective for delayed emesis. Both acute and chronic treatment may be required. To prevent ulceration, a proton pump inhibitor such as oral omeprazole may be advised; if oral agents cannot be administered, intravenous Prevacid or Nexium may be beneficial.

Hematologic
   Assess blood counts frequently. Neupogen (G-CSF) should be started prophylactically in the case of a severe overdose (approximately 24 hr after chemotherapy, until counts return to normal). Blood transfusions may also be required. Anti-infectives should be started prophylactically.

Hepatic
   Liver function may be significantly altered and should be assessed frequently. Other hepatotoxic agents should be avoided. Few drugs are effective for treating frank liver disease in people or animals. Ursodeoxycholic acid (Ursodiol) has been given to humans as a hepatoprotective agent where it decreases hydrophobic bile acids that act to damage hepatocytes. Dog doses are approximately 10 to 15 mg/kg every 24 hours or divided and given every 12 hours. However, ursodeoxycholic acid may be less effective in dogs, since their primary circulating bile acid is taurocholate. Oral cholestyramine was recently reported to reduce taurine plasma concentrations in dogs and may have potential for binding taurocholate.[38]

Flu-Like Syndrome
   The exact mechanism of flu-like syndrome is unknown and there is no suggested supportive care noted. It does appear to be dose related and may be seen more frequently with overdoses.

Miscellaneous Effects
   Local application of hot packs may help pain and burning at the injection site. CSF concentrations are approximately 14% of the plasma concentration, so seizures may occur at very high doses and should be treated appropriately. Phenobarbital has been

demonstrated in human medicine to enhance metabolism of dacarbazine significantly, but its acute effects are unknown.

Drug Removal

The efficacy of hemodialysis for dacarbazine overdoses in vivo is unknown. However, in vitro studies suggest that hemodialysis may be effective.[35]

Management of Dactinomycin (Actinomycin-D) Overdoses

Reports of actinomycin-D overdoses are uncommon in the literature. A number of reports are available in the human literature. Errors have primarily involved mistakes in verbal orders being misinterpreted, such as a verbal order called in by an oncologist for actinomycin-D 4 mg over 4 days that was incorrectly filled as actinomycin-D 4 mg daily for 4 days. The patient died 6 days after completing the course of actinomycin-D. Manifestations of overdoses in humans have typically included nausea, vomiting, diarrhea, mucositis, stomatitis, gastrointestinal ulceration, skin disorders (including exanthema), desquamation, epidermolysis, severe bone marrow suppression, veno-occlusive disease, and hepatic failure. Choonara et al.[39] described a case of a 17-year-old boy who received a total dose of 3.3 mg/m^2 (0.1 mg/kg) who had severe and prolonged electrolyte abnormalities, generalized seizures, and skin rashes. Brogan et al.[40] further described an 18-month-old boy who received a massive overdose of actinomycin-D that developed severe, acute toxicity affecting many organ systems and had multiple prolonged complications. A ten-fold overdose (0.15 mg/kg/day) was given for the first 3 days of the induction phase of chemotherapy. By day 5 after initiation of therapy, the patient presented with respiratory distress, oliguria, severe mucositis, hepatic insufficiency, pancreatitis, hyponatremia, hypocalcemia, melena, and pancytopenia. On day 6 the patient was febrile and irritable and had extensive alveolar-interstitial infiltrates. He subsequently developed pneumomediastinum with subcutaneous emphysema, coagulopathies, anuria, hypotension, a lesion of the cerebral cortex, choreoathetosis, and dysarthria. He was discharged 50 days following the overdose with minimal neurologic dysfunction.

Maximum Intravenous Dosage*

Dogs

0.5–0.9 mg/m^2

Cats

Not used

*Dosage adjustments (reductions) may be required in geriatric patients who are more sensitive to this drug or when using in combination with other cytotoxic drugs. Doses should be based on body surface area in obese or edematous patients.

Toxicities Associated with Dactinomycin Overdoses

Hematologic

Hematologic toxicity is dose dependent following actinomycin D. Anemia, pancytopenia, reticulopenia, agranulocytosis, and aplastic anemia are commonly seen with high-dose therapy. A decrease in platelet counts may be observed first followed by a total myelosuppression. Leukocyte and nadirs may be delayed for 14 to 21 days, and may

not return to normal for 3 to 4 weeks. Following severe overdoses in humans, pancytopenia is noted as early as 5 days following the overdose.[40]
Gastrointestinal
   Gastrointestinal side effects are considered dose dependent following actinomycin D. Nausea and vomiting are acute following large doses of actinomycin-D (1–2 hr). Later effects may be severe stomatitis, dysphagia, esophagitis, ulcers, and pharyngitis. Severe stomatitis may occur as early as 5 days after overdose.[40]
Liver Dysfunction
   Ascites, hepatotoxicity, hepatitis, hepatic failure resulting in death, veno-occlusive disease (mainly hepatic), intravascular clotting, and hepatomegaly have all been reported with actinomycin- D. Hepatotoxicity appears to be dose related. The risk of veno-occlusive disease is greater in children (<4 years old) and may be greater following overdoses in animals.
Dermatologic
   Alopecia, skin eruptions, and flare-up of erythema occur commonly with the drug, but large doses may involve more serious skin disorders including exanthema, desquamation, and epidermolysis.
Other
   Electrolyte abnormalities, malaise, lethargy, growth retardation, fever, myalgia, pneumonitis, and anaphylactoid reactions are reported in patients following actinomycin D treatment. Overdoses appear to have a higher risk of hypocalcemia, hyponatremia, pancreatitis, respiratory distress, renal failure, hypotension, and neurologic dysfunction. Neurologic impairment may be severe and has included hyperintense regions of the cerebellar white matter and lesions of the cerebral cortex consistent with an infarct in the area of the left middle cerebral artery. Dysarthria and choreoathetoid movements of all extremities and weakness in one extremity have been reported.

Treatment of Dactinomycin Overdoses
Hematologic
   Neupogen (G-CSF) should be started prophylactically (day 2–3) in the case of an overdose to prevent potentially severe neutropenia. Blood transfusions may also be required. Broad spectrum antibiotics should be started prophylactically. Blood cultures should be done if possible.
Gastrointestinal
   Acute nausea, vomiting, and diarrhea are anticipated. Delayed gastrointestinal upset may be the result of hyperammonemia if renal failure occurs. Selective inhibitors of type 3 (5-HT-3) serotonergic receptors (granisetron, ondansetron, dolasetron) or a substituted benzamide (metoclopramide) may be effective. For nausea and vomiting refractory to these, a combination of both, with or without a corticosteroid (dexamethasone, methylprednisolone) should be considered.
Liver Dysfunction
   Liver enzymes must be monitored carefully. Hepatic toxicity may be severe to fatal following an overdose. Hepatic veno-occlusive disease associated with intravascular clotting disorder may also occur and should be monitored closely. There is no antidote, and hepatoprotective agents such as milk thistle and SAM-E remain to be evaluated for

efficacy. Avoidance of other hepatotoxic agents (cimetidine, antifungals, TMS, etc.) may be of some benefit.

Dermatologic

Dermatologic side effects following actinomycin-D overdoses may be severe. Patients should be evaluated closely and supportive care given if required.

Other

Supportive care is required with severe respiratory distress. Mechanical ventilation may be required. Continuous veno-venous hemofiltration has been useful in human patients with severe overdoses.[40] Hypotension refractory to dopamine and epinephrine was successfully treated with norepinephrine and stress doses of hydrocortisone in at least one case.[40] Renal failure may resolve within 3 to 4 weeks if the patient has good supportive care. Intravenous normal saline given at twice the maintenance rate and mannitol (0.25–0.5 g/kg IV q 4–6 hr) and/or furosemide (1–2 mg/kg IV q 6–12 hr) may help to maintain renal function and assist in drug elimination.

Drug Removal

Dialysis has not been proven to be effective. Many of the side effects of actinomycin-D are dose related and may benefit by improved clearance of drug. Approximately 30% of the drug is excreted in the urine and feces in 9 days in humans. The drug is excreted primarily as unchanged drug in urine so that hydration and diuresis may be of some benefit in increasing renal clearance of drugs.

Management of Doxorubicin (Adriamycin) Overdoses

Overdoses from doxorubicin are reported in the human literature, and most cases have involved severe bone marrow depression and cardiac failure. Both acute and latent reactions have been severe. Doxorubicin toxicity has also been reported more commonly in geriatric patients, particularly with pre-existing cardiac disease. Its use in breeds that have MDR-1 gene mutations may also be a predisposing factor for toxicity. Latent cardiac failure has been significantly decreased with prophylactic use of dexrazoxane, but its efficacy remains to be evaluated in overdoses. There are few reports in the literature describing overdoses of doxorubicin in veterinary medicine. We described at least one case of doxorubicin toxicity in a 5-year-old, spayed English Springer Spaniel that inadvertently received twice (60 mg/m^2) its normal dose (30 mg/m^2) of doxorubicin. The animal developed hemorrhagic gastroenterocolitis, leukopenia, absolute neutropenia, thrombocytopenia, anemia, and elevated liver enzymes. The animal recovered fully with blood transfusions and supportive care that included fluids, antibiotics, iron, and gastrointestinal protectants (cimetidine, misoprostol).

