CHAPTER 18

Toxicologic Considerations in the Pediatric Patient

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A relatively unexplored area in veterinary medicine is that of age-related responses to toxic xenobiotics. The majority of differences between adult and pediatric patients exposed to toxicants are developmental. These differences can markedly affect the four components of drug disposition: absorption, distribution, metabolism, and excretion. The information contained in this chapter is designed to illustrate these differences and how they may affect the toxin-exposed pediatric patient.

Physiologic Considerations in the Pediatric Patient

Pups and kittens may be exposed to xenobiotics through several routes—ingestion (including the ingestion of mother's milk), topical exposure, inhalation, and ocular contact. In dogs and cats the term *pediatric* generally refers to the first 12 weeks of life.[1] Further division into neonatal (0 to 2 weeks), infant (2 to 3 weeks), and pediatric (6 to 12 weeks) stages is justified because of the significant developmental changes that occur during this 12-week period. Physiological alterations associated with these maturation stages can predispose the pediatric patient to be more susceptible to adverse reactions.

Differences between adult and pediatric physiology can significantly impact a victim's response to xenobiotic exposure, both toxic and therapeutic. Pediatric patients have differences in regional organ blood flow that may alter toxin disposition. Proportionally greater blood flow to the heart and brain in pediatric patients increases the risk of adverse effects resulting from exposures to lower concentrations of cardiac and central nervous toxins.[1]

Pediatric patients have no significant blood-brain barrier until 3 months of age. This protects the brain from deficiencies in nutritional fuels in stressful states because oxidizable substrates such as lactate can pass from the blood into the central nervous system.[2] However; this mechanism also increases the potential for central nervous system exposure to toxins, particularly because pediatric patients have an increased central nervous system (CNS) blood flow relative to adults. Most xenobiotics will have equivalent plasma and CNS concentrations. Brain cells normally protected in adults are at higher risk of exposure to toxins in the neonate.

Pediatric patients have decreased blood pressure; arterial pressure approaches adult levels by 6 weeks to a few months of age dependent on the breed maturation rate. Also decreased are the stroke volume and vascular resistance. The heart rate, cardiac output, and plasma volume are increased in these patients. Central venous pressure approaches adult levels by 7 months. The autonomic nervous system is incomplete in the heart and blood vessels. This limits the ability to increase cardiac output by altering contractility or affecting preload, making the neonate less responsive to either xenobiotics or therapeutics that target the autonomic nervous system. Preservation of cardiac output is dependent on increased heart rate and preserving low vascular resistance.

Pediatric patients also have minimal glycogen stores and limited capacity for gluconeogenesis or glycogenolysis. Additionally, nephrogenesis is not complete until 3 weeks. Cortical blood flow alterations and maturation of nephrons cause various regions of the kidney to be very vulnerable to drug toxicities. Protein, glucose, and amino acid levels are normally higher in pediatric urine than in the adult.

Packed red cell volume is approximately 47% at birth and drops to a nadir of approximately 24% at 6 weeks of age. Hematopoiesis does not begin until about 6 to 12 weeks of age. Prothrombin time, partial thromboplastin time, and antithrombin levels are increased compared with adults until approximately 1 week of age. Hemoglobin concentrations are less than those for adults.

Following is a review of aspects of drug disposition—absorption, distribution, metabolism, and excretion—affected by these dramatic developmental changes as the neonate matures[3,4] (Box 18-1).

Absorption

Following oral exposure, toxin absorption occurs primarily in the small intestine. The pediatric patient has a decreased gastric emptying time and irregular peristalsis because motility is more controlled by distention than electrical activity until 40 days of age, causing a slower rate of absorption resulting in lower peak plasma toxin levels.[5,6] This decreased rate of absorption may actually protect against toxic drug concentrations. However, in neonates before colostrum is absorbed these protective mechanisms may not be present. Before colostrum absorption the permeability of the intestinal mucosa is increased, which also increases the rate of toxin uptake including the uptake of compounds that normally would not reach the systemic circulation. Intestinal permeability rapidly decreases after colostrum ingestion.[6,7] This closure may well be induced by endogenous release of hydrocortisone or adrenocorticotropic hormone. Exogenous supplementation of these hormones to the mother within 24 hours prepartum prevents the increase in permeability and uptake of colostrum.

