Impact of age on antibiotic distribution and efficacy in calves

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Abstract

Calfhood diseases have a major economic impact on beef and dairy operations, due to the costs associated with mortality, treatment, and the long-term effects on growth and performance. With very limited approved drugs for use in "pre-ruminant" calves and heifers, questions remain about the effectiveness of these drugs in young animals. It is important to prevent unnecessary use of antibiotics in calves to limit the development of resistant bacteria and residues, as well as take into account the developmental changes that occur in neonatal calves that would affect the distribution, therefore efficacy of selected drug therapy. The purpose of this article will give an overview of the effects of age on absorption, metabolism, distribution, and elimination of commonly administered drugs and its impact on efficacy in different ages of calves.

Key words: calves, antibiotics, pharmacokinetics, therapy

Résumé

Les maladies chez les veaux ont un impact économique majeur dans les élevages de vaches laitières et de boucherie en raison des coûts associés à la mortalité, aux traitements et aux effets à long-terme sur la croissance et la performance. Parce qu'il y a très peu de drogues approuvées pour utilisation chez les jeunes veaux et chez les génisses, l'efficacité de ces drogues chez les jeunes animaux est donc questionnable. Il est important de prévenir le recours inutile aux antibiotiques chez les veaux afin de limiter le développement de bactéries résistantes et de résidus résistants. Il est aussi important de prendre en compte les changements développementaux chez les veaux néonataux qui pourraient affecter la distribution et par le fait même l'efficacité des thérapies médicamenteuses choisies. Le but de cette présentation est de donner un aperçu des effets de l'âge sur l'absorption, le métabolisme, la distribution et l'élimination des drogues couramment utilisées et son impact sur l'efficacité de ces drogues chez les veaux.

Introduction

Pediatric patients are distinctly different than their adult counterparts, especially in regards to pharmacological therapy, due to the many physiological changes that take place. In the field of veterinary medicine, where these age groups mature much more rapidly than human pediatric patients, these differences can be profound, and have a large impact on the pharmacokinetics and pharmacodynamics of any given compound. Ruminants, including cattle, goats and sheep, are unique in veterinary medicine due to the fact that these animals undergo dramatic physiological changes in their specialized gastrointestinal tract as well as changes in the 4 key processes that make up the field of pharmacokinetics: absorption, distribution, metabolism, and elimination (ADME). These ADME processes differ in neonatal calf populations compared with adults and have consequences on the pharmacokinetic profile of a drug. An understanding of these differences and likely outcome is important to ensure effective antimicrobial therapy.

Overview of Regulatory Classification of Calves

From a regulatory standpoint, the major issue that arises is the use of the term "pre-ruminant" vs "ruminant" calf when it comes to selecting appropriate and legal drug use. Many producers and veterinarians have varying ideas on what constitutes a pre-ruminant vs ruminant and distinguishing both of those from a veal calf. According to Food and Drug Administration's Guidance for Industry #191, veal calves are defined as immature cattle, including beef and dairy breeds that lack a functional rumen and are intended for meat production. Veal calves are recognized as a distinct regulatory class from suckling calves because of their handling, housing, and proximity to slaughter. Even though there are many differences in the management and husbandry of these young animals, as well as diet, gastrointestinal, hepatic, and renal function, very little research has been done to demonstrate how these physiological changes affect pharmacokinetic profiles of drugs of pre-ruminant vs ruminant calves. For the purpose of this review, pre-ruminant calves are defined as any immature cattle under 3 weeks of age fed primarily a milk-based diet, and a ruminating calf as a fully weaned calf with a developed rumen to provide the majority of its energy and protein needs.

Absorption

In contrast to intravenous administration, drugs administrated extravascularly must undergo absorption in order to reach the systemic circulation. Absorption of a drug is characterized by 2 parameters: the rate and the extent of

drug absorption. The former affects the onset of action of the drug, and the latter essentially controls the effective dose.

In a newborn calf's gastrointestinal tract, several age-related anatomic and physiological changes have the potential to affect drug absorption. At birth, the abomasum is the largest component of the gastrointestinal tract. Young calves' reticular groove serves as a direct line for milk to bypass the rumen and empty into the omasal canal and abomasum. Any drugs that are extensively inactivated by rumen microorganisms or undergo extensive metabolism in the liver would be expected to have higher absorption rate and systemic bioavailability (extent of absorption) in pre-ruminant calves. The systemic bioavailability of orally administered procaine penicillin G to calves, for example, demonstrated a 46% decrease in the area under the plasma drug concentration time curve (AUC), along with a shorter time to maximum concentration (T_{MAX}), and lower maximum concentrations (C_{MAX}) in the 5-week-old calves compared to 1-week old calves.[1]

Absorption of drugs from parenteral routes of administration, including intramuscular and subcutaneous (s.c.) injections, may be affected due to decreases in muscle mass or reduced muscular perfusion. Additionally, absorption can vary in neonatal calves depending on physiochemical properties of the drug, such as molecular weight, solubility, and pH. Decreased muscle contractility in young calves can result in slower rates of intramuscular drug absorption and lower peak serum concentrations. Water-soluble drugs tend to have greater intramuscular absorption in neonates than children or adults due to higher muscular water content and increased density of skeletal muscle capillaries in neonates.[2] Depending on drug formulation and absorption capability at site of injection, s.c. injections in pre-ruminant calves may also have a faster and more complete absorption of drugs due to the relatively larger absorption surface, which can be seen in plasma as higher peak plasma drug concentrations.

