

Drugs in Neonates: Principles and Guesses

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It is estimated that 20-30% of puppies die within their first few weeks of life. It is difficult to believe that this should be assumed to be an acceptable mortality rate with the level of veterinary care that is widely available today, but much work yet remains in even determining the etiologies of this high rate of mortality. Drug therapy in neonatal puppies (or kittens), like much of our drug therapy in veterinary medicine, is as much art as science as the science piece is sorely lacking in the literature. However, there has been significant work in this area in humans and enough work in dogs, that although the accessible knowledge base is far from comprehensive, we can extrapolate enough information to serve our neonatal patients to their benefit. Because pediatrics (let alone neonatology) is one of the few specialties in human medicine not represented in veterinary practice, theriogenologists are perhaps our equivalent to perinatologists or neonatologists in human medicine. However, general small animal practitioners are most commonly asked to deal with these patients when veterinary intervention is requested.

The neonatal period does not have a set definition and apparently varies between species. In humans, it is generally accepted that the neonatal period is the first month of postnatal life. An equivalent time in dogs is perhaps 10-12 weeks. During this period there are specific physiological differences between neonatal animals and their older counterparts. When considering drug therapy one cannot merely think of a neonatal puppy as just a smaller version of an adult dog. Significant differences in thermoregulation, glucose regulation, and neurological, cardiopulmonary, immunologic development and responses have all been well documented in the neonatal puppy. While often contributing factors to neonatal morbidity or mortality those differences are less important (although not meaningless) when we consider drug therapy in neonates. It could be credibly argued, that drug therapy in neonates is infrequently required, but when it is, it must be administered with forethought of the special circumstances these patients present.

Pharmacokinetic Alterations in Neonates

Differences in the physiological parameters that influence a given drug's pharmacokinetic profile are where this presentation will focus. As a brief review, pharmacokinetics is the study of how drugs are "handled" by the organism. A given drug's properties of absorption, distribution, biotransformation (metabolism) and elimination in a patient are the primary pharmacokinetic parameters studied and any physiologic differences in neonates that influence those issues are our predominant concern. A major challenge of neonatal drug therapy is that these physiologic, and hence pharmacokinetic properties are dynamic. As a puppy matures, how it handled a drug a week ago may be significantly different than today and these differences could be clinically significant depending on the condition treated and/or the therapeutic index of the drug.

Drug Absorption

Absorption of medications can differ in neonates when given either orally or parenterally. Intramuscular injections of drugs may be sporadically absorbed due to reduced vascularity and the small size of muscles. Intramuscular injections are generally avoided when plasma

drug concentrations are important to therapy. Subcutaneous injections are frequently used in neonatal puppies but absorption rates can also vary with age. Neonates have far less fat as percentage of body weight than adequately nourished adults and subcutaneous injections may be more rapidly absorbed in the neonate. As previously mentioned, thermoregulation of neonates (particularly newborns) is very dependent on external factors and cold ambient temperatures or hypothermic conditions can impair subcutaneous absorption. When giving drugs or fluids to neonates the resulting osmolality of the solution should not exceed 460 mOsm/kg. Hypertonic solutions have resulted in intracranial hemorrhage after parenteral administration and large volumes of hypertonic orally administered drugs or fluids can cause a necrotizing enterocolitis.

Oral absorption of drugs in neonates is altered by several factors. During the first few days of life when colostrum is presented, intestinal permeability to large molecules is increased. During this phase, drugs not normally absorbed from the GI tract may be absorbed and increased absorption may occur with others, but this attribute is generally not useful clinically as it is difficult to predict the absorptive characteristics for a given drug, and may actually lead to toxicity when drugs are administered orally during this time. Beyond this initial phase, the extent of oral absorption is usually not altered, but the rate at which a drug is absorbed can be reduced secondary to delayed gastric emptying and variable intestinal motility. This may lead to lower peak plasma drug concentrations, which can be significant particularly with antibiotic therapy.

Non-traditional drug administration routes may be indicated in some neonatal patients. On occasion when vascular access is not possible, intraosseous or intraperitoneal administration of drugs or fluids is performed. Endotracheal administration of diluted lipid-soluble drugs such as atropine, epinephrine, naloxone or lidocaine may be used. When oral or intravenous drug administration is not indicated or possible, rectal administration may be a viable alternative in the neonate.