Several other factors may affect small intestinal drug absorption in pediatric patients. Newborns have a neutral gastric pH, and the rate of progression to adult levels depends

Box 18-1 Altered Xenobiotic Disposition in Pediatric Patients

Alteration	Impact
Increased intestinal permeability	Increased oral uptake; toxic plasma concentrations
Increased gastric pH	Increased oral uptake of weak bases and acid-labile compounds; prolonged and elevated plasma levels; toxic plasma concentrations
Altered peristalsis (decreased gastric emptying time)	Decreased absorption; lower plasma levels of toxin
Decreased plasma proteins	Toxin may accumulate, leading to more unbound compound and thus a potentially longer half-life
Decreased body fat	Increased plasma levels; decreased accumulation of lipid-soluble toxins
Increased total body water (more extracellular fluid)	Decreased plasma concentrations; longer half-life
Increased uptake of volatile gases	High plasma concentrations; increased response and toxicity
Increased dermal absorption	Higher or prolonged plasma exposure levels; toxicity increased
Immature P-glycoprotein system	Poor ability to clear toxins

on the species involved.[5,7] Achlorhydria (increased gastric pH) may cause decreased absorption of many compounds that require disintegration and dissolution or that need to be ionized in a more acidic environment (e.g., weak acids). Milk diets can interfere with absorption of toxic compounds by reducing gastric motility or interacting directly with the toxins. The "unstirred water layer" adjacent to the surface area of the mucosal cells is thicker in the neonate compared with the older pediatric patient, and this may limit the rate of absorption of some compounds.

Newborns have decreased bile flow and lower bile acid concentrations until 8 weeks of age. Absorption of fat-soluble compounds increases as biliary function develops. Both extrahepatic metabolism and enterohepatic circulation may be altered as microbial colonization of the gastrointestinal tract occurs.[8,9] Absorption from the rectal mucosa is rapid in neonates.

Absorption of xenobiotics administered parenterally to pediatric animals varies from that in adults. As muscle mass develops, with its accompanying increase in blood flow and maturation of the vasomotor response, the rate of absorption following intramuscular administration of xenobiotics is altered.[8] Subcutaneous administration of potentially toxic drugs may exhibit variable absorption rates relative to the patient's age. Smaller amounts of body fat but greater water volume may result in quicker absorption of xenobiotics compared to that in adults.[10]

Ambient temperature directly affects physiologic responses in the neonate. As an example a normal neonatal body temperature is 96° F with a normal heart rate of 200 to 250 bpm. A drop of body temperature to 70° F results in a heart rate of 40 bpm. Body temperature of less than 94° F induces gastrointestinal ileus and decreased lymphocyte function. It is suspected that environmental temperature influences subcutaneous absorption. This is especially true in neonates whose thermoregulatory mechanisms are poorly functional. If the neonate is in a cold environment, subcutaneous xenobiotic absorption tends to be reduced.

Percutaneous absorption of xenobiotics may be greater in pediatric patients. Percutaneous absorption is directly related to skin hydration, which is highest in neonates. Topical exposure to potentially toxic lipid-soluble compounds (e.g., hexachlorophene and organophosphates) places the pediatric patient at higher risk of significant absorption.

Volatile gases are absorbed rapidly from the pediatric respiratory tract owing to greater minute ventilation. Pediatric patients have two- to threefold higher oxygen tissue demand relative to their body weight compared to adults. This results in a higher respiratory rate. Tidal volumes are similar to those in adults; however, pediatric patients have a lower functional residual capacity. The respiratory system approaches that of the adult by 3 weeks of age. If normal environmental temperatures are present, panting is almost always an indicator of respiratory distress.

Distribution

The two major differences between adult and pediatric patients relative to xenobiotic distribution are those of body fluid compartments and toxin or drug binding to serum proteins. Body fluid compartments undergo tremendous alterations as the neonate grows. As the neonate matures, significant changes occur in both the percentage of total body water and the ratio of compartmental volumes. Although both the percentage of total body water and the volume of the extracellular versus the intracellular compartment decrease as the animal ages, the change in the ratio of extracellular to intracellular volume is significantly greater.[11] Daily fluid requirements are greater in neonatal and pediatric patients because a larger proportion of their body weight is represented by body water. The net effect on xenobiotic distribution depends on these differences in body compartments. Most water-soluble compounds are distributed into extracellular fluids. Plasma concentrations of these compounds are lower in pediatric patients compared with adults, because the volume into which the compound is distributed is greater in the young. Unbound lipid-soluble compounds have the same type of distribution because they are distributed into total body water. Changes in xenobiotic distribution directly alter the half-life of that xenobiotic. Increases in distribution

directly decrease the plasma concentration, a fact that may potentially protect the pediatric patient from toxic xenobiotic concentrations.[12]

