Drug Use in Neonates and Geriatric Patients

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Neonatal and pediatric patients

The neonatal period is from birth to 2-4 weeks of age for puppies and kittens, and the pediatric period extends from 4 to 12 weeks of age. Because of major changes in physiology during these periods, drug disposition and response are likely to be varied. However, compared to humans, relatively little information is available on drug response in neonatal and pediatric dogs, and virtually nothing is known about neonatal cats.

Gastrointestinal absorption

Neonatal dogs have markedly increased intestinal permeability in the first 24 hours post partum, which allows the absorption of immunoglobulins from colostrum. Oral drugs may have unexpectedly high bioavailability in this time frame. Intravenous or intraosseous administration may give more predictable absorption from standard dosages for most drugs. Oral neomycin can reach high systemic plasma levels in premature infants, and should be avoided in newborn puppies and kittens.

Young pups have relatively high gastric pH (> 3.0 though 5 weeks of age) due to low numbers of acid-producing parietal cells. Because of this, empirical use of pump blockers and H_2 blockers is not indicated in this population. High gastric pH may also decrease the bioavailability of drugs that require an acid environment for absorption, such as ketoconazole, itraconazole, and iron supplements. Fluconazole may be better absorbed in these patients, since its absorption is unaffected by gastric pH.

Nursing puppies and kittens may absorb some oral drugs poorly due to drug binding by milk components, particularly calcium. This is likely the case for enrofloxacin, for which oral bioavailability in nursing kittens is low. The same may be true for doxycycline, which is also bound by dietary calcium. These drugs should be given parenterally in nursing pups and kittens.

Puppies < 6 weeks old also have relatively immature gastrointestinal innervation and motility; therefore, it is unclear whether prokinetics such as metoclopramide or cisapride would be effective in this age group. Ileus and reflux accompanied by hypothermia may respond well to supplemental warming.

Factors affecting drug disposition

Low body fat, relative hypoalbuminemia, low muscle mass, and high total body water can each lead to altered drug disposition in young patients, and make dosing decisions difficult. Low body fat may lead to higher plasma and CNS concentrations of lipid-soluble drugs such as most anesthetics. Low plasma albumin (which approaches adult levels by 16 weeks) could lead to increased free fraction of highly protein bound drugs such as benzodiazepines, possibly leading to increased sedative effects following single doses.

High total body water may lead to greater distribution and lower plasma concentrations of water-soluble drugs such as aminoglycosides, although this may be offset by decreased renal elimination of these antimicrobials. Low muscle mass makes intramuscular (IM) administration of drugs to neonates difficult. In addition, in hypothermic or hypovolemic patients, blood flow to skin and muscles will be low, leading to poor subcutaneous (SC) and IM drug absorption. Intravenous access in these patients is therefore very important.

Hepatobiliary function

Biliary function is not fully developed at birth, leading to a mild physiologic cholestasis; however, bile flow reaches normal adult levels by 4 to 6 weeks of age in puppies. Cytochrome P450 content is low in newborn puppies but also approaches adult levels by 4 to 6 weeks of age. This physiologic delay is associated with impaired hepatic clearance of some drugs in very young animals. For example, lidocaine has delayed elimination in puppies < 2 weeks old. Theophylline has a 3–fold longer elimination half-life in 1 week old puppies , but is also distributed to greater volume (probably due to higher total body water). The suggested dosing regimen of theophylline in newborn puppies is a slightly higher dose given half as often as in adult dogs.

Glucuronidation is also incompletely developed in newborn dogs, and like cytochrome P450 activities, reaches adult levels by 4 to 6 weeks of age. Drugs that rely on glucuronidation for elimination, such as carprofen, aspirin, and acetaminophen, are likely to have markedly delayed clearance in these neonates.

After weaning, most cytochrome P450 activities in puppies rise to levels higher than those of adults. This is likely an evolutionary response to exposure to a wider variety of dietary chemicals at weaning. This may lead to *increased* hepatic clearance of some drugs in patients of vaccination age, as has been shown for theophylline in 8 week old puppies, and aspirin in 12 to 16 week old puppies. During this period of high cytochrome P450 activity, it is possible that more frequent dosing of some drugs may increase efficacy. However, this has not been evaluated enough to make recommendations. The use of drugs with a wide therapeutic window can counteract this variability.