Distribution

Once the drug enters the bloodstream, it distributes throughout the vascular system and to other areas of the body. A drug's distribution characteristics are summarized by the parameter apparent volume of distribution (Vd) which is the ratio of the amount of drug in the body to the corresponding plasma concentration. Clinically, Vd is an important consideration in young animals because it controls the value of a loading dose, and when linked with a drug's clearance, it determines a drug's half-life.[3] A drug's Vd is determined by tissue binding, plasma protein binding, and the physiochemical properties of the drug, such as lipid and water solubility, which impacts the body compartments a drug can distribute into. When a drug has a large Vd, it suggests that the plasma concentration is relatively small, whereas a small Vd indicates that the plasma concentration is relatively high in comparison to the amount of drug in the body. This low Vd suggests less-extensive distribution from the plasma, and may indicate that a drug is highly bound to plasma proteins, a process that inhibits the distribution of drug from the plasma.

Maturational changes in calves impact the distribution into different body compartments. As calves mature, there is an increase in body fat:water ratio which could possibly sequester lipid-soluble drugs in adipose tissue. In neonates, total body water is increased, in which highly water-soluble compounds, such as ceftiofur sodium, have larger volumes of distribution when compared to adults. The Vd of ceftiofur sodium decreased linearly within the first 3 months of life in cattle, indicative of decreased extracellular fluid volume as calves matured.[4]

In humans, plasma protein binding of drugs tends to be lower in neonates and infants, due not only to the reduction of the total amount of plasma proteins, but also to the lower binding affinity and the high concentrations of endogenous competing substrates. In preliminary studies from our lab, we evaluated plasma protein binding of 4 drugs (danofloxacin, tulathromycin, flunixin, and florfenicol) in individual animals as they aged to 21 days and compared them to 8-week-old and 6-month-old calves. Our preliminary data suggests that for these commonly administered drugs, plasma protein binding may not differ significantly across ages. In theory, reduced protein binding may result in an increased concentration of free and available drug, which can increase the amount of drug free to distribute from the plasma to the rest of the body.[5]

Metabolism/Elimination

Hepatic metabolism, which usually involves a 2-step elimination process (phases I and II), is the main mechanism of drug elimination.[6,7] Phase I metabolism typically involves reactions mediated by cytochrome P450 enzymes, which increase the hydrophilicity of many compounds. In calves, cytochrome P450 enzyme activity increases 2-fold during the first week after birth and remains constant thereafter.[8] Mixed-function oxidase activity also develops over time, with some enzyme activities in 1-day-old calves only 17% to 50% of those in 42-day-old calves.[8] Phase II reactions contribute primarily to the systemic clearance of drugs by a series of conjugation pathways and other enzymes. Xenobiotic-metabolizing enzymes are generally deficient in food-producing animals at birth and gradually increase during the first few months after birth.[9]

The maturation of renal pathways is dependent on renal blood flow and glomerular filtration rate. At birth, there is a large decrease in renal vascular resistance and increase in cardiac output and renal blood flow, which contribute to the growth and maturation of renal tubules and tubular processes.[10] For drugs that are dependent primarily on renal excretion, immature renal clearance mechanisms can result in a prolonged elimination half-life, but the pharmacokinetic parameters for those drugs are quite variable and complex

owing to factors other than renal clearance such as protein binding and affinity.[11]

Pathophysiological Differences in Disease

Clinical therapeutic success is largely governed by the response mechanisms of the host. In neonatal calves, these immune functions may be immature, and patient parameters of age and disease state are important considerations when selecting an antimicrobial therapy. Septic animals have a critical need for rapid antibacterial activity, so the appropriate selection of a therapy is critical to improve prognosis. Drug disposition may be altered by disease states, including fever, dehydration, liver and renal disease. In calves, antimicrobials are commonly administered for diarrhea and respiratory disease. The disease pathogenesis may induce additional changes in drug concentrations at the site of action due to increased inflammatory response and local tissue changes.

In cattle diagnosed with sepsis/endotoxemia, pathophysiological changes in organ function, as well as compromised tissue perfusion, may affect drug disposition. Drug absorption following intramuscular, subcutaneous, transdermal, and oral administration may be reduced due to a decreased perfusion of tissues. On the contrary, the increase in capillary permeability and interstitial edema during sepsis and septic shock may enhance drug distribution. In some diseases, tissue barriers such as the blood-brain barrier, granulation tissue, and abscess capsules inhibit transfer of the drug from plasma to the site of infection. In these cases, although a pathogen may be susceptible, cultures and sensitivity have the potential to overestimate the likely efficacy if a drug cannot reach these specific sites. Antimicrobial selection should be tailored to each case and a balance between efficacy, judicious use, and cost are needed to establish a therapeutic value for each animal.

Summary and Conclusions

An increase in understanding of maturational changes in cattle have facilitated improvements in drug therapies for young calves. Simply extrapolating dosing regimens from adult cattle to neonates may not be sufficient to achieve therapeutic success in different ages of calves. An understanding of age-related physiological variables, disease impacts, and basic pharmacokinetic principles can serve as guides for safe and effective drug and dosage selection for different populations of cattle.

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