Maximum Intravenous Dosages*

Cats

1 mg/kg or 25 mg/m^2

Dogs

Small (<15 kg): 1 mg/kg; large (>15 kg): 30 mg/m^2

*Dose reductions should be considered in the case of existing neutropenia and renal failure. In patients with abnormal fluid retention, doses should be based on the ideal body weight.

Toxicities Associated with Doxorubicin Overdoses

Hematologic

Leukopenia (primarily granulocytopenia) is the primary dose-limiting side effect of standard doses. Deaths may occur from severe leukopenia at high doses from septicemia. Anemia and thrombocytopenia may also occur.

Cardiac

At least three types of cardiac toxicity occur following standard doxorubicin treatments: (1) transient (abnormal ECG findings, S-T wave changes, prolonged Q-T, and arrhythmias), (2) chronic: related to cumulative dose (progressive loss of cardiac myocytes, thinning of ventricular walls, decreased systolic performance), and (3) subacute: latent onset from prior exposure in juveniles. Cardiotoxicity has been related to peak drug concentrations in humans so that cardiotoxicity may be more prevalent with overdoses. Animals with an increased risk of cardiomyopathy such as Dobermans, boxers and other giant breeds or those with prior cardiac disease may be at much higher risk. Following standard doses to the maximum dose (240 mg/m^2 over eight cycles), the incidence of cardiotoxicity is between 4% and 16%.[41,42] However, it has also been noted following only two cycles of 30 mg/m^2.[43]

Gastrointestinal

Stomatitis and esophagitis (mucositis) would be expected to occur with high doses. Gastrointestinal toxicity (nausea, vomiting, anorexia, diarrhea), which is only moderate following standard doses, may be severe with overdoses. Following the two-fold overdose in the case described above, severe hemorrhagic gastroenterocolitis was noted. Ulceration and necrosis of the colon and cecum have occurred in humans and dogs that can lead to fatal infections.

Dermatologic

In humans, palmar-plantar erythrodysesthesia (swelling, pain, erythema, and desquamation of the hands and feet) has been reported with the liposomal product (Doxil) and appears dose related. It is also a dose-limiting toxicity of dogs treated with Doxil.

Nervous System

Peripheral neuropathy (sensory and/or motor) and seizures have been reported with high doses of doxorubicin in humans.

Hyperuricemia

Extensive purine catabolism may occur at high doses and result in hyperuricemia. Serum uric acid concentrations should be monitored.

Nephrotoxicity

Nephrotoxicity (azotemia, reduced specific gravity) has been noted with high cumulative doses (300 mg/m^2) of doxorubicin in two of six cats and may be seen following high acute doses.[44,45]

Miscellaneous

Hypersensitivity reactions (fever, chills, urticaria, anaphylaxis) may occur but are not dose related. Elevated liver enzymes were also noted following the two-fold overdose noted previously.

Treatment of Doxorubicin Overdoses

Hematologic

Neupogen (G-CSF) should be started prophylactically in the case of a severe overdose (approximately 24 hours after chemotherapy, until counts return to normal). Blood transfusions may also be required. Antibiotics should also be started prophylactically.
Cardiac

Dexrazoxane (Zinecard) is typically given just prior to doxorubicin to reduce the risks of cardiotoxicity. Its efficacy in overdoses has not been proven. It is an effective cardioprotectant for cumulative cardiotoxicity and helps to neutralize doxorubicin extravasations. Suggested dosing for cardiotoxicity is a 10:1 ratio of dexrazoxane to doxorubicin (or 300 mg/m^2 of dexrazoxane for a 30 mg/m^2 dose of doxorubicin). Supportive care using digoxin, diuretics, and after-load reducers may also be beneficial.
Gastrointestinal

Selective serotonergic receptor inhibitors or metoclopramide CRI may be effective for nausea and vomiting. Typically doxorubicin gastrointestinal side effects are seen a few days after chemotherapy with standard doses. This is frequently treatable with both metoclopramide and sucralfate. However, following overdoses, severe nausea, vomiting, and gastroenteritis may occur. Intravenous proton pump inhibitors may be required for the prevention of severe ulceration. Prophylactic antibiotics should also be prescribed.
Nervous System

Since neurotoxicity is dose related, any reduction in doxorubicin plasma concentration will potentially reduce neurologic complications.
Dermatologic

The use of oral pyridoxine (vitamin B$_6$) to prevent cutaneous reactions (palmer-plantar erythrodysesthesia [PPES]) from Doxil has been evaluated in dogs. Pyridoxine (50 mg/kg po TID) was reported to delay the onset and severity of PPES from Doxil, which permitted dogs to have fewer delays and discontinuations in treatment.[46] Following overdoses of Doxil and possibly doxorubicin pyridoxine may have some benefit.
Nephrotoxicity/Hyperuricemia

Hydration and alkalinization of urine may minimize or prevent hyperuricemia and reduce renal toxicity.
Drug Removal

Hemodialysis does not effectively reduce plasma concentrations of doxorubicin.[35] Hemoprofusion using a charcoal filter (1.5–4 hr) or Amberlite filter has been successful if initiated early (<18 hr) after the overdose. Amberlite hemoprofusion (2 x 4-hour) was also successful if performed early after overdoses in humans.[47,48]

Management of 5-Fluorouracil (5-FU) Overdoses

There are few documented cases of 5-fluorouracil (5-FU) overdoses in the human literature. However, because of the frequent side effects of this agent even at standard doses, much is known about its toxicities. A single case report of a woman receiving an accidental intravenous overdose of 5-FU (infusion of 4000 mg/m^2 over 4 hours vs. 4 days) was reported to be due to the incorrect programming of an infusion pump. The woman developed nausea, vomiting, and throat discomfort 2 days after infusion and then went on to develop mucositis, pancytopenia, hemodynamic collapse, and multi-organ failure. She died 22 days after the event.[49] Severe and toxic reactions have also been attributed to deficiency of dipyrimidine dehydrogenase activity in some human patients,

which prolongs the clearance of 5-FU. Typically more than 90% of the 5-FU dose is accounted for by either excretion in urine or expired CO_2 within 24 hours in humans, so removal of drug (emesis, gastric lavage) following overdoses should be done rapidly if possible.

Although little information exists in the veterinary literature on 5-FU overdoses with intravenous administration, there are multiple reports of oral ingestion of human-labeled commercial ointment and solutions used by the owners. Most ointments and solutions contain 2% to 5% 5-FU, which is 20 to 50 mg of 5-FU per gram or milliliter of product. The minimum toxic dose of 5-FU according to manufacturer data is 8.6 mg/kg and the lethal dose is 20 mg/kg. If a 55-lb dog were to ingest a 30-g tube of the 5% Ont., then 30 g $\times$ 50 mg 5-FU/1 g Ont. = 1500 mg 5-FU. Therefore 1500 mg/25 kg dog = 60 mg/kg. This is three times the lethal dose. Unfortunately, toxicity from ingestion of 5-FU is fairly common in dogs.[50] One survey suggests that of 72 dogs ingesting 5-FU, 63% died or were euthanized because of poor treatment response. Various anecdotes to 5-FU have been studied experimentally, but their efficacy in clinical overdoses is still being investigated.

New drugs that may prove effective against 5-FU overdoses include agents such as triacetyluridine (Wellstat Therapeutics Corp. Gaithersburg, MD). This is an oral pro-drug of uridine that is orally more bioavailable than uridine itself. Uridine itself is poorly absorbed orally and results in osmotic diarrhea at the doses required to achieve effective plasma concentrations as an antidote. When uridine is given intravenously in large doses, it may also result in hyperthermia and phlebitis. Triacetyluridine may be effective even up to 48 hours following an overdose.[51] The enzyme inhibitor 5-(phenylthio) acyclouridine (PTAU), a uridine phosphorylase inhibitor also shows promise when used in combination with uridine in the rescue of mice treated with lethal overdoses of 5-FU.[52] Although these agents may be very promising, their current availability is limited to investigational use only.