Distribution of lipid-soluble compounds that accumulate in the fat (e.g., some organophosphates and chlorinated hydrocarbons) may be decreased owing to a smaller proportion of body fat in the pediatric patient. Xenobiotic plasma concentrations may be higher, but the half-life is shorter. The movement of many fat-soluble compounds may be facilitated by their high tendency to bind to plasma proteins. This binding decreases their ability to be distributed to target tissues.

Predicting the distribution of highly protein-bound compounds is complicated in the pediatric patient. Most compounds are bound to serum albumin, and basic toxins have a high affinity for alpha-1-glycoproteins. Both of these proteins are available in lower concentrations in pediatric patients.[13] Albumin levels reach adult values at approximately 8 weeks of age and exposure before this age can be an issue, with protein-bound drugs resulting in an increase in active compound or increased t½. Additionally, differences in albumin structure and competition with endogenous substrates (e.g., bilirubin) for binding sites may decrease protein binding.[6,14] If bound toxins are displaced, the risk of toxicity increases as the concentration of free pharmacologically active compound rises. When a compound has a narrow therapeutic index and is highly protein bound, these age-related changes are significant. Xenobiotic half-life may rise owing to increased amounts of compound that are unbound, allowing free distribution to the tissues and decreasing the plasma concentration.[14] Despite the increased volume of distribution, the half-life of a compound may be "normalized" by the increased clearance of free toxin.

Metabolism

Pediatric metabolism is significantly different from that of the adult. Hepatic and renal excretion is limited in neonatal and pediatric animals, thus decreasing toxin elimination. Intoxication by xenobiotics in young animals may be induced by decreased clearance.[3,6]

Pediatric patients have decreased protein synthesis and immature hepatic enzyme systems until 5 months of age, including microsomal cytochrome P450, which directly results in incomplete hepatic metabolism affecting reduction, hydroxylation, and demethylation of xenobiotics. Both phase I (e.g., oxidative) and phase II (e.g., glucuronidation) reactions are reduced.[15-17] Maturation of various metabolic pathways occurs at different rates. Neonatal puppies may not manifest phase I activity until the ninth day of life; this activity steadily increases after day 25 until it reaches adult levels at day 135.[16] Because hepatic xenobiotic metabolism is decreased, plasma clearance of toxins is decreased, plasma half-life is increased, and toxic plasma compound concentrations may result.

The oral bioavailability of compounds with a significant first-pass metabolism is probably greater in pediatric patients. Xenobiotics whose toxicity is generated from toxic metabolites may be less hazardous because there is decreased formation of active components. For example, children less than 9 to 12 years of age have a lower incidence of hepatotoxicity following overdose of acetaminophen than adults.[18] Pediatric hepatic metabolizing enzymes (e.g., cytochrome P450) do appear to be inducible by phenobarbital and other drugs.

Excretion

Alterations in toxin excretion are manifest in several ways. Significant differences in renal blood flow can result in alterations in toxin excretion.[19,20] Pups have reduced renal excretion, which decreases the clearance of renally excreted parent compounds and the products of hepatic phase II metabolism. As pups age glomerular filtration and renal tubular function steadily increase.[20,21] The total number of glomeruli remains constant. Adult levels of glomerular filtration and tubular function are attained by 2½ months of age. If normal levels of body fluids and electrolytes are maintained, pediatric renal tubular resorption is equivalent to that in adults.[22,23] In this pediatric renal environment water-soluble toxins

have decreased clearance and extended half-lives. Decreased urine blood flow results in decreased glomerular filtration rate (GFR). Water soluble compounds have decreased clearance and increased elimination half-lives (t½). GFR and tubular function is at adult function levels by 3 months of age. Normal pediatric urine specific gravity generally is in the 1.006 to 1.017 range for the first 8 weeks of life.

An example of this phenomenon is the recommendation that pediatric patients require higher doses (because of the increased volume of distribution) and longer dosing intervals (because of increased distribution and decreased clearance) of gentamicin. One can anticipate alterations in excretion in sick or dehydrated pediatric patients.

