Pharmacology in Neonatal Calves

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Although many of the same pathogens that invade the juvenile or adult bovine also can produce disease in the neonatal calf, several physiological differences in the neonate make it much different than just a "miniature cow". These physiological differences can alter the disposition of pharmaceutical agents (pharmacokinetics) in the neonate as well as alter the response of the neonate to a specific therapeutic agent (pharmacodynamics). After a brief overview of some terms used in pharmacokinetics, this paper will describe some physiological differences in neonates compared to adult cattle that are pertinent in drug disposition and response. Next, some specific examples of developmental changes in pharmacokinetics and pharmacodynamics will be described. Finally, some recommendations for drug therapy in neonatal calves will be suggested.

Terminology

Pharmacokinetics mathematically describes the processes of absorption, distribution, metabolism, and excretion of a compound in an animal or a population of animals. The *bioavailability* of a drug is the extent of absorption from a non-intravenous dose compared to that from an intravenous dose, in which instance bioavailability is considered to be 100%. This is determined by comparing the area under the plasma concentration vs. time curve for both routes of administration.

The extent of distribution of drug from the vascular system into extravascular tissues and fluids is quantitated by the term *volume of distribution* (Vd), which has units of volume/unit of body weight (e.g., l/kg). A larger value of Vd indicates more distribution from the vascular system into extravascular tissues and fluids and/or a larger intravascular volume, whereas a smaller value for Vd indicates that drug is retained to a larger degree within the vascular system, due to plasma protein binding or decreased extracellular fluid or tissue into which the drug can distribute.

Systemic clearance (or *total body clearance,* Cl_B) of a compound is the volume of blood or plasma that is cleared of drug per unit of time. Glomerular filtration rate is a clearance term, indicating the volume of plasma cleared of solute by glomerular filtration, with units of ml/min/kg. Systemic clearance of a drug is dependent on organ function and organ blood flow.

Potentially the most widely described pharmacokinetic term is that of depletion or elimination *half-life* ($t_{½}$), which is the time it takes for the concentration in plasma (or tissues) to decrease by 50%. This depletion is dependent upon both distribution and clearance of a drug, as described by the equation:

$$t_{½} = (0.693)(Vd)/Cl_B$$

For instance, if a drug is distributed more out of the bloodstream, then a lower concentration is presented to the organ(s) of elimination, thereby decreasing the total mass of drug that is excreted per unit of time. Alternatively, if the organ of elimination is either not receiving sufficient blood to it or is dysfunctional, clearance is decreased causing less drug to be excreted per unit of time. In both instances, $t_{½}$ is increased because the time it takes for half of the body burden of the drug to be eliminated is prolonged. Therefore, $t_{½}$ must be interpreted in terms of both distribution of drug and clearance of drug from the body.

Physiology of the neonatal calf

Digestion

The rumen is nonfunctional and undeveloped at birth in cattle, so there is no reductive environment to reduce drugs. Furthermore, because of reticular groove closure when a calf suckles, most drugs administered by suckling completely bypass the immature rumen and substantially reducing the time it takes for a drug to reach the small intestine. Because the diet of the neonate is primarily milk and/or milk replacer, compounds that may interact with the dietary components in a much different fashion than in adults. The maturation of the rumen is much faster in calves on pasture (about 3 months of age) than milk-fed calves. Finally, because the tight junctions of the intestinal mucosa are not closed within the first 24-48 hours of birth thereby allowing absorption of maternal antibodies from the gastrointestinal tract, drugs that are not normally absorbed orally in mature animals may be absorbed to a much greater degree in healthy newborns.

Body Composition

At birth, calves (and other mammals) have considerably more total body water (75-80%) and extracellular fluid (40-50%) than mature cows (60-70% and 20-25%, respectively). Plasma volume is also higher in neonates

than adults (7-8% compared to 4-5%), and hematocrit is lower in neonates than adults. Total plasma proteins are lower in neonates than adults, primarily due to lower concentrations of neonatal albumin, which has a lower affinity for many drug molecules than adult albumin. Furthermore, fat content is very low at birth, and the muscle mass:body mass ratio is lower in neonates than in adults. On the other hand, surface area:body weight ratio in neonates is higher than in adults. As a consequence of these differences, water-soluble compounds are distributed more out of the bloodstream in neonates than adults, whereas lipid-soluble drugs remain in the vascular system to a larger degree in neonates (Table 1). Because of the larger volume of extracellular fluid, the drug that does distribute out of the vascular system is diluted in the larger fluid volume, resulting in lower concentrations of drug in extracellular fluid. In addition, drugs that are highly protein bound in adult cattle may be less protein bound in neonates, resulting in a larger free (and hence active) fraction of drug, since drug must be unbound by plasma proteins to reach the site of action and be active.