Maximum Intravenous Dosages*
Cats
   LETHAL: Not given because of neurotoxicity
Dogs
   150 mg/m^2
   *Dose reductions should be considered in the case of existing renal or liver failure or with pre-existing bone marrow suppression. Doses should be based on the patient's lean body weight if obese or if serious weight gain from edema, ascites, etc. is present.
Toxicities Associated with 5-Fluorouracil Overdoses
Hematologic
   Thrombocytopenia, leukopenia, agranulocytosis, pancytopenia, and hemolytic anemia may occur. Leukopenia and neutropenia may occur between 7 and 14 days, but the maximum depression may be delayed for up to 20 days. Myelosuppression is noted to be concentration and time dependent in humans with bolus administration resulting in the most severe myelosuppression.
Cardiac
   Cardiac arrhythmias, myocardial ischemia, angina, and ischemic heart failure have all been reported and may result in death.

Gastrointestinal

Nausea, vomiting, diarrhea, ulceration, stomatitis, mucositis, esophagopharyngitis, and anorexia can occur. Gastrointestinal toxicity is due to damage to rapidly dividing cells and is worse with continuous infusions. Diarrhea may be severe and life threatening. Animals surviving seizures may be at risk for gastrointestinal necrosis. Oral and esophageal ulcers can occur as well as severe hemorrhagic gastritis.

Nervous System

Lethargy, tremors, ataxia, nystagmus, and seizures may develop within a few hours of oral ingestion of 5-FU in animals. Severe seizures may result in death. Acute neurotoxicity presents as encephalopathy or cerebellar syndrome. Delayed neurotoxicity has been associated with multi-focal leukoencephalopathy. Extrapyramidal and cortical dysfunction may also occur but is typically reversible. Human patients with dihydropyridine dehydrogenase deficiencies are at higher risk of 5-FU neurologic and cardiac toxicities. To date, no such correlation has been reported in animals.

Other

Rashes, dry skin, fissures, anaphylaxis, thrombophlebitis, epistaxis, loss of nails, photosensitivity, pigmentation, palmer-plantar erythrodysesthesia syndrome, oculomotor disturbances, optic neuritis, and lacrimal duct stenosis have all been reported in humans.

Treatment of 5-Fluorouracil Overdoses

Hematologic

Bone marrow suppression should be monitored every 3 to 4 days for at least 2 weeks. Blood transfusions, platelets, and anti-infective therapy should be initiated if suppression occurs. Neupogen should be initiated prophylactically prior to severe suppression. In severe overdoses, it may be started as soon as 5 to 6 days.

Cardiac

Myocardial toxicity has been associated with the active 5-FU monofluorinated, organic metabolites. Myocardial toxicity in humans has been treated with supportive care, including morphine, oral nitrates, and calcium channel blockers.

Gastrointestinal

Gastrointestinal protectants including proton acid pump inhibitors, metoclopramide, and sucralfate should be initiated prior to the occurrence of gastritis. Metoclopramide should be used with caution since it may also contribute to neurologic signs. Vomiting may occur within hours of ingestion and require intravenous CRI of metoclopramide and intravenous administration of pump inhibitors. Hypovolemic shock may result from blood and fluid loss from the gastrointestinal tract and should be closely monitored.

Nervous System

Both acute and chronic neurotoxicity of 5-FU has been associated with its monofluorinated organic metabolites: monofluoroacetic acid (FA) and alpha-fluoro-beta-alanine (FBAL). Seizures following oral ingestion of 5-FU in animals may occur within hours of ingestion and have been difficult to control. Benzodiazepams may not control seizures alone. Seizures may require constant rate infusions with propofol, diazepam, and/or pentobarbital. Animals with severe seizures may have a worse prognosis. Acute encephalopathies following 5-FU in humans have been treated with thiamine infusions with various degrees of success.[53] Delayed leukoencephalopathy may respond to steroids.[54]

Drug Removal

Studies evaluating the pharmacokinetics of 5-FU in humans with chronic renal failure receiving dialysis suggest that the parent drug does not accumulate in renal failure. Although the parent drug does not accumulate, the active metabolites that are mainly excreted in urine do accumulate and are responsible for the majority of toxicities seen. The final 5-FU catabolite FBAL in humans has been shown to accumulate in renal failure and may be removed by hemodialysis (extraction ratio of 0.6–0.85 over the filter membrane).[55] Therefore, hemodialysis may be useful in reducing the concentrations of active metabolites and reduce their associated toxicities after overdoses.

Management of Lomustine (CCNU or CeeNU) Overdoses

Lomustine is given as oral therapy and is only available in 10, 40, and 100 mg (CeeNu) capsules. Overdoses have frequently occurred in human medicine when they are supplied with more than one treatment course at a time. Directions are frequently misinterpreted as one capsule daily rather than one capsule on day 1 of each treatment cycle. Overdoses in humans have resulted in multi-organ failure, including severe pancytopenia and liver, brain, and lung toxicities.[56] Because of the relatively high incidence of overdoses with this very potent drug, it is generally recommended that no more than one dose is prescribed and filled for each treatment cycle. Ideally, this drug should be administered in the clinic with each dose adjusted based on the animal's nadir from the prior dose. If administered at home, clients should be clearly instructed on exact dosing instructions and on the proper handling of cytotoxic drugs. If the animal vomits within 30 minutes after dosing, it is unlikely to have absorbed the drug. If vomiting occurs between 30 and 60 minutes, it is most likely due to the absorbed drug, and re-dosing should not be considered since this may inadvertently overdose the animal.

Maximum Oral Dosages
Dogs
   80–90 mg/m^2 PO q 3 weeks
Cats
   10 mg/cat or 50 mg/m^2 PO q 3 to 4 weeks
   *Dose reductions should be considered in patients with compromised bone marrow function or with renal insufficency.

Toxicities Associated with Lomustine Overdoses
Hematologic
   Bone marrow suppression is cumulative with CCNU and may be both acute and delayed with overdoses (4–5 weeks). In dogs, the acute dose-limiting toxicity is neutropenia approximately 7 days after CCNU administration.[57] Thrombocytopenia is less common but appears to be a cumulative toxicity in dogs. In rare cases, thrombocytopenia can also be progressive and irreversible.[57,58] In humans, a case report on lomustine overdose (four-fold) resulted in grade 4 neutropenia and thrombocytopenia.[59] Neutropenia is noted even after standard doses of lomustine in dogs and cats and appears dose related in cats.[60,61]
Nervous System

CCNU is highly lipophilic and non-ionized at physiologic pH, so it readily crosses into the CNS where levels are reported to be approximately 50% of plasma levels (manufacturer's label). High CNS concentrations of CCNU following overdoses may result in seizures. Generalized convulsions have been reported in humans at four-fold the standard dose of CCNU and would be expected in animals following overdoses.[59] Disorientation, lethargy, ataxia, dysarthria, optic atrophy, and visual disturbances may also occur at high doses.

Pulmonary

Pulmonary toxicity is dose related and may be severe following CCNU overdoses. Toxicity is typically seen with large cumulative doses and may be delayed in nature but has been reported acutely with overdoses.[59] Infiltrates and/or fibrosis have occurred in humans from 6 months to 17 years after treatment. Lung fibrosis has been progressive and fatal in humans.

Gastrointestinal

Nausea and vomiting occur early after oral dosing (3–6 hr) and appear to be lessened by fasting patients. Vomiting typically only lasts for 24 hours in humans. If the patients vomit 30 to 45 min after dosing, do not repeat the dose. This may be more severe and protracted in animals receiving overdoses. Stomatitis may also occur.

Renal

Progressive azotemia and reduced kidney size and function may occur following large cumulative doses of CCNU but may occur acutely in animals with large overdoses.

Hepatic

A reversible hepatic toxicity is reported in humans following overdoses and is manifested by increased transaminases, alkaline phosphatase, and bilirubin. In dogs, a delayed, cumulative, dose-related, and irreversible hepatotoxicity is associated with CCNU even at standard doses.[58,62,63] Liver enzymes should be monitored for weeks to months following overdoses.[58,62] The median duration to detection of hepatic toxicity following CCNU is 11 weeks (range, 2–49 weeks).[62]

Treatment of Lomustine Overdoses

Hematologic side effects are the primary dose-limiting side effect of lomustine and may be very severe following overdoses of the drug. Delayed thrombocytopenia and leukopenia are the primary concern.

Hematologic

Grade 4 neutropenia and thrombocytopenia have been reported even at standard doses of lomustine in companion animals, and the incidence is expected to be much higher with overdoses.[60,61] Myelosuppression has typically been noted a week or so after inadvertent daily doses of lomustine in human patients. Careful monitoring following an overdose is required since many of the toxicities of lomustine may be somewhat delayed. Neupogen (G-CSF) and blood transfusions will most likely be required and should be initiated prior to severe bone marrow suppression. Antibiotics should also be started prophylactically (avoid the use of TMS, which may have combined hepatic toxicity with lomustine).