Maternal Transfer of Toxin

Almost all xenobiotics cross the placenta and reach pharmacologic concentrations in the fetus after exposure of the mother. (See Chapter 17, "Considerations in Pregnant or Lactating Patients.") Drugs administered to the mother may cross the placenta by passive diffusion, facilitated transport, and active transport. Protein-bound xenobiotics do not cross the placenta. Factors affecting the pharmacokinetics and xenobiotic effects on mother and fetus are (1) altered maternal absorption, (2) increased maternal unbound xenobiotic fraction, (3) increased maternal plasma volume, (4) altered hepatic clearance, (5) increased maternal renal blood flow and glomerular filtration rate, (6) placental transfer, (7) placental metabolism, (8) placental blood flow, (9) maternal-fetal blood pH, (10) preferential fetal circulation to the heart and brain, (11) undeveloped fetal blood-brain barrier, (12) immature fetal liver enzyme activity, and (13) increased fetal unbound xenobiotic fraction.

Passive diffusion is the most common route in which xenobiotics enter milk. Xenobiotics pass through the mammary epithelium by passive diffusion down a concentration gradient on each side of the membrane. The higher the dose received by the mother, the more xenobiotic will pass into the milk. Generally, milk proteins do not bind xenobiotics well. Because milk (pH 7.2) is slightly more acidic than plasma (pH 7.4), compounds that are weak bases are more likely to pass into milk than weak acids. The more lipid soluble the xenobiotic, the greater the quantity and the faster the transfer into milk.

Most Common Inquiries to Poison Centers for Pediatric Patients

Common exposures in pediatric canine and feline patients are listed in Box 18-2.

Rodenticides

Rodenticides (e.g., bromethalin, anticoagulants) are commonly available and dogs are intoxicated more frequently than any other domestic animals. The veterinarian should read the product label to identify the exact compound involved. The majority of anticoagulant rodenticides inhibits the recycling of vitamin K_1, blocking the victim's ability to clot. More than half of the victims exhibit anorexia, weakness, coughing, epistaxis, and dyspnea. Laboratory tests show prolonged clotting times and possibly thrombocytopenia. Administration of vitamin K_1 is therapeutic but may take several hours to have a therapeutic effect.

Nonsteroidal Antiinflammatory Drugs

Nonsteroidal antiinflammatory drugs (NSAIDs) (human and animal products) are a common cause of toxicity in puppies and kittens. These animals have extensive enterohepatic recirculation of NSAIDs, increasing their toxicity. NSAIDs are a particular problem for cats because they are deficient in glutathione hepatic pathways, thereby prolonging the half-life of these compounds. The most common clinical manifestations are gastrointestinal. Clinical signs include vomiting, depression, diarrhea, anorexia, ataxia, bloody stool, polyuria, polydipsia, and tachypnea. There is no specific antidote and treatment is largely supportive.

Box 18-2 The Most Common Groups of Toxicants (Both Serious and Not So Serious) for Animals under 1 Year of Age

Dogs
Rodenticides (bromethalin, anticoagulants, and unknown) were the top category
NSAIDs (human and animal products)
Antidepressants
Herbicides
Mushrooms
Silica gel
Cleaning products
Chocolate
Amphetamines (prescription and illicit)
Birth control pills

Cats
Flea products (sprays, spot-ons, collars, dips) far and away the #1 category
NSAIDs
Silica gel
Insoluble calcium oxalate plants
Liquid potpourri

Courtesy Tina Wismer, ASPCA Animal Poison Control Center.

Antidepressants

Antidepressant exposures generally involve the tricyclic antidepressants or serotonin reuptake inhibitors or monoamine oxidase inhibitors. Once ingested, clinical signs usually develop within 60 minutes initially but their anticholinergic activity can inhibit gastrointestinal motility, slowing further uptake. These drugs are highly protein bound. Several compounds have toxic metabolites. Life-threatening clinical signs are related to the compounds' effects on the central nervous system and cardiovascular aberrations. Clinical signs include ataxia, lethargy, hypotension, disorientation, vomiting, dyspnea, mydriasis, hyperactivity, urine retention, ileus, seizures, and cardiac arrhythmias.

Herbicides

Herbicide exposure from pesticide-treated plants is unlikely to result in intoxication in puppies and kittens. Exposure to concentrates can induce clinical signs and treatment is supportive. Acute exposures rarely induce altered biochemical profile data, unlike long-term feeding trials. Vomiting is a common nonspecific clinical sign.

Mushrooms

Mushroom ingestion can occur year round. Common clinical signs are those of gastrointestinal distress including abdominal pain, vomiting, and diarrhea. A wide variety of toxins are available in mushroom ingestion. These compounds can affect the gastrointestinal tract, nervous system (excitation, hallucinogenic, and muscarinic), kidneys, red blood cells, and liver. A confirmed diagnosis is difficult to obtain, and clinicians should become familiar with the mushroom species available in their geographic region.

Silica Gel

Silica gel is used as a desiccant and often come in paper packets or plastic cylinders. They are used to absorb moisture in a variety of packaging. Silica is considered "chemically and biologically inert" upon ingestion. Clinical signs, though rare, would consist of gastrointestinal upset manifested as nausea, vomiting, and inappetence.

Home Cleaning Products

The list of home cleaning products is extensive, highlighting the need for the owner to bring in the toxin container if possible.

Methylxanthines

The active (toxic) agents in chocolate are methylxanthines, specifically theobromine and caffeine. Methylxanthines stimulate the CNS, act on the kidney to stimulate diuresis, and increase the contractility of cardiac and skeletal muscle. The relative amounts of theobromine and caffeine will vary with the form of the chocolate (see Chapter 60).

The lethal dose of 50% theobromine and caffeine are 100 to 300 mg/kg, but severe and life-threatening clinical signs may be seen at levels far below these doses. Based on Animal Poison Control Center experience, mild signs have been seen with theobromine levels of 20 mg/kg, severe signs have been seen at 40 to 50 mg/kg, and seizures have occurred at 60 mg/kg. Accordingly, less than 2 ounces of milk chocolate per kg is potentially lethal to dogs. Clinical signs occur within 6 to 12 hours of ingestion. Initial signs include polydypsia, bloating, vomiting, diarrhea, and restlessness. Signs progress to hyperactivity, polyuria, ataxia, tremors, seizures, tachycardia, PVCs, tachypnea, cyanosis, hypertension, hyperthermia, and coma. Death is generally caused by cardiac arrhythmias or respiratory failure. Hypokalemia may occur later in the course of the toxicosis. Because of the high fat content of many chocolate products, pancreatitis is a potential sequela.

Amphetamines

Amphetamines (prescription and illicit) have a minimum oral lethal dose of 20 to 27 mg/kg for amphetamine sulfate and 9 to 11 mg/kg of methamphetamine hydrochloride in dogs. Victims generally manifest hyperactivity, restlessness, mydriasis, hypersalivation, vocalization, tachypnea, tremors, hyperthermia, ataxia, seizures, and tachycardia.

Birth Control Pills

Birth control pills generally come with each packet containing 21 tablets of estrogen and/or progesterone and possibly 7 placebo pills. Estrogen could cause bone marrow suppression at levels greater than 1 mg/kg in adult dogs. Some oral contraceptives also contain iron. Decontamination is not necessary unless the level of estrogen is greater than 1 mg/kg or the level of iron is greater than 20 mg/kg.

Flea Products

Flea products (sprays, spot-ons, collars, dips) are still a major problem for inducing toxicity although much less now that organophosphates are no longer the mainstay of treatment for flea control. These compounds reversibly alter the activity of sodium ion channels in nervous tissue. Clinical signs result from allergic, idiosyncratic, and neurotoxic reactions. The majority of toxicities are from pyrethrin and pyrethroid flea products applied to cats. Cats are much more sensitive than dogs and the dog products have several times higher concentration of the active ingredient (cat products often 2%, dog products often 45%–65%). The most common problem is misapplication of dog products onto the cat or splitting a large dog product onto several cats.

Calcium Oxalate Plants

Insoluble calcium oxalate plants are generally overrated as a toxic exposure. The calcium oxalate contained in the plant is an irritant to the mucous membranes, which generally inhibits ingestions of large volumes.

Liquid Potpourri

Liquid potpourri may contain essential oils and cationic detergents; because product labels may not list ingredients, it is wise to assume that a given liquid potpourri contains both ingredients. Essential oils can cause mucous membrane and gastrointestinal irritation,

central nervous system depression, and dermal hypersensitivity and irritation. Severe clinical signs can be seen with potpourri products that contain cationic detergents. Dermal exposure to cationic detergents can result in erythema, edema, intense pain, and ulceration. Ingestion of cationic detergents may lead to tissue necrosis and inflammation of the mouth, esophagus, and stomach. Treatment is symptomatic and supportive.

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