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Factors affecting pharmacokinetics of benzimidazole anthelmintics in food-producing animals: The consequences and potential risks

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ABSTRACT

Benzimidazoles are frequently and widely used veterinary anthelmintics. Unfortunately, an administration of these anthelmintics does not always result in the expected therapeutic success. Many host-related factors modify pharmacokinetic behavior and efficacy of a chosen anthelmintic. Pharmacokinetics of anthelmintics varies among animals of different species, sex and age. Also diseases, medication, feed and environmental conditions can significantly affect behavior of anthelmintics and resultant drug efficacy in animals. The presented review gathers information, gained in last 20 years, on factors which bring about the variability in performance of benzimidazole anthelmintics in food-producing animals. It is focused particularly on differences in absorption and metabolism of these anthelmintics as these stages of the pharmacokinetic process seem to be the most important for the overall anthelmintic efficacy. The consequences of abnormalities and alterations in pharmacokinetics of benzimidazole anthelmintics are summarized and discussed.

1. Introduction

Veterinary medicine struggles with helminthoses all over the world. Several approaches have been used to combat helminthoses, such as regulations of parasitic vectors in populations, zootechnical strategies, breeding of resistant animals and treatment of animals with anthelmintics. The last mentioned option is the most practiced approach in the last four decades in the form of pharmacotherapy and pharmacoprophylaxis. Anthelmintics have become the most frequently and the most widely used veterinary drugs. Unfortunately, the administration of anthelmintics does not always result in the expected therapeutic success. Among factors responsible for the therapeutic failure are (1) inadequate integration between management strategies and chemotherapy, (2) incorrect use of anthelmintic drugs due to insufficient knowledge of their pharmacological features, (3) insufficient understanding of the relationship between pharmacological properties, and (4) several host-related factors that modify pharmacokinetic behavior and efficacy of a chosen drug (Lanusse et al., 2009).

Undoubtedly, the choice of a suitable type of a drug, its dosing and route of administration is crucial for efficacy and overall safety of therapy. On the other hand, this choice is not simple as every animal patient represents unique individual of certain species characterized by animal breed, sex, age, health status, medications, feeding, social status, etc. All aforementioned factors can affect the drug behavior in a treated animal and its reachable efficacy.

Benzimidazoles represent important and worldwide-adopted class of anthelmintics used in the treatment and prevention of parasitic diseases in food-producing animals. The importance of benzimidazoles in veterinary medicine is documented by the wide spectrum of substances used, as well as the variety of pharmaceuticals and dosage forms. For example, veterinary registration in United Kingdom includes the following items: albendazole (14 preparations), febantel (prodrug, 3 preparations), fenbendazole (35 preparations), flubendazole (3 preparations), mebendazole (5 preparations), netobimin (prodrug, 2 preparations), oxfendazole (11 preparations), oxibendazole (1 preparation), thiophanat (prodrug, 1 preparation), thiabendazole (1 preparation) and triclabendazole (2 preparation) (Jacobs and Taylor 2001).

Every benzimidazole anthelmintics has its recommended dosage scheme for main target species. This dosage scheme fits to a standard animal – adult, healthy, normally fed, without other medication, etc. But in many cases, the anthelmintics are also administered to non-standard animals: infant or very old animals, animals infected with more than one helminthosis, animals suffering from other infective or non-infective diseases, animals with different diets, animals with other medication or animals in different breeding and environmental conditions. Considering these facts, great variability in behavior and efficacy of anthelmintics is hardly surprising. Some factors that determine pharmacokinetics of benzimidazole anthelmintics have been briefly summarized and some derivable recommendations have become available (Lanusse and Prichard, 1993; Lanusse et al., 2009) but other factors have been

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studied only marginally and their importance to efficient anthelmintic therapy remains underestimated.

Generally, the factors affecting drug pharmacokinetics can be split into two groups: inter-individual and intra-individual, depending on whether they vary between or within given individuals, respectively (Testa and Caldwell, 1995). The inter-individual factors (species, sex, and genetics) remain constant during the life span of an organism while intra-individual factors (age, gestation, stress, medication, food, and environment), changing during the life, are related to physiological and pathological state of an organism. From other point of view, one can distinguish between the internal factors (species, sex, genetic, age, and disease) and external (diet and environment) ones (Gibson and Skett, 2001; Krämer and Testa, 2008).

2. Species-differences in pharmacokinetics of benzimidazole anthelmintics

The anatomy and physiology of each animal species determines drug behavior in organism. Owing to this fact, inter-species differences in anthelmintics pharmacokinetics and efficacy have been expected and documented.