Nervous System

There is no antidote to lomustine-induced neurotoxicities. Because it is dose related and may be severe, any reduction in plasma lomustine concentrations may be of benefit. Although the initial half-life of lomustine is short (6 hr), the second phase may take days

(5–6 days) and active metabolites may remain in the system much longer than that. Appropriate anticonvulsants may be required if seizures occur.

Pulmonary

Pulmonary fibrosis is not easily treated and the treatment course may be very prolonged. The use of corticosteroids may be of some benefit.

Gastrointestinal

Nausea and vomiting will be severe if the patient has had a single high dose of lomustine or a high cumulative dose (over days). In general, nausea and vomiting start early after dosing (45 minutes to 6 hr) and may last for days; at high doses this may continue for longer periods and be much more severe. Selective serotonergic receptor inhibitors in combination with a metoclopramide CRI may be effective. This has been combined further with corticosteroids for treatment of acute emesis.

Hepatic

Hepatic toxicity is common even at standard doses of lomustine and may be severe to fatal following an overdose. There is no antidote, and hepatoprotective agents such as SAM-E and milk thistle remain to be evaluated for efficacy. Avoidance of other hepatotoxic agents (cimetidine, antifungals, TMS, etc.) may be of some benefit. Although not proven clinically, the use of phenobarbital prior to CCNU was noted to prevent CCNU hepatotoxicity in laboratory rats.[64] The mechanism was believed related to the altered metabolism of CCNU, shifting the metabolic profile to a less toxic species as well as reversing cholestasis and enhancing biliary excretion and washout of toxic metabolites. Other antioxidants (butylated hydroxyanisole, alpha-tocopherol) or iron chelators (deferoxamine) have been studied in vitro with some success.[65] The use of bile acid sequestrants (cholestyramine, colestipol) that alter biliary bile acid secretion or products that increase bile flow similar to phenobarbital (theophylline) may reduce exposure to toxic metabolites as well as reduce the high serum bile acid concentrations noted in dogs with CCNU-induced hepatotoxicity.[62,66]

Drug Removal

Following known oral overdoses of CCNU, emesis and gastric lavage may be performed if soon after ingestion. There is no information concerning dialysis of lomustine, but the majority of the drug is excreted via the kidneys (75%). Another alkylating agent (BCNU), which is structurally similar, is removed from plasma by dialysis; this suggests that lomustine may be at least partially removed by dialysis. The prolonged secondary half-life of lomustine is believed to be related to enterohepatic circulation of drug and protein binding. Gastrointestinal lavage with charcoal and potentially cholestyramine resin may also help to reduce plasma levels of drug over time.

Management of Melphalan (Alkeran) Overdoses

Overdoses caused by melphalan have been reported in the human literature. Patients receiving melphalan doses of more than 100 mg/m^2 intravenously have developed severe mucositis, stomatitis, colitis, diarrhea, and GI bleeding. Bone marrow aplasia was noted but reversed within 3 weeks. Larger intravenous overdoses of melphalan (290 mg/m^2) have resulted in severe nausea, vomiting, ulceration of the mouth, decreased consciousness, seizures, muscular paralysis, and cholinomimetic effects. Elevations in liver enzymes, hepatic veno-occlusive disease, adult respiratory distress syndrome,

nephrotoxicity, and severe hyponatremia from SIADH have all been noted. Reports in animals receiving high doses of melphalan suggest that bone marrow suppression and gastrointestinal toxicities are the primary dose-limiting toxicities.

Maximum Oral Dosages*
Cats
   2 mg/cat PO q 3 days
Dogs
   0.1 mg/kg PO once daily. For cytoxan, substitute 20 mg/m^2
   * Doses should be reduced in patients with pre-existing renal failure. Studies indicate that the dose should be reduced in proportion to the degree of renal failure (i.e., 50% reduction in dose with 50% reduction in renal function).

Toxicities Associated with Melphalan Overdoses
Hematologic
   Hematologic toxicity is the primary dose-limiting toxicity of melphalan. Leukopenia and thrombocytopenia are the primary hematologic toxicities seen with high doses. Studies looking at dose escalation in dogs have shown that small dogs may have a disproportionately greater risk of severe myelosuppression when dosed on a milligram-per-square-meter (mg/m^2) basis. Myelosuppression may be delayed (1–3 weeks), but leukopenia may occur much sooner (3–5 days) and last for several weeks.[67] Anemia, hemolytic anemia, pancytopenia, and agranulocytosis may also occur.
Cardiovascular
   Arterial or venous thrombosis and pulmonary emboli have been noted in humans. Hepatic veno-occlusive disease has also been reported. At least one human patient developed cardiac arrhythmias, which resulted in death following an overdose of 290 mg/m^2 of melphalan.[68]
Gastrointestinal
   Nausea and vomiting may occur after high doses of melphalan. Diarrhea, stomatitis, and ulceration may also occur. Intravenous doses of more than 125 mg/m^2 have resulted in severe gastrointestinal side effects in humans, including hemorrhagic diarrhea and bowel perforation.[68]
Hypersensitivity Reactions
   Rashes, dermatitis, anaphylaxis, edema, tachycardia, bronchospasm, and dyspnea have occurred in human patients receiving melphalan intravenously.
Other Toxicities
   A syndrome of inadequate ADH secretion and electrolyte disturbances has been reported in the human literature following melphalan overdoses.[68]

Treatment of Melphalan Overdoses
Hematologic
   Neupogen (G-CSF) should be started prophylactically in the case of a severe overdose. Leukopenia may be absolute even with G-CSF. Because of the early occurrence of leukopenia, G-CSF should be started at least 48 hours following the overdose. Blood transfusions may also be required. Antibiotics should also be started prophylactically. Hematologic parameters should be monitored for at least 3 weeks following the overdose.

Cardiovascular

Patients should be monitored closely for signs or symptoms of cardiac arrhythmias and treated appropriately.

Gastrointestinal

Selective serotonergic receptor inhibitors or metoclopramide may be effective. Typically gastrointestinal side effects are mild with standard doses. However, following overdoses frank ulceration may be more common. Proton pump inhibitors may be useful in the prevention of severe ulceration. Prophylactic antibiotics should also be prescribed.

Hypersensitivity Reactions

This is typically only after repeat doses of intravenous melphalan and should not be at any greater frequency following overdoses.

Other Toxicities

If SIADH is present, treatment should involve fluid restriction (urine output plus insensible loss) and the use of furosemide for diuresis. Hypertonic crystalloids may be given to increase sodium solutes. Hyponatremia can lead to seizures or coma and should be monitored frequently. Slowly increase the sodium concentration at a rate of 0.5 to 1.0 mmol/L/hr, so that central pontine myelinolysis is not induced.

Drug Removal

Hemodialysis and hemoprofusion do not alter the clearance of melphalan from plasma. If melphalan has been given orally and the overdose is recognized immediately, emesis may be induced. Administration of activated charcoal via gastric lavage may be useful. The drug is incompletely absorbed and is extremely variable in absorption. Melphalan is eliminated by chemical hydrolysis in plasma, and its metabolites may accumulate in renal failure. In humans, 50% of the dose is excreted into feces within 6 days, suggesting that continued presence of activated charcoal or cholestyramine could reduce the total amount of drug absorbed.

Management of Methotrexate (MTX) Overdoses

Most cases involving MTX overdoses in the literature are accidental human overdoses with either oral or intrathecal MTX. Many are related to accidental daily, instead of weekly, administration of MTX.[69] In general, MTX oral absorption and clearance rates vary widely and toxicity is believed dependent on the duration of exposure to drug, rather then high peak levels. MTX appears to be better tolerated in cats than in dogs.

Maximum Intravenous Dosages*
Cats
0.8 mg/kg IV or SQ
Dogs
0.5 mg/kg IV or SQ
*Doses should be reduced in patients with renal or hepatic failure as well as in geriatric patients or patients with a high degree of third spacing.

Toxicities Associated with MTX Overdoses
Hematologic

Leukopenia, thrombocytopenia, anemia, hemorrhage, aplastic anemia, granulocytopenia, hypergammaglobulinemia, and pancytopenia have all been reported in humans and animals and would be expected from high-dose therapy or overdoses. Bone marrow suppression may occur rapidly (2–7 days) after large doses.

Gastrointestinal

Glossitis, pharyngitis, stomatitis, enteritis, ulcerations, bleeding of the mucous membranes, anorexia, nausea, vomiting, hematemesis, diarrhea, melena, hemorrhagic enteritis, and intestinal perforation leading to death can occur. Gastrointestinal side effects are very common with high doses and overdoses in humans.

Hepatic

Both acute (elevated transaminases) and chronic (potentially fatal fibrosis and cirrhosis) hepatotoxicity can occur. Hepatotoxicity in humans is correlated to high cumulative or total doses of MTX. Hepatotoxicity from MTX is difficult to diagnosis, since fibrosis and cirrhosis may develop without alterations in liver function tests. Biopsies may be required for assessment of the degree of toxicity here.