Drug Distribution

When compared to adults, distribution of drugs can vary significantly in neonates. Neonates have a higher percentage of body weight as water than their adult counterparts. One may think of them as “little bags of water” when considering drug distribution. At birth a puppy may have 84% of its body weight as water. This value slowly decreases to 70% at 42 days of age and at one year old, is approximately 59%. Conversely, total body fat is very low at birth and increases with time. Distribution of body water is also different in the neonate. At birth about 62% of body water is in the extracellular fluid. This ratio actually increases to 66% at day 42 and then slowly reverses until the percentages of extracellular and intracellular fluids are about equal at 6 months of age. The pharmacokinetic ramifications of these differences are that with highly water-soluble drugs, plasma drug concentrations can be reduced. Because total body fat is decreased, drugs with high lipid solubility may have increased plasma concentrations that could lead to toxicity.

Plasma protein concentrations are significantly lower in neonatal puppies versus adults. During the first four weeks of life, total protein averages about 4 g/dl (vs. 5.4 – 7.4 g/dl in adults). However, neonatal serum albumin levels are generally similar (albeit slightly lower)

to adult values. While albumin levels are only slightly below those of adults, neonatal albumin does not exhibit as high degree of affinity for many drugs as in the adult. Neonates also have decreased levels of α_1 -acid glycoprotein, which is important for certain drugs such as lidocaine. The net result is that drugs that are normally very highly protein bound in the adult, may have increased “free” levels in the neonate thereby exhibiting greater therapeutic or toxic effects.

The so-called blood-brain barrier is more permeable in neonates than adults. CNS permeability can be up to 6 times “normal” for drugs such as morphine or pentobarbital.

Drug Biotransformation (Metabolism)

Biotransformation for certain drugs can be altered significantly in the neonate. Hepatic enzyme systems responsible for metabolizing many drugs (*e.g.*, cytochrome P-450, hydroxylation, demethylation, etc.) may not be equivalent to adult capacities until puppies are 5 months old. Drugs that have a high first-pass effect (*i.e.*, propranolol) after oral dosing or are extensively metabolized may need to have their dosages reduced. Certain pro-drugs (primidone, methylprednisolone, prednisone) may have their efficacy reduced as formation of the active metabolite may be delayed.

Drug Elimination (Excretion)

Elimination of drugs is primarily by renal routes and neonates have reduced capabilities to excrete drugs via renal mechanisms. Glomerular filtration rate (GFR) and tubular secretion are reduced in neonatal puppies. At birth, GFR is approximately 20% of the adult value. Physical development of the kidneys is not complete until puppies are three weeks old and renal excretion of drugs may be reduced when compared with adult values for the first few months of life. Drugs most clinically important are those that are highly water soluble and have significant toxic potential such as aminoglycoside antibiotics.

With all the variables associated with pharmacokinetic parameters of a given drug in neonates of a specific age and species, how does one dose a drug for a specific patient?

This is the reason I chose the title I did for this presentation, because for the majority of drugs available we must guess a dose. An educated guess perhaps where we apply the principles we know for both that drug and our neonatal patient, but a guess nonetheless. Fortunately, most neonatal conditions and resultant drug therapy for dogs or cats revolve around 3 or 4 major areas of concern. The first is supportive and resuscitative care, including oxygen, thermoregulation, fluid, electrolyte, glucose/nutrition and acid-base balance treatment. This proceeding will not focus on those areas in depth and the reader is referred to the references by Moon *et al* and Poffenbarger *et al* as well as chapters in small animal theriogenology or pediatric texts for more in-depth discussion (see reference list). Secondly, neonatal septicemia is a major instance when drug therapy is mandated, and thirdly, neonatal parasitic infestations or infections are major concerns in the neonatal patient. Viral infections such as canine parvovirus (CPV), canine herpes virus (CHV), or canine distemper virus (CDV) can all be significant pathogens in puppies at various ages, but treatment is basically preventative and supportive at this time.