Table 1. Water-soluble and lipid-soluble antibacterial agents.

Water-soluble antibiotics
penicillins (e.g., ampicillin)
cephalosporins (e.g., ceftiofur)
aminoglycosides (e.g., gentamicin)
oxytetracycline
sulfonamides (e.g., sulfadiazine)
Lipid-soluble antibacterial agents
macrolides (e.g., erythromycin)
lincosamides (e.g., lincomycin)
trimethoprim
minocycline
fluoroquinolones (e.g., enrofloxacin)

Metabolism

In general, hepatic metabolism is slower at birth than in adulthood, with a gradual maturation occurring from birth to puberty. Unfortunately, the rate of "maturation" of specific drug-metabolizing enzymatic systems varies tremendously. As a consequence, metabolism of drugs cannot be predicted solely based on the age of the animal without some knowledge of the specific drug-metabolizing enzymes critical to the metabolism of the drug.

Renal function

Glomerular filtration rate is lower at birth than normal, particularly if the calf is born premature. However, glomerular filtration by the kidneys matures faster than any other process in the animal, reaching adult values within 2-3 days of birth. On the other hand, active renal tubular secretion, which is a function of renal blood flow (which increases 4-5 fold from birth to maturity), matures within 20-30 days of birth. Thus, during the first month of life, renal secretion develops asynchronously with filtration by the glomerulus. There is no evidence for reduced reabsorptive capacity in neonates; however, because neonates are not on a roughage diet early in life, the more acid pH of the urine caused by their diet may decrease the ionization of weakly acidic compounds (such as aspirin), increasing the fraction of excreted drug that can be reabsorbed passively by the renal tubules.

Barriers and defenses of the body

In general, these systems are poorly developed at birth. The blood-brain barrier is poorly developed at birth, allowing compounds to reach the brain and spinal cord that would not ordinarily reach those tissues. Likewise, the outer layers of the skin (stratum corneum) are not as much of a barrier to percutaneous absorption as they are in adults, in part because the layers are thinner and in part because the higher water content of the stratum corneum in neonatal animals allows more water-soluble drugs to penetrate the skin. Respiratory defenses to infection, including the mucociliary apparatus and the pulmonary macrophage system, are not as vigilant at birth as in the mature animal. Finally, because the tight-junctions of the gastrointestinal mucosa are not completely closed within the first 24-48 hours of birth, not only can colostral antibodies be absorbed but so can toxins and microorganisms.

Drug disposition in the neonatal calf

Absorption

Absorption of most compounds is increased within the first 24-48 hours of birth due to the "open-gut" phenomenon and decreased first-pass hepatic metabolism. This is exemplified by apramycin, an aminoglycoside antibiotic that is usually not absorbed appreciably in adult animals. Buck and co-workers (1990) showed that the relative bioavailability of apramycin (as measured by area under the serum concentration vs. time curve) administered orally to 1 day old calves was nearly 7-fold larger than that in 21-day old calves. Furthermore, because the permeability of the gastrointestinal mucosa is changing so rapidly during the first two days of life, extremely variable absorption of drug may ensue. This may lead to unexpectedly high and/or extremely variable plasma and hence tissue concentrations which may have toxicity or human food safety implications. Conversely, drugs such as oxytetracycline that bind to divalent cations (e.g., calcium) are absorbed substantially less in neonates when coadministered with milk or milk replacer than with water (Luthman and Jacobsson, 1986),

because the chelated complex is neither effectively absorbed nor microbiologically active.

Percutaneous absorption is increased for most compounds in neonates due to the thinner, more permeable stratum corneum; and due to the larger surface area:body weight ratio in neonatal animals compared with adults. This latter point results in "overdosing" the animal when an "equal" dose based on body weight is accidentally administered percutaneously. Finally, parenteral absorption is variably altered in neonates due to altered blood flow to intramuscular and subcutaneous injection sites, the decreased muscle mass:body weight in neonates compared to adults, and the altered activity level in veal calves (lower) or beef calves (sometimes higher) than adults.