Neurologic

Acute chemical arachnoiditis and subacute and chronic leukoencephalopathy may occur and can result in fatalities. Ataxia, dementia, elevated CSF pressure, seizures, and coma have been reported in pediatric patients at high doses and adult humans following overdoses. Although MTX does not cross the blood–brain barrier significantly, high doses of drug in the presence of inflammation after radiation or with large tumor burdens may increase penetration into the blood–brain barrier. Intrathecal administration of large doses of MTX in cats and in people appears to produce "multifocal axonopathy" without necrotizing lesions. Axonal degeneration and fibrin exudation in the walls of vessels occur, suggesting that a toxic effect on blood vessels is another mechanism of MTX-induced neurotoxicity.[70] In cases of large overdoses, seizures are frequently seen.[71]

Respiratory

Pulmonary toxicity is rare and does not appear to be dose related. Symptoms may be vague or extreme. Typically human patients present with a dry cough, fever, dyspnea, hypoxemia, and pulmonary infiltrates on x-rays. Fibrosis and acute or chronic interstitial pneumonitis may occur at any time. Pulmonary toxicity may not be reversible and can be fatal.

Cardiovascular

Pericarditis, pericardial effusions, hypotension, and thrombotic complications may occur.

Renal

Severe nephrotoxicity occurs in humans and animals and further predisposes them to other toxicities. Azotemia, hematuria, renal failure, and necrosis of the epithelium of the renal tubules may all occur. Fatalities resulting from renal failure have been reported in humans.

Other

Rashes, exfoliative dermatitis, skin necrosis, elevated serum uric acid, tumor lysis syndrome, visual changes, conjunctivitis, and stress fractures have been rarely reported in humans.

Treatment of MTX Overdoses

In cases in which the overdose is identified early, leucovorin is indicated to prevent toxicity. Leucovorin calcium is a potent folic acid antagonist commonly used as an antidote to MTX toxicity. Leucovorin is most effective if administered within 4 hours of MTX administration. Beyond 6 to 12 hours, the efficacy decreases substantially with time. A minimum of 72 hours of leucovorin rescue are suggested. Ideally the dose of leucovorin should be determined by obtaining serum MTX levels. Toxicities (mucositis, bone marrow suppression) are correlated with MTX concentrations (>1 uM) (1×10^{-6} M) for more than 48 hours. Leucovorin rescue should continue until MTX serum concentrations are <0.1 to 0.01 uM. Alternatively, the dose of leucovorin should be equal to or greater than that of MTX.[72] Hydration and urinary alkalization may also be needed to prevent precipitation of the drug or metabolites in the renal tubules. Intermittent high-flux polysulfone dialyzer systems are effective at reducing MTX serum concentrations but may not be readily available. Other agents may also be of benefit, including oral cholestyramine, which actively binds the parent MTX compound in the gastrointestinal system and prevents further enterohepatic recirculation of MTX and its active metabolites that get converted back to MTX.[73-75]

In humans, carboxypeptidase G_2 (CPDG2, glucarpidase)—a recombinant form of the bacterial enzyme CPG2, cloned from Pseudomonas strain RS-16—has recently become available for compassionate human use (developed by CTEP and Protherics Inc, Brentwood, TN). The enzyme rapidly hydrolyzes the glutamine residue from circulating MTX and inactivates it. The inactive metabolite DAMPA is then excreted non-renally. Clinical studies in humans suggest that in patients with MTX-induced renal failure, MTX concentrations are reduced by 98% within 15 minutes.[76-79] Studies suggest that carboxypeptidase G2 can be administered up to 96 hours after MTX infusion and can be given with leucovorin.[76] Current human recommendations are to administer CPDG2 to patients with sustained MTX concentrations greater than 10 uM at 42 to 48 hours after the MTX infusion.[76]

Hematologic

Bone marrow suppression may occur rapidly and should be monitored for closely. In cats, neutropenia is witnessed even at standard doses. Leukopenia, thrombocytopenia, anemia, and pancytopenia have been seen with human MTX overdoses. The use of leucovorin and other agents to improve MTX clearance (cholestyramine, CPDG2) will help to prevent bone marrow suppression. Blood counts should be assessed frequently. Neupogen (G-CSF) should be started prophylactically in the case of a severe overdose (approximately 24 hours after chemotherapy, until counts return to normal).[80] Blood transfusions may also be required. Anti-infectives should be started prophylactically.

Gastrointestinal

Gastrointestinal side effects caused by MTX are dose related and caused by direct mucosal injury. Selective serotonergic receptor inhibitors or metoclopramide may be effective. Typically gastrointestinal side effects are seen a few days after chemotherapy with standard doses. This is frequently treatable with both metoclopramide and sucralfate. However, following overdoses, frank ulceration may be more common. Proton pump inhibitors may be useful in the prevention of severe ulceration and hemorrhagic enteritis. Prophylactic antibiotics should also be prescribed to prevent bacterial invasion. Diets enriched with glutamine, short-chain fatty acids, and transforming growth factors

(TGF)–β have demonstrated decreased weight loss, acidosis, and hypoalbuminemia in rats treated with MTX.[81]

Hepatic/Cardiovascular

There are no treatments for either hepatic or cardiac side effects of MTX. Liver function tests may not always be indicative of developing liver disease, and liver biopsies would be contraindicated after overdoses. Hepatitis and cardiac side effects are related to delayed elimination of MTX, so all interventions to increase MTX elimination are beneficial here. Avoid all other hepatotoxic drugs.

Neurologic

High-dose leucovorin should be administered within the first hour after MTX if possible. Corticosteroids may help to minimize CNS inflammation. If available, CPDG2, an enzyme that rapidly hydrolyzes MTX, may also be used and can be administered up to 96 hours after MTX administration. Following an overdose of MTX administered intrathecally to a child, CSF drainage, ventricular-lumbar perfusion, intravenous dexamethasone and leucovorin, CPDG2, hydration, and alkalinization successfully rescued the patient. Seizures following overdoses may not be controlled with benzodiazepines. Phenobarbital-induced coma may be required in some overdose circumstances.[82] Intravenous thymidine continuous infusions have also been recommended in humans until plasma MTX concentrations are less than 0.5 µm.[31]

Respiratory

Treatment of MTX-induced pulmonary toxicity is primarily supportive in nature and may require mechanical ventilation if severe. Corticosteroids may provide some benefit.

Renal

Nephrotoxicity is primarily due to precipitation of MTX and 7-hydroxymethotrexate in the renal tubules. Early leucovorin administration, hydration, and urine alkalization with D_5W, and sodium bicarbonate (pH >7.0) are recommended. Measurements of serum MTX and creatinine concentrations are essential to avoid further MTX-induced toxicities.

Other

Administration of large volumes of fluids and alkalinization of the urine may be of benefit if serum uric acid levels are high. Drugs that decrease the renal excretion of MTX (cisplatin, salicylates, sulfas, probenecid, and penicillins) should be avoided.

Drug Removal

Hemodialysis does not effectively alter MTX elimination. Alternatively, acute intermittent hemodialysis with a high-flux polysulfone dialyzer (F-80-B Fresenius dialyzer) has been shown to be effective at increasing MTX clearance in acute renal failure resulting from MTX.[83]

MTX is primarily metabolized in the liver. However, intracellular metabolism and bacterial degradation in the gastrointestinal tract also play a role. Metabolism results in MTX polyglutamates that can then undergo hydrolysis back to MTX. Metabolites remain in tissues for extended periods and prolong cytotoxicity. Following intravenous doses, MTX is primarily excreted via the kidneys, and MTX clearance is directly associated with creatinine clearance in humans. Following oral dosing, a large amount is excreted via feces. Enterohepatic recirculation is believed to occur for both the MTX parent compound and its metabolites. The use of adsorbents (cholestyramine, activated charcoal) to bind MTX and metabolites from being reabsorbed may therefore be very useful. MTX is an anionic drug, and anion-exchange resins accelerate the excretion of drug. Following

high-dose MTX in an 11-year-old girl, serum MTX concentrations 24 hours after MTX infusion with cholestyramine were about 50% of the concentrations measured after the first course of MTX given without cholestyramine. Cholestyramine appears to bind MTX and its active metabolites better than activated charcoal. The binding capacity of MTX to cholestyramine exceeds that of activated charcoal by a factor of 5.4.[75]

Management of Mitoxantrone (Novantrone) Overdoses

   Mitoxantrone overdoses are frequently reported in the human literature. Most overdoses have been due to misinterpretation of the shorthand use of "MTX" for methotrexate, which inadvertently gets filled for mitoxantrone. Because doses of MTX are often very large in human medicine compared with mitoxantrone, this typically results in a significant overdose. As a result, the side effects of mitoxantrone overdoses are fairly well understood in people. No veterinary overdoses were found in the literature at this time. Animal toxicology studies report that mitoxantrone has a spectrum of activity and toxicity similar to other anthracyclines but is much less toxic. In beagles, safety assessment studies using mitoxantrone (2.58 or 5.15 mg/m^2 q 3 weeks × 30 weeks) resulted in gastrointestinal toxicity and marrow suppression, but much less cardiotoxicity than doxorubicin.[84] Myocardial changes as measured by sequential endocardial biopsies were also shown to be unrelated to dose or time at the maximum tolerated dose of 0.25 mg/kg or 5.15 mg/m^2.[85] In mouse studies, animals were noted to have severe bone marrow suppression starting on day 4 after an LD$_{50}$ dose of 6.6 mg/kg/day for 21 days. Myocardial changes (mitochondria swelling, vacuoles) also appeared starting on day 4. At extremely high doses (5–10 mg/kg), dogs were noted to have a rapid drop in blood pressure and slowing of heart rate.[86] Cardiotoxicity and bone marrow suppression have been the two primary established side effects following toxic doses of mitoxantrone.