Resuscitative Drug Therapy in Neonates

Resuscitative treatment of the neonatal patient is a major therapeutic challenge. The patient's small size, rapid changes in clinical status, difficulty in monitoring and unknown pharmacokinetic capabilities all contribute. While much of this topic revolves around the supportive care discussed above, certain specific drugs do warrant additional mention:

Atropine for bradycardia in newborns: Atropine is generally not recommended because bradycardia in newborns is likely caused by direct myocardial depression and is not vagally mediated. Therefore atropine is unlikely to be effective and could actually increase cardiac oxygen demand.

Doxapram for respiratory stimulation: Although a time-honored treatment for neonatal apnea, doxapram's use is not supported by the literature for this indication. It may increase ventilatory efforts of the newborn after they have started, but its duration of effect is very short.

Epinephrine for cardiac arrest: While still the drug of choice for neonatal cardiac asystole, there is debate about dosages and routes of administration. Adult dosages (0.2 mg/kg) may yield the best results, but increase the risk of significant hypertension. Some are proponents of endotracheal administration, but because of unpredictable absorption, intravenous or intraosseous administration, if available, are generally preferred.

Naloxone for apnea or narcotic reversal: The opiate reversal agent, naloxone has not been demonstrated to be an effective therapy to reverse apnea of newborns and its routine use for this is not indicated. If the dam has received opiates during parturition, naloxone may still be effective to reverse opiate-induced respiratory depression in newborns.

Antibiotic Drug Therapy in Neonates

There does not appear to be consensus on the safety and recommended dosage adjustments (if any) for antibiotic therapy in neonates. One reference may state to avoid a certain drug while another states that it is safe to use. Most tend to agree that beta-lactam antibiotics (penicillins, cephalosporins) are most likely the least toxic choices in neonates and should be considered for use first. But as neonatal septicemia is an acute, life-threatening disease in neonates and the most commonly reported causative microorganisms are both Gram negative and Gram positive pathogens (β -hemolytic streptococci, *Staphylococcus intermedius*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterocloacae* species) that may be relatively resistant to many antibiotics, adequate coverage may not be possible with many of the beta-lactams. Additionally, because of the acuity of the disease, broad-spectrum antibiotic treatment must begin before the pathogen and antibiotic susceptibilities are determined. For that reason, clinicians have an extra challenge in treating without doing harm. The following are my conclusions and recommendations:

- For serious systemic bacterial infections avoid oral antibiotics at least during initial treatment, because of the inherent unpredictability of oral absorption of drugs in neonates and patients with critical illnesses. Subcutaneous, intravenous or intraosseous administration of drugs are all preferred over PO or IM dosing in seriously ill neonates.
- No antibiotic is absolutely contraindicated in these patients. If the only antibiotic that shows activity is one to "avoid", be prepared to use it if the infection warrants treatment.
- Every antibiotic (even beta-lactams) carries some risk in these patients.

Chloramphenicol

Although there is controversy surrounding its safety, because of the potential for serious adverse effects in newborns, chloramphenicol is rarely recommended for use in small animal neonates and is probably best reserved for documented infections resistant to other antibiotics or those where central nervous system infection is suspected. Chloramphenicol may cause hematologic changes in neonates. Polychromasia, anisocytosis, target cells, and basophilic granulation have all been described in 8-12 week old puppies receiving chloramphenicol. In human neonates, chloramphenicol may cause acute myocardial depression, the so-called “Gray-Baby Syndrome”. If used to treat mycoplasma infections, one reference (Poffenbarger et al 1991) suggests that the dosage be reduced to 22 mg/kg q8h for up to 7 days.

Tetracyclines

Tetracyclines are also not recommended in neonates, not because they generally cause acute toxicity, but because of their chelating effects on calcium. On developing teeth, tetracyclines can cause varying degrees of staining and enamel dysplasia. High or sustained dosing can inhibit bone growth or cause deformities in growing bone. Tetracyclines may also have a greater effect on disturbing normal gut flora because they are enterohepatically re-circulated in the gut.

Potentiated Sulfas

Sulfonamides with either trimethoprim or ormetoprim are probably relatively safe to use in neonates, but some recommend avoiding these drugs because of the potential that hepatitis, anemia, KCS or polyarthritis could occur. They should not be used in patients with anemia or other blood abnormalities. Dosage intervals may need to be extended in very young animals as half-lives of sulfonamides tend to be extended in these patients.