Delatour et al. (1990) and Lanusse et al. (1992, 1993a) studied pharmacokinetics of albendazole (ABZ) in cattle and sheep and described differences in plasma concentrations of anthelmintically active ABZ sulfoxide (ABZSO) and inactive ABZ sulfone ($ABZSO_2$) after ABZ or netobimin (NTB; ABZ prodrug) administrations. Biological half-life and mean residence time (MRT) of ABZSO were significantly higher in sheep than in cattle. Also the plasma ratio of $ABZSO_2$/ABZSO was lower in sheep than in cattle. Therefore ovine enzymes have higher ability of ABZ sulfoxidation and lower ability of ABZ sulfonation than bovine ones. The systemic availability of ABZ and ABZSO was also significantly higher in goats than in sheep after ABZ intraruminal administration. The result indicates the necessity of higher ABZ dose in goats than in sheep (Hennessy et al., 1993).

When Delatour et al. (1991) compared the concentrations of ABZSO enantiomers in plasma after treatment of sheep, goat and cattle with ABZ, they established significant inter-species differences. After NTB administration, no ABZ was detected in ovine plasma while a significant amount was found in chicken plasma. Lanusse et al. (1992) compared two-step ABZ oxidation and ABZSO reduction in ruminal, abomasal and ileal fluid from sheep and cattle. No biotransformation of ABZ or ABZSO occurred in abomasal fluids, but oxidation of ABZ to ABZSO and reduction of ABZSO to ABZ were observed in ruminal and ileal fluids from both species. ABZ ruminal and ileal oxidation was faster in cattle than in sheep. On the other hand ABZSO reduction was stronger in ovine than in bovine fluids. Back-reduction of ABZSO caused prolongation of ABZSO persistence in ovine comparing to bovine plasma (Lanusse and Prichard, 1990; Lanusse et al., 1992).

Pharmacokinetic studies of ABZ in horses revealed high ABZSO plasma concentrations and slow $ABZSO_2$ formation (Gokbulut et al., 2009). On the other hand, in fenbendazole (FBZ) and oxfendazole (OFZ) pharmacokinetic studies, low concentrations of active sulfoxides and rapid deactivation were observed (McKellar et al., 2002; Gokbulut et al., 2002). Comparing FBZ and OFZ pharmacokinetics in horses and ruminants, faster deactivation, lower bioavailability and shorter persistence of active substances in horses were found (Capece et al., 2009a). The results mentioned above indicated the necessity to administer higher FBZ or OFZ doses in horses than in ruminant species.

A comparative pharmacokinetic study of triclabendazole (TCBZ) was conducted in cattle and sheep. The plasma concentration profiles of the main metabolites triclabendazole sulfoxide (TCBZSO) and triclabendazole sulfone ($TCBZSO_2$) were analysed. The values of AUC and C_{max} of TBZSO did not differ between species, while other kinetic parameters were higher in cattle than in sheep. Almost all kinetic parameters for $TCBZSO_2$ had higher values in cattle than in sheep (Mestorino et al., 2008).

In related species, one would assume similar pharmacokinetics of a given drug. However, such a presumption may not correspond to reality. For example, Sanyal (1995) tested concentrations of TCBZSO and $TCBZSO_2$ in buffalo and cross-bred cattle after intraruminal administration of TCBZ. Plasma concentrations of both metabolites were significantly lower in buffalo than cattle, which resulted in a significantly smaller AUC and C_{max}. Thus the dose recommended for cattle may not be sufficiently effective in buffalo (Sanyal and Gupta, 1996).

Species differences in pharmacokinetics of drug lie often in species-specific drug metabolizing enzymes that significantly affect drug absorption, distribution, biotransformation as well as drug elimination from animal body. Drug metabolizing enzymes comprise biotransformation enzymes and drug transporters. Biotransformation enzymes catalyze the chemical modifications of drugs and other xenobiotics with the aim to facilitate their elimination. Transporters translocate drugs and other compounds across the membranes and in this way they regulate the entry and the efflux of the compounds to and off an organism. Expression and activity of drug metabolizing enzymes may vary also in phylogenetically close species (Nebbia, 2001). Szotáková et al. (2004) compared *in vitro* activities of main biotransformation enzymes in pig, cattle, goat and sheep. The related small ruminant species – sheep and goat – differed significantly in a half of the tested enzyme activities. In cattle, very high (5- to 10-fold higher than in other species) activity of cytochromes P4501A (CYP1A) was found. In pig and sheep, cytochrome P4503A (CYP3A) activity predominated. The highest activities of conjugation enzymes were observed in sheep. Significant differences in activities of several biotransformation enzymes were also described among deer species (Machala et al., 2003). Inter-species differences in activities of biotransformation enzymes correlate with inter-species differences in anthelmintics metabolism. In both sheep and cattle, CYP3A participated in oxidation of albendazole (ABZ) to ABZ sulfoxide (ABZSO). This reaction was faster in ovine than in bovine hepatic microsomes (Lanusse et al., 1993b). In addition to CYP3A, also flavine monooxygenases (FMO) catalyzed ABZSO formation. ABZSO has a chiral centre and it is likely that formation of (−)-