Maximum Intravenous Dosages*
Cats
   5.5 mg/m^2
Dogs
   5.5 mg/m^2
   *Doses should be reduced in patients with severe hepatic disease.

Toxicities Associated with Mitoxantrone Overdoses
Gastrointestinal
   Immediate onset of nausea and vomiting would be expected in an overdose. Stomatitis, mucositis, and diarrhea may also occur.
Cardiovascular
   Cardiovascular side effects are more rare with mitoxantrone then doxorubicin, but it remains the dose-limiting side effect in humans. Transient arrhythmias, congestive heart failure, and cardiomyopathy may occur. A rapid drop in blood pressure and slowing of the heart rate may also occur. Following mitoxantrone overdose (100 mg/m^2) in a 9-year-old girl, echocardiograms demonstrated a reversible decrease of the shortening fraction of the left ventricle.[87] In three patients overdosed with mitoxantrone (2 × 100 mg/m^2) and another receiving 183 mg/m^2, acute cardiotoxicity was not evident.[88]

Hematologic

Severe bone marrow suppression should be expected after an overdose and has been witnessed in human case reports of overdoses and in animal toxicity studies. The primary toxicity has been a profound but reversible neutropenia and thrombocytopenia in all human overdose case reports.

Hepatic

Elevated liver enzymes have been reported in humans at standard doses and may be more frequent in overdoses. Frequent assessment should be made. Avoid using other hepatotoxic drugs (TMS).

Miscellaneous

Renal failure, urinary tract infections, blue-green urine/skin, and toxic leukemias have also been reported.[89] Hypersensitivity reactions have been reported but are rare and not concentration dependent.

Treatment of Mitoxantrone Overdoses

Gastrointestinal

Selective inhibitors of serotonergic receptors or metoclopramide may be effective. For nausea and vomiting refractory to these, a combination of both, with or without a corticosteroid, should be considered. Both acute and chronic treatment may be required. To prevent severe gastroenteritis, a proton pump inhibitor should be initiated.

Cardiovascular

Dexrazoxane (Zinecard) has recently been studied in the prevention of mitoxantrone-induced cardiotoxicity in humans and appears to be very effective.[90] It is an effective cardioprotectant for cumulative cardiotoxicity of mitoxantrone in patients with multiple sclerosis. Its efficacy in overdoses has not been proved. Suggested dosing for cardiotoxicity is a 10:1 ratio of intravenous dexrazoxane to anthracycline (or 300 mg/m^2 of dexrazoxane for a 30-mg/m^2 dose of anthracycline) just prior to chemotherapy. Supportive care using digoxin, diuretics, and after-load reducers may also be of benefit.

Hematologic

Neupogen (G-CSF) should be started prophylactically in the case of a severe overdose (approximately 24 hr after chemotherapy, until counts return to normal). Blood transfusions may also be required. Anti-infectives should also be started prophylactically.

Hepatic/Renal

These side effects have typically been seen with chronic dosing but should be assessed frequently. Concurrent administration of hepatotoxic or nephrotoxic drugs should be avoided. Hydration and alkalinization of urine may help to minimize renal toxicity.

Drug Removal

Hemodialysis has not been demonstrated to be effective in vitro[35] or in vivo.[90,91] Amberlite or charcoal hemoprofusion (2×4 hr) may be effective if initiated early (<18 hr) but has not been proven.

Management of Vinblastine (Velban) Overdoses

In general, side effects of vinblastine are dose related and reversible. Vinblastine toxicity may result from inadvertent overdoses or failure to adjust doses in patients with severe liver disease. In addition, animals deficient in P-glycoprotein pump capacity

(mutation of the MDR-1 gene) may also be much more sensitive to vinblastine. Overdoses occurring during prolonged, consecutive day infusions appear to be more toxic than acutely administered high single doses. Vinblastine and vincristine are agents that have commonly resulted in drug errors because of their similar names. Most serious errors have resulted when prescriptions for vinblastine are inadvertently filled with vincristine (a much more toxic drug that is dosed at a much lower dose). Mistakes have also occurred when multiple patients are receiving the same drug and doses are inadvertently switched. This occurred in at least one case at our institute that inadvertently received a vinblastine dose for a dog. The cat received a four-fold overdose (1.6 mg of vinblastine instead of 0.39 mg, the recommended dose). In this case, the 11-year-old cat with lymphoma received the overdose as part of its second chemotherapy cycle. Life-threatening toxicities occurred much earlier than expected and included bone marrow suppression, gastrointestinal toxicity, neuromuscular weakness, and severe electrolyte abnormalities. Symptoms similar to SIADH were also noted. The patient recovered completely from the overdose with intensive nutritional, pharmaceutical, and supportive care.

Maximum Intravenous Dosages*
Cats
    1.5 mg/m^2
Dogs
    2.0–2.5 mg/m^2
    *Dose reduction (50%) is needed in severe hepatic disease.
Toxicities Associated with Vinblastine Overdoses
Gastrointestinal
    Vinblastine has gastrointestinal side effects at standard doses but typically less so than vincristine. At higher doses much more severe toxicities have been reported. Anorexia, diarrhea, constipation, abdominal pain, ileus, stomatitis, hemorrhagic enterocolitis, rectal bleeding, and ulcerations may all occur. At a four-fold overdose in the cat described previously, diarrhea was noted on day 1 following the overdose. On days 2 to 10, diarrhea, anorexia, and vomiting were noted that were refractory to ondansetron.
Hematologic
    Hematologic effects even at standard doses of chemotherapy are dose limiting. Leukopenia (granulopenia) occurs most frequently, and with high doses may take longer to recover. Thrombocytopenia is less frequent but may also occur more frequently with overdoses. In the same overdose described previously, neutropenia was evident on day 2 and by day 4 the cat became febrile (103.7° F) and had profound (grade 4) neutropenia (neutrophils = 0.006×10^3/µl). Thrombocytopenia (platelets = 100×10^3/µl) (grade 2) and non-regenerative anemia (grade 3) were also seen.
Neurologic
    Neurotoxicity is not frequent at standard doses but is seen following overdoses. Acute onset numbness, peripheral neuropathy and neuritis, loss of deep tendon reflexes, weakness, seizures, and autonomic nervous system dysfunction (urinary retention, sinus tachycardia, dry mouth) are reported in humans. In a 12-year-old child overdosed with 25 mg/m^2, severe musculoskeletal pain and fever were followed by intestinal hypotonia, severe esophagitis, and peripheral neuropathy.[92] Following the four-fold overdose of

vinblastine in the cat previously mentioned, generalized weakness, depression, and inability to jump was noted on day 1. Eighth cranial nerve damage, nystagmus, vertigo, hearing impairment, and dizziness have also been reported in humans.

Cardiovascular

Hypertension, ECG abnormalities, and myocardial infarction have been reported in humans following high doses of vinblastine but were not apparent in the aforementioned cat.

Miscellaneous

Rarely, acute shortness of breath, bronchospasm, and dyspnea have occurred in human patients. Alopecia is common and dermatitis (vesiculation of the skin) may also occur. SIADH resulting from vinblastine has also been reported in humans and was noted in the aforementioned cat case.[93,94] Hyponatremia and hypokalemia were seen in the face of no apparent abnormal fluid balances.

Treatment of Vinblastine Overdoses

Gastrointestinal

Multiple agents were required to control the refractory nausea, vomiting, and diarrhea in the feline case mentioned previously. Metoclopramide, ranitidine, and sucralfate were ineffective at controlling side effects. Ondansetron (0.22 mg/kg IV q 8 hr) in combination with prochlorperazine (0.3 mg/kg SC q 8 hr) were only partially effective. Continuous rate infusion of metoclopramide (0.01 mg/kg/hr IV) and gut rest with parenteral nutrition were started on day 8 that appeared to help resolve the severe diarrhea and vomiting.