Aminoglycosides potentially can cause ototoxicity and nephrotoxicity. However, in this author’s opinion a suspected or confirmed “hot” Gram-negative septicemia is best treated with a drug like amikacin. An initial IV dosage of perhaps 20 – 25 mg/kg seems reasonable (guess!) and ideally blood levels are drawn to determine pharmacokinetic parameters to guide further dosing. If this is not feasible, then “young” neonates may be re-dosed in q48 hours and “older” neonates q36 hours. Dogs older than 6 weeks of age should probably be re-dosed at the adult dosage of 15-20 mg/kg once a day. Again, because of the potential toxicity and dynamic excretion rates of these drugs, therapeutic drug monitoring is highly recommended.

Fluoroquinolones

Significant controversy exists about the use of these agents in neonatal or pediatric populations. While labeled as being contraindicated or relatively contraindicated in pediatric populations of dogs, the potential benefit of therapy may outweigh the risk of cartilage abnormalities associated with these drugs. While perhaps not drugs of first choice in this patient population, in conjunction with informed consent by the owner on the potential risks, they may be very useful.

Beta-Lactam Antibiotics

Most sources recommend this class of antibiotics as being the safest yet still efficacious for many neonatal infections. Potentiated ampicillins, first or third generation cephalosporins are most often recommended. Parenteral methods (IV, SC, or intraosseous) of administration are preferred over oral routes. The majority of these agents are excreted via renal mechanisms and half-lives may be prolonged and as they are water soluble, peak plasma levels may be decreased when using “normal” doses; some sources recommend increasing the initial dose. But because they are relatively safe, dosing intervals probably do not need adjustment except in newborns. There have been anecdotal reports of these drugs at high dosages causing bleeding in puppies. One reference (Root Kustritz 2003) recommends dosages for cefazolin at 10-30 mg/kg or cefotaxime 25- 50 mg/kg SC or intraosseous q8h for pediatric puppies (Note: The actual reference states the route as “PO”, but the author assures me this is a “typo”).

Other Antibiotic Classes

Macrolides

Macrolides include drugs like tylosin, erythromycin and some newer agents like azithromycin. Erythromycin is unlikely to be indicated in neonates because of limited spectrum and significant gastrointestinal effects. Tylosin has been successfully used for mycoplasma infections in neonates. Azithromycin is extensively used in human pediatric patients and may find a role in small animal medicine, but not enough data presently is available to recommend its use in neonatal dogs or cats. Usually, dosages or dosing intervals do not need adjustment for these drugs in pediatric populations.

Lincosamides

Drugs like lincomycins or clindamycin are generally not recommended in neonates as they potentially could cause extensive alterations in normal gut flora and severe diarrheas.

Metronidazole

Metronidazole is potentially safe to use in neonates for anaerobic infections, but CNS toxicity is worrisome. Until further research is published on the use of this agent in this patient population dosages should be reduced and/or dosage interval increased. An oral dose is recommended for giardiasis in the next section.

Antiparasitic Drug Therapy in Neonates

For *Ancylostoma* species and *Toxocara* species in neonatal dogs and cats, **pyrantal pamoate** appears to be both safe and effective to reduce parasite burdens. Pyrantal pamoate appears safe to administer at a dose of 5-10 mg/kg PO as early as 2 weeks of age. In situations where poor husbandry exists, this dosage should be repeated every 2-3 weeks until the animal is at least 12 weeks old. Both hookworms and roundworms can also be treated with **fenbendazole** at dose 50 mg/kg PO for 3 consecutive days. For giardiasis or mixed giardial infections fenbendazole can be administered at the same dosage but for 7 consecutive days. By administering fenbendazole to the dam in the last trimester of pregnancy, the risk for passing *Ancylostoma caninum* L3 larvae to the puppies via maternal milk can be reduced. Giardiasis can also be treated with **metronidazole** in puppies 2- 6 weeks of age at a dosage of 30 mg/kg PO once daily (not *s.i.d.*!) for 7 – 10 days. For coccidiosis in puppies, **sulfadimethoxine**

appears to be safe and relatively effective at a dosage of 50 mg/kg PO on day 1, then 25 mg/kg PO once a day until signs regress.

Choosing Other Drugs and Dosages for Neonates

Despite the lack of detailed recommendations in the literature for dosage adjustment in neonatal puppies and kittens a clinician can make reasonable clinical judgments in choosing direct therapy by using the information known about neonates in general and the drug in particular. Several of the veterinary references listed for this paper, have either specific or general (“reduce dose”) neonatal dosage recommendations for a limited number of drugs that are often used in neonatal small animal patients. For drugs not mentioned, the reader is referred to human pediatric references that are probably the best alternative to hard data in the species we treat. Although there are many good ones, I particularly like the drug formulary in: *Johns Hopkins: The Harriet Lane Handbook: A Manual for Pediatric House Officers*, 16th ed., 2002 Mosby. This reference not only includes information on pediatric and neonatal dosing in human patients, but drug safety in pregnancy and nursing in an easy-to-use format.

Occasionally, blanket statements such as: “reduce the dose by 30-50% or lengthen the dosage interval” are suggested when altering an adult dose for use in a neonate. While these alterations may be appropriate, the clinician must first carefully consider why they are using the drug in the first place, the relative toxic potential of the drug, and the drug’s pharmacokinetic distribution and elimination characteristics. Finally, the clinician should answer the following “universal” therapeutic questions to guide their treatment choices:

1. Is treatment necessary or wise? What are the relative risks of treating versus not treating with this (or any) particular agent?
2. Is there a “safer” drug that will do?
3. How much do we truly know about the drug(s) in this patient population?
4. If we don’t know very much, can we extrapolate data from other species (especially human)?
5. Is the owner “on board” with treatment options and decisions?
6. What are our therapeutic endpoints? And how will we monitor efficacy and toxicity? What will determine when we can halt therapy?
7. Should we be treating littermates (and/or the mother) prophylactically?

“Indirect” Drug Therapy: Drugs in Maternal Milk

When nursing mothers are given medications there is the potential for administering clinically significant quantities of that drug or its active metabolites to nursing puppies. Unfortunately, there is little or no data specific to dogs (or cats) available on this subject, but there is a substantial amount written on the subject for humans and dairy animals. Certain drugs can be found in maternal milk in quantities that may be clinically significant to a nursing neonate. Among these include antineoplastic agents and certain immunosuppressant drugs. While there is some debate about whether certain antibiotics (tetracyclines, metronidazole, chloramphenicol and aminoglycosides) should be used, they probably are safe. Practically speaking, any drug with a narrow therapeutic index given to a nursing mother should be investigated with regard to its safety to nursing puppies. There are a variety

of references on this subject for human patients that are readily available (see references) and can be used to guide the veterinarian when this question arises.

In humans, the following drugs (that may be used in small animal medicine) are considered by the American Academy of Pediatrics during breast-feeding to be:

Contraindicated: Cyclosporine, doxorubicin and cyclophosphamide because they have the potential to be immunosuppressive in the neonate.

Unknown effects, but **of concern: Fluoxetine, sertraline, metronidazole**

Other drugs that may be of concern in veterinary medicine include **atenolol**; in humans it concentrates in breast milk (3:1; milk:plasma) and one report of bradycardia in an infant has been reported.

Penicillin and its derivatives (including cephalosporins) are considered to be safe to use in nursing mothers. Levels found in milk are very low and would unlikely to cause significant problems.

Chloramphenicol, tetracyclines, metronidazole and the aminoglycoside and quinolone antibiotics are often listed as contraindicated or to be avoided in breast feeding in humans, but in this author's opinion all of these agents could be used if the dam's infection warrants their use and "safer" (*e.g.*, beta-lactams) drugs are not indicated. Although gentamicin is found in breast milk and half of human infants tested have detectable levels in their serum, it is unlikely to cause clinical effects. While tetracyclines would be thought to be contraindicated, the drug's high binding to calcium and protein in milk limits its absorption in the newborn and is unlikely to cause tooth staining or delayed bone growth.

Although not directly harmful to offspring, certain drugs may inhibit lactation and should be avoided if possible. These drugs include **estrogens, thiazide diuretics, and bromocriptine**.

In conclusion, the vast majority of drugs given to lactating females possess little risk to offspring. Except when the few agents mentioned above are administered, dams able to nurse, should do so.

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