Drug Distribution

In general, compounds distribute into media in which they are soluble. Therefore, water-soluble compounds tend to distribute out of the vascular system into extracellular fluids. Because there is more ECF in neonates than adults, more (water-soluble) drug distributes out of the vascular system in neonatal calves than adults. For examples, Clarke *et al.* (1985) showed that the Vd of gentamicin is 0.38 L/kg in 5-day old calves compared to 0.13 L/kg in adults. He also found that the volume of the central compartment for gentamicin, a reflection of intravascular volume, was 0.15 L/kg in 5-day old calves compared to 0.06 L/kg in adults (Clarke *et al.* 1985). Burrows *et al.* (1987) found the same differences in the disposition of gentamicin in neonatal calves, and found that the "maturation" of the distribution of gentamicin was gradual over a 3-6 month period and was similar to that of adults at 9 months of age. Because Cl_B of gentamicin was shown not to change dramatically from 15 days of age to adulthood, the difference in $t_{½}$ of gentamicin seen in baby calves compared to adults is a reflection of the differences in Vd of gentamicin in immature animals. Similarly, oxytetracycline Vd is larger in neonatal calves compared with adults (Burrows *et al.* 1987; Nouws *et al.* 1984). Consequently, $t_{½}$ of oxytetracycline decreases from approximately 700 minutes in newborn calves to approximately 375 minutes in cattle greater than 9 months of age (Burrows *et al.* 1987).

As a result of the larger volumes into which the water-soluble drugs distribute in the neonate, lower drug concentrations will be observed in both the plasma and the extravascular fluids. Tissue concentrations will be variably altered, depending on the aqueous fluid content of the specific tissue. Sojka and Brown (1986) found a similar disparity between foals less than 3 months of age and adult horses with normal renal function. As a result, they proposed a dosage regimen in foals of 3.3 mg/kg every 12 hours compared with their recommendation of 2.2 mg/kg every 8 hours in adults, both of which targeted peak gentamicin concentrations of 10-12 mg/L and trough gentamicin concentrations of 1-2 mg/L. A similar relative dosage alteration may also be required for other water-soluble antibiotics in neonatal calves and foals compared to the adult dosage regimen for the same antibiotic.

On the other hand, lipid-soluble drugs have less extracellular tissue (e.g., fat) into which they can distribute in neonatal animals. As a result, the Vd is decreased (relatively more drug remains in the vascular system) for lipid-soluble drugs such as trimethoprim. Shoaf *et al.* (1989) showed that, although the Vd of sulfadiazine was larger in neonatal calves and decreased as the calves matured, the Vd of trimethoprim was smaller in neonatal calves than adults by about 20%. Other lipid-soluble compounds may also behave in a similar fashion.

Finally, drugs that are highly bound to plasma proteins may have substantially altered distribution because of altered (usually decreased) binding to albumin. However, this is much more variable and considerably less predictable than the distribution changes due to altered body composition.

Renal drug clearance

Drugs that are excreted solely by glomerular filtration have Cl_B that rapidly mature in the neonatal calf (Table 2). For instance Cl_B of gentamicin (and undoubtedly other aminoglycosides) is either "mature" or larger than "mature" values in calves 5 days of age (Clarke *et al.* 1985; Burrows *et al.* 1987). This "supra-mature" clearance may be a function of adult cows having various degrees of age-related renal deterioration that was not assessed in the study by Clarke *et al.* (1985). In the comparisons made by Burrows *et al.* (1987), gentamicin Cl_B reached "mature" values by two weeks of age in cattle.

Table 2. Antibacterial agents that are metabolized or renally excreted.

Exclusively renally excreted
penicillins
cephalosporins (some exceptions)
aminoglycosides
Primarily renally excreted with some metabolism
sulfonamides
oxytetracycline
floroquinolones
Extensively metabolized with minor renal excretion
lincosamides
macrolides
trimethoprim
minocycline

Although studies are limited for drugs that undergo renal tubular secretion, it can be anticipated that renal clearance for these drugs will reach adult values by 1 month of age. On the other hand, for weakly acidic compounds that can undergo renal tubular reabsorption when they are nonionized (e.g., aspirin, phenylbutazone), renal clearance may be lower in milk-fed neonates than ruminating animals on roughage because the urine pH will be lower.