Hematologic

Neupogen (G-CSF) should be started prophylactically in the case of a severe overdose. In the case listed previously, Neupogen (5 µg/kg subcutaneously q 24 hr) was started directly after the overdose was identified and was continued until day 6, at which point the neutrophil count was $8.33 \times 10^3/\mu l$. Blood transfusions may also be required. Antibiotics should also be started prophylactically.

Cardiovascular

Cardiovascular effects were not noted in the case mentioned previously and may not be dose related.

Neurologic

Neurologic impairment is seen frequently in humans getting high doses of vinblastine and was noted in the four-fold feline overdose reported previously. In this case, neurologic side effects were all reversible and treatment was not necessary. Anticonvulsant therapy may be required in some cases.

Miscellaneous

If SIADH is present, treatment should involve fluid restriction (urine output plus insensible loss) and the use of furosemide for diuresis. Hypertonic crystalloids may be given to increase sodium solutes. Hyponatremia can lead to seizures or coma and should be monitored frequently. Slowly increase the sodium concentration at a rate of 0.5 to 1.0 mmol/L/hr, so that central pontine myelinolysis is not induced. Aggressive intravenous potassium supplementation was also required in the aforementioned cat.

Drug Removal

Hemodialysis has not been demonstrated to be effective in vitro.[35] Plasma exchange was reported to reduce morbidity in a 12-year-old child overdosed with vinblastine (25

mg/m^2).[92] The gastrointestinal sequestering of vinca alkaloids by cholestyramine may also be of benefit. Although only anecdotal information exists for the vinca alkaloids, cholestyramine more effectively sequesters intestinal secretion of many acidic drugs than charcoal and increases their rate of elimination, particularly when the primary route of elimination is via hepatobiliary excretion. In humans, it has been shown to significantly increase clearance of drugs following overdoses of drugs including methotrexate, meloxicam. warfarin, acetaminophen, and digoxin.[95] In dogs, it has been reported to bind acidic drugs (tenoxicam; pKa = 5.3) with a much greater binding capacity (1.63 g/g of adsorbent) than charcoal (0.18 g/g of adsorbent). Cholestyramine increases the total body clearance of acidic drugs and reduces the elimination half-life as well as the mean residence time of the drug in the body.[96] Doses of 2.5 g of cholestyramine powder have been given orally TID diluted in 6 ml of water × 72 hours to a canine patient following an overdose of vincristine at our institute and was well tolerated. Its efficacy in reducing blood levels following a presumed overdose is unknown but it may be an alternative when other options are not available.

Management of Vincristine (Oncovin) Overdoses

Vincristine overdoses are commonly reported in the human literature, primarily because of name similarity with vinblastine. Because of this particular error, we instituted a chemotherapeutic order sheet that specifically lists separate drugs that must be marked off by clinicians rather than hand written. Unfortunately, errors that have occurred in humans with vincristine have been fatal in many instances. Because vinca alkaloids bind rapidly to tissues, serum half-lives are short, but tissue concentrations may last much longer (72 hr) and continue to be toxic. Metabolism is primarily hepatic with excretion via the biliary system. Only small amounts of drug appear in dialysate, so that hemodialysis is of little benefit in the treatment of vincristine overdoses. With recent advances in plasmapheresis and plasma exchange technology in human medicine, overdoses caused by vincristine may now be more favorable. While these may not be available in veterinary medicine, hydration with forced diuresis may be of some benefit in reducing plasma vincristine concentrations.

Maximum Intravenous Dosages*
Cats
   0.025 mg/kg
Dogs
   0.7 mg/m^2
   *Drug doses should be significantly reduced (50%) in patients with significantly elevated bilirubin concentrations or other evidence of severe hepatic impairment.

Toxicities Associated with Vincristine Overdoses
Gastrointestinal
   Vincristine has significant gastrointestinal side effects at standard doses but is much more severe with overdoses. Adynamic ileus, upper-colon impact, constipation, abdominal pain, and stomatitis have all been reported in humans following overdoses.
Neurologic

The primary dose-limiting side effect of vincristine is neurotoxicity. Peripheral (mixed sensorimotor) is common. Loss of deep tendon reflexes, paresthesias, numbness, pain, and tingling occur even at low doses. High-dose therapy in humans has resulted in wrist drop, foot drop, cranial nerve palsy, atrophy, cramps, ataxia, and jaw pain. Eighth cranial nerve damage, nystagmus, vertigo, hearing impairment, and dizziness have also been reported in humans. Autonomic and CNS toxicity may also occur at high doses. Bladder atony, incontinence, urinary retention, dysuria, and polyuria may occur. Depression, agitation, insomnia, seizures, encephalopathy, respiratory difficulty, and coma have also been reported with high doses.

Hematologic

Bone marrow toxicity is less than that produced by many other products but still may occur with overdoses. Leukopenia, thrombocytopenia, and anemia may occur.

Cardiovascular

Hypotension and hypertension, ECG abnormalities, and myocardial infarction have been reported in humans following overdoses.

Miscellaneous

SIADH resulting from vincristine may also occur. Hyponatremia and hypokalemia have been reported in the face of no apparent abnormal fluid balances.

Treatment of Vincristine Overdoses

Gastrointestinal

Selective inhibitors of serotonergic receptors or metoclopramide may be effective. For nausea and vomiting refractory to these, a combination of both, with or without a corticosteroid, should be considered. Both acute and chronic treatment may be required. A metoclopramide CRI and a prokinetic agent (cisapride) may be necessary when severe gastroparesis is noted. Constipation in humans has been treated with high enemas and laxatives. Agents such as mirtazapine (Remeron) have been used in humans for severe gastroparesis refractory to conventional prokinetic treatment.[97]

Neurologic

In humans, multiple products have been tried to reduce neurotoxicity including folinic acid (Leucovorin) rescue (18 mg q 3 hr for 16 doses), pyridoxine (50 mg IV or PO q 8 hr), or glutamic acid (glutamine) given orally at 500 mg TID for 1 month was reported to decrease vincristine neurotoxicity with no additional side effects.[98]

Hematologic

Neupogen (G-CSF) should be started prophylactically in the case of a severe overdose. Blood transfusions may also be required. Anti-infectives should also be started prophylactically.

Cardiovascular

Cardiovascular effects may not be dose related but should be carefully monitored, particularly if prior radiation to the mediastinal area has been received.

Miscellaneous

If SIADH is present, treatment should involve fluid restriction and the use of furosemide for diuresis. Hypertonic crystalloids may be given to increase sodium solutes. Hyponatremia can lead to seizures or coma and should be monitored frequently. Slowly increase the sodium concentration at a rate of 0.5 to 1.0 mmol/L/hr, so that central pontine myelinolysis is not induced. Aggressive intravenous potassium supplementation may also be required.

Drug Removal

Hemodialysis has not been demonstrated to be effective in vitro.[35] Plasmapheresis (1.5 times the plasma volume) may be effective if performed within 6 hours of the overdose.[99] Drug levels may be reduced by as much as 50% by plasma exchange. Kosmidis et al[100] reported success in two thirds of patients treated with plasmapheresis in combination with folinic acid rescue. Anecdotally, enhanced fecal excretion of vinblastine by cholestyramine may also be of benefit. Cholestyramine more effectively sequesters intestinal secretion of many acidic drugs than charcoal and increases their rate of elimination. Doses of 2.5 g of cholestyramine powder have been given orally TID (diluted in 6 ml of water) for 72 hours to a canine patient and were well tolerated. Its efficacy in reducing blood levels following a presumed overdose is unknown but it may be an alternative when other options are not available.

Conclusion

In a review of the literature, overdoses from chemotherapeutic drugs in veterinary medicine are reported less frequently than in human medicine. This is most likely a reflection of the fewer number of animals treated with chemotherapeutics than a smaller error incidence. Unfortunately, human error plays the most significant role in the inadvertent chemotherapeutic "mishaps" reported in the literature from both human and companion animals. Illegible prescription writing (vincristine vs. vinblastine), use of easily misinterpreted abbreviations on prescriptions ("MTX," SID, etc.), absence of a leading zero (.1 mg vs. 0.1 mg), miscalculation of doses (based on lbs vs. kgs or M^2), mix-ups in patient numbers, lack of training for nursing staff on computerized infusion control devices, and lack of sufficient client consultation on outpatient directions for use all appear to account for the majority of errors made by clinicians. Inadvertent ingestion of medications caused by the lack of pet owners "animal proofing" their homes has also resulted in a significant number of overdoses of chemotherapeutic agents in animals (5-FU). Although these errors are not commonly reported in the veterinary literature, they have potentially resulted in substantial morbidity and mortality that has not been documented. Documentation and publication of case reports following chemotherapeutic overdoses are essential to further our knowledge base on the prevention and treatment of these errors.

In an effort to eliminate chemotherapeutic errors at our institute, a protocol was developed that has helped to prevent some of these errors from occurring. A typed prescription sheet for chemotherapeutics that forces the clinician to mark off a drug rather than write the name has been established. The form provides the final concentration of the reconstituted drug (mg or IU per ml) and maximum tolerated dose for each drug and species. The weight in "kgs" and "lbs" as well as M^2 is written by the veterinarian. The veterinarian checks the box corresponding to the drug being ordered, rather than hand-writing the drug. The clinician then calculates the dose in mgs or IUs and the final volume (mls) to be administered. This is then double-checked by pharmacy staff prior to filling and compared with the maximum tolerated dose via the route of administration. A final check is performed with the product, the patient number, calculations, and the dose drawn up. Chemotherapeutic errors have largely been eliminated since the institution of these measures. Further institution of checking the dose against the degree of renal,

hepatic, and biliary function as well as the degree of bone marrow suppression may also be helpful in reducing the overall incidence of side effects from standard doses of drug inadvertently administered to animals requiring dose adjustments.

Although specific antidotes are not available for many chemotherapeutic drugs following overdoses, we have found that intensive prophylactic measures to support hematologic, gastrointestinal, and other organ functions have been extremely beneficial in the management of overdose cases. To date, we have successfully managed between four- and ten-fold overdoses of chemotherapeutic drugs including vincristine, vinblastine, and doxorubicin without fatalities or irreversible consequences. Because the efficacy of many anecdotes and prophylactic measures are time dependent, protocols outlining plausible treatment of overdoses should be in place prior to administering chemotherapeutics.

The rapid removal of drug following oral ingestion via emesis or gastric lavage is recommended if the error is identified soon after oral ingestion. Once the drug is absorbed systemically, hemodialysis if available is the most efficient mechanism of drug removal, if the drug is dialyzable. Alternatively, activated charcoal and cholestyramine are useful if the drug undergoes enterohepatic circulation. Hydration and alkalinization of urine are also beneficial for some drugs that are eliminated primarily renally. Increased renal clearance of the parent drug or its active metabolites may reduce the overall toxicity of some drugs.

The identification of and close monitoring of anticipated side effects may help to circumvent some of the morbidity and mortality if supportive care is instituted prophylactically. Prophylaxis for neutropenia with G-CSF and antibiotics, as well as gastroprotective agents (proton pump inhibitors, H_2 blockers, etc.) for gastroenteritis are typically suggested for most chemotherapeutic overdoses since these appear to be the dose-limiting toxicities for many chemotherapeutic drugs used in companion animals. As new technology and antidotes become increasingly available and less costly, chemotherapeutic overdoses will eventually become less of a significant threat. Alternatively, current emphasis should be placed on prevention rather than management of chemotherapeutic overdose toxicities.

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Table 1

The Use of Adjuvant Drugs in the Supportive Care of Chemotherapy Overdoses

Indication	Category	Drug Name	Dose
Nausea/Vomiting	Serotonergic (5-HT-3) receptor inhibitor	Ondansetron (Zofran)	**Canine** = 0.11–0.22 mg/kg IV slow push **Feline** = 0.01–0.15 mg/kg q 6–12 hr
		Dolasetron (Anzemet)	**Canine** = 0.6 mg/kg IV q day **Feline** = 0.6 mg/kg IV q day
	Substituted benzamides (dopaminergic inhibitor)	Metoclopramide (Reglan)	**Canine** = 0.2–0.4 mg/kg q 6 hr PO, SC, IM, or 1–2 mg/kg/day as a continuous IV infusion **Feline** = 0.2–0.5 mg/kg q 3–4 times daily PO, SC, or as continuous IV infusion 0.01–0.02 mg/kg/hr
	Neurokinin-1 receptor antagonist	Maropitant citrate (Cerenia)	**Canine** = 1–2 mg/kg/day SC × 5 days Max, or 2 mg/kg/day PO × 5 days Max (must have 2 days washout prior to continuing Rx) **Feline** = Suggested to be half the canine dose
	Phenothiazine	Chlorpromazine (Thorazine)	**Canine** = 0.05–4.4 mg/Kg IV q 6–8 hr 3.3 mg/kg PO q 6–8 hr 0.25–0.5 mg/kg SC, IM q 6–8 hr

Gastritis/Ulcer	Proton pump inhibitor	Esomeprazole (Nexium)	**Canine** = 0.7 mg/kg IV
		Omeprazole (Prilosec)	**Canine**=0.7–2 mg/kg PO q 12–24 hr **Feline** = 0.7–1.5 mg/kg PO q 12–24 hr
	Histamine-2 blocker	Famotidine (Pepcid)	**Canine** = 0.5 mg/kg IV or PO BID **Feline** = 0.5 mg/kg PO, SC, IM q 12–24 hr
	Coating agent	Sucralfate (Carafate)	**Canine** = 0.5–1.0 g PO q 2–4 times daily **Feline** = 0.25–0.5 g PO q 8–12 hr
Neutropenia	Granulocyte-stimulating factor	G-CSF (Neupogen)	**Canine** = 5 µg/kg SC once daily **Feline** = 5 µg/kg SC once daily, until neutrophil count exceeds 3000/µl × 2 days
	Antibiotic prophylaxis	Want antibiotics that cover enteric organisms (fluoroquinolones, Clavamox, aminoglycosides, metronidazole, etc.). Avoid hepatotoxic drugs (i.e., TMS, macrolides, chloramphenicol).	**Canine =** For persistent fever or WBC <2000 cells/µl or <1000 neutrophils/µl without fever **Feline =** For persistent fever or WBC <2000 cells/µl or <1000 neutrophils/µl without fever
Nutritional support	Appetite stimulants	Cyproheptadine (Periactin)	**Feline =** 2 mg/cat 1/4 - 1/2 tab) po TID
		Megasterol acetate (Megace)	**Canine =** 10 mg/kg PO q day × 1 week
Anemia	Biosynthetic	Epoetins	**Canine** = 100

	erythropoietin	(Epogen)	U/kg SC 3 times weekly until hematocrit range of 37%–45% is attained **Feline** = 75–100 U/kg SC 3 times weekly until hematocrit is 30%–40%
Antidotes	Cisplatin cytoprotective	Amifostine (Ethyol)	**Canine** = Amifostine dose in humans is 740–910 mg/m^2 (up to 3 doses in 24 hr). Give IV over 15 min; monitor for hypotension. Bolus fluid if needed.
	Adsorbents (anion exchange)	Cholestyramine (Questran)	**Canine** = 2–6 g of resin (4 g resin/9 g powder in Questran) diluted in liquid and given PO TID. Monitor for constipation, hyperchloremic acidosis. **Feline** = 1 g/3 kg cat or 0.34 g/kg/day diluted in 4 ml of distilled water
		Activated charcoal	**Canine** = 1–4 g/kg PO as a slurry as needed (use 1 g/5 ml water)
	Uroprotectants	Sodium 2-mercapto-ethanesulphonate (MESNA)	**Canine =** Must be given with ifosphamide; administer 20% of ifosphamide dose via IV bolus followed with saline diuresis. May give

			additional doses at 2 and 5 hr during diuresis
	Hepatoprotectives	Milk thistle (Silymarin) Marin Brand	**Canine** = Doses vary from 50–200 mg PO q 12–24 hr. Marin Brand (Nutrimax) for dogs; Silybin, vitamin E, zinc **Feline** = Use Marin Brand (Nutrimax) for cats; Silybin, vitamin E, w/o zinc
		S-adenosyl-L-methionine (SAMe) (Denosyl SD4; Nutrimax)	**Canine** = Dogs up to 5.5 kg = 90 mg PO q day 6.0–15.5 kg =225 mg; 16.0–29.5 kg = 425 mg; 30–54.5 kg = 2 × 425 mg; over 54.5 kg =3 × 425 mg
		SAMe plus Silybin A+B (Denamarin-Nutrimax)	**Canine** = Small dogs: 90 mg SAMe + 9 mg silybin PO q day Medium dogs: 225 mg SAMe + 24 mg silybin Large dogs: 425 mg SAMe + 35 mg silybin **Feline** = 90 mg SAMe + 9 mg silybin PO q day
		Ursodiol (Actigall)	**Canine** = 5.0–15.0 mg/kg PO q day or BID **Feline** = 5.0–15.0 mg/kg PO q day or BID or 1/6 capsule (300 mg) sprinkled on food

	Cardioprotective	Dexrazoxane (Zinecard)	**Canine** = Give 10 × the anthracycline dose; administered as a slow IV bolus