Renal function

Neonatal puppies have immature renal tubular function prior to 8 weeks of age, with relatively low numbers of capsular nephrons, inefficient tubular secretion of drugs, and low glomerular filtration rates (GFR). Renally cleared drugs with narrow margins of safety, such as NSAIDs, should be avoided in these young patients. For example, the elimination half-life of digoxin is 4 times longer in 10 day-old puppies than in adult dogs.

Puppies less than 3 weeks old cannot excrete potassium efficiently because of low numbers of functional nephrons; therefore, serum potassium should be monitored carefully in young puppies on IV potassium supplementation. Neonates also show immature proximal tubular reabsorption of glucose and amino acids. Glucosuria and proteinuria can be seen in normal young puppies, and will resolve with maturation; these findings do not require additional diagnostics or treatment.

Response to anesthetics

Neonates are particularly susceptible to adverse effects from anesthetics for many reasons, including immature drug elimination pathways, low body fat for drug redistribution, and low resting arterial blood pressures. For puppies being delivered by Caesarian section, anesthesia of the mother with propofol and isoflurane has been associated with greater puppy vigor and survival, compared to the use of ketamine, xylazine, thiamylal, or methoxyflurane. Epidural anesthesia, if available, is ideal. For analgesia in injured puppies, fentanyl infusions may be preferable to morphine, since the respiratory depressant effects of morphine are marked at birth and vary dramatically over the first month of life. In contrast, fentanyl has a more consistent effect in puppies from 2 to 35 days old.

Neonates are predisposed to hypotension under anesthesia due to poor cardiac compliance, immature baroreceptors, and incomplete sympathetic innervation to the heart. Neonates are also prone to hypothermia, due to low body fat, high body surface area, ineffective vasoconstriction, and lack of shivering (which develops after the first week). Hypothermia further leads to delayed elimination of anesthetics, hypotension, and ileus. Hypothermia also places a large energy demand on the neonate to maintain body temperature. Heating pads are not as effective as warmed air or radiant heat. Heated incubators or Bair huggers (forced air warming units), prewarmed IV fluids, and heat lamps (e.g. during radiography) are helpful in these patients.

In very young puppies (< 4 days of age) hypoxia leads to bradycardia instead of a compensatory tachycardia. In addition, puppies up to 2 weeks of age do not respond to atropine with an increase in heart rate. For young puppies with bradycardia, treatment with oxygen and warming, rather than atropine, is recommended.

While doxapram has traditionally been used as a respiratory stimulant in newborn puppies and kittens, this drug works poorly in the presence of hypoxia. Physical stimulation, airway suctioning, oxygen by mask, and warming are recommended for apnea.

Susceptibility to drug toxicities

It is well known that fluoroquinolones can lead to cartilage toxicity in growing puppies. This adverse effect is dose-dependent, and weight-bearing joints in large breed pups are particularly susceptible. In growing kittens, cartilage lesions are not seen when fluoroquinolones are used at label doses. Tetracycline causes a yellow discoloration of enamel in erupting teeth in humans, dogs, and cats. This is much less common with doxycycline, with only rare reports of tooth discoloration in doxycycline-treated children.

Aminoglycosides are nephrotoxic in neonatal dogs and cats, as in adults. However, classic signs of nephrotoxicity, such as granular casts and a rise in serum creatinine, are not observed in neonatal pups given gentamicin, despite the development of renal lesions and impairment of GFR. Because these markers cannot be used to detect early nephrotoxicity, aminoglycosides should be avoided whenever possible in very young patients.

Key points: Neonates

- Avoid oral drugs with low safety margins in the first 24-48 hours post partum
- Hepatobiliary function matures by 4-6 weeks of age
- Renal function matures by 8 weeks of age
- Monitor for hypothermia, hypotension, bradycardia, and ileus associated with anesthesia.

Geriatric patients

Geriatric patients are defined as those that have reached 75% of their expected lifespan. Adverse drug reactions are reported to be 2-3 times higher in geriatric humans compared to younger adults. Although some of this risk can be attributed to patient confusion and errors in dosing, pharmacokinetic and pharmacodynamic factors are also involved. Changes in renal function, hepatic blood flow, body composition, and compensatory physiologic responses alter drug response in the elderly.

Age-related nephron loss

Age-related renal insufficiency is the most important factor affecting drug dosing in geriatric human patients. Nephron loss leads to diminished GFR and renal tubular secretion of drugs. The prevalence of renal insufficiency in older dogs and cats has not been established, but appears to be higher in cats. Even patients without overt azotemia are likely to have decreased GFR associated with aging. This may lead to decreased elimination and increased toxicity of renally-cleared drugs such as metoclopramide, aminoglycosides, and fluoroquinolones.

Aminoglycosides should be avoided whenever possible in geriatric patients; if they must be used, they should always be accompanied by fluid administration and daily urine sediment evaluation for granular casts. Enrofloxacin has been associated with retinal toxicity in elderly cats at the label dose of 5 mg/kg/day and higher. Since this ocular toxicity is dose-dependent, cases seen in older cats are likely due to decreased renal clearance of the drug. While orbifloxacin and marbofloxacin are also cleared by the kidneys, they are less retinotoxic at higher doses, and may be safer for geriatric cats.

Nephron loss may predispose older patients to exaggerated effects from ACE inhibitors such as enalapril, which is renally cleared. Benazepril has the advantage of not accumulating in mild to moderate renal insufficiency in dogs or cats. Nephron loss in older patients can also lead to the local elaboration of renal prostaglandins to sustain renal blood flow. NSAIDs can block these protective

prostaglandins, leading to renal decompensation when elderly patients become somewhat dehydrated. This risk applies to both non-selective and COX-2 selective NSAIDs.

Age-related hepatic changes

Cytochrome P450 content and other drug metabolizing enzymes are fairly well conserved in most elderly human patients. However, decreased blood flow to the liver is seen in older humans, and can lead to decreased clearance of some drugs. Such "flow-limited" drugs are those that are efficiently metabolized once they reach the liver, but depend on high liver blood flow for effective clearance. Such drugs include propranolol, amitriptyline, lidocaine, and fentanyl in humans, for which lower dosages (e.g. by 50%) are often used in older patients. Propofol is also a "flow-limited" drug, and its clearance is diminished in geriatric dogs (> 8-9 years old), with both higher plasma drug concentrations and apnea seen in some older dogs given 5 mg/kg IV.

Changes in body composition

Older patients usually have decreased muscle mass compared to young adult animals. This may lead to increased plasma concentrations of drugs that normally distribute to skeletal muscle, such as digoxin. Older patients also typically have decreased total body and interstitial water. This can lead to increased plasma concentrations of water-soluble drugs such as aminoglycosides, and erratic subcutaneous absorption of drugs such as insulin. Decreased body water also makes older dogs and cats more susceptible to dehydration when given diuretics such as furosemide.

Older pets may be overweight, which can affect drug distribution. For polar, water-soluble drugs with poor fat distribution, such as aminoglycosides or digoxin, dosing should be based on lean body weight (ideal body weight). This can be estimated from patient's conformation and breed standards, or from previous medical records for individual patients. Alternatively, an empirical dose reduction by 15-20% can be estimated (for example, for obese cats given aminoglycosides).

Decreased compensatory physiologic responses

In elderly humans, sensitivity to circulating catecholamines is diminished. In addition, myocardial fibrosis or myxomatous valvular disease may decrease the ability to increase cardiac output. In addition, older patients have loss of respiratory muscle mass, which leads to decreased ventilatory capacity. These changes may blunt compensatory responses to anesthesia-induced hypovolemia or hypoxia, and increase the risk of hypotension in older patients given anti-hypertensive drugs.

Older human patients also have age-related decline in dopamine concentrations and alterations in GABA receptors, which makes them more susceptible to tremor from metoclopramide and sedation from benzodiazepines, respectively. Changes in CNS neurotransmitters and diminished cardiovascular responses, as well as decreased drug elimination, probably contribute to the observation that elderly dogs and cats require much lower dosages of most anesthetics.

Key points: Geriatrics

- Assume a high likelihood of clinical or subclinical renal insufficiency
- Use caution with drugs that rely on high hepatic blood flow for clearance (propranolol, amitriptyline, fentanyl, propofol, and lidocaine)
- Anticipate and monitor for anesthetic complications, such as hypotension, hypoventilation, fluid overload, and hypothermia (particularly in geriatric cats).