Hepatic drug metabolism

Both sulfadiazine and trimethoprim are metabolized by the liver; however, sulfadiazine is also renally excreted, whereas trimethoprim relies much more heavily on hepatic metabolism as the primary mechanism for excretion. Sulfadiazine Cl_B increases with age as the animals mature, reflected by a parallel increase in urinary clearance of parent compound through tubular secretion (Shoaf *et al.* 1989). On the other hand, the Cl_B of trimethoprim increases nearly 10-fold from birth to 6 weeks of age, a change that was not reflected by any difference in urinary excretion of parent compound. This indicates that the age-related increase in Cl_B of trimethoprim is primarily due to increased ability of the older animal to metabolize it. As a consequence, $t_{½}$ of trimethoprim decreases from over 8 hours in 1-day old calves to approximately 1 hour in 6-week old calves (Shoaf, *et al.* 1989). Interestingly, the combination of trimethoprim and sulfonamides is optimally synergistic at a ratio of 1:5; however, the differential metabolism of trimethoprim and sulfadiazine in neonatal and maturing calves does not maintain the same ratio of trimethoprim and sulfadiazine in the bloodstream. The therapeutic significance of this phenomenon is not known presently.

Flumequine is the only fluoroquinolone that has been studied in neonatal calves and older cattle. Both Vd and Cl_B increased with age, resulting in a $t_{½}$ that changed very little as calves matured (Mevius *et al.* 1990). A result of these minor differences, the authors' recommended slightly higher doses in older calves to achieve similar plasma concentrations.

Although chloramphenicol must not be used in food-producing animals, a study by Martin and Wiese (1988) using chloramphenicol in neonatal pigs illustrates an important point. In that study, chloramphenicol in colostrum-deprived newborn pigs had a longer $t_{½}$ than in colostrum-fed pigs, due entirely to a smaller Cl_B in the colostrum-deprived pigs. Plasma protein binding of chloramphenicol was higher in colostrum-deprived pigs, probably contributing to the lower Cl_B observed. This suggests that, for some drugs in which protein binding and/or hepatic metabolism are important, neonatal animals deprived of colostrum may have a diminished ability to clear drugs from their system.

Pharmacodynamics

Relatively little information exists regarding the pharmacodynamics, or response to a given concentration of drug at the site of action, in neonatal calves. However, because most of the therapeutic agents used in neonatal calves are targeting bacteria and not the host, the pharmacodynamics of antimicrobial agents would not be expected to be different due to the maturity of the animals. On the other hand, the host defenses in the newborn are poorly developed. Phagocytic activity, pulmonary macrophage function, mucociliary apparatus function, and active immunity are all poorly functional at birth. Because of this, bactericidal antibacterial agents are preferred to bacteriostatic antibacterial drugs in neonatal calves (Table 3). Furthermore, because the blood:brain barrier is not fully formed at birth, many compounds that would not be expected to cause CNS signs or have activity there in adults may in fact do so in neonatal calves.

Table 3. Bactericidal vs. bacteriostatic antibacterial agents

Bactericidal antibacterial agents
penicillins
cephalosporins
aminoglycosides
fluoroquinolones
diaminopyrimidine/sulfonamide combinations (e.g., trimethoprim/sulfadiazine)
Bacteriostatic antibacterial agents
macrolides
lincosamides
sulfonamides
tetracyclines
trimethoprim

Recommendations

The following recommendations derived from Vaala (1985) can be used as guidelines for drug therapy in calves:

1. Minimize drug therapy to the dam to decrease the possible placental and/or mammary transfer of the drug to the neonate.
2. Minimize *unnecessary* drug therapy to the calf.
3. When possible, select drugs that are *not* highly metabolized or highly plasma protein bound unless specific information is available regarding use of that drug in the neonatal calf.
4. Use broad-spectrum, bactericidal antimicrobial

agents aggressively when the choice is made to treat the animal.

5. Parenteral drugs are preferable to orally administered drugs because of the extreme variability in enteral absorption of drugs during the first few days of life.

6. An accurate diagnosis followed by specific bactericidal therapy will maximize the benefit:risk ratio for the calf.

7. Intelligent direction by the attending veterinarian regarding drug therapy and withdrawal of drug from the calf prior to slaughter is critical to optimizing the outcome for the calf and ensuring a safe and wholesome food supply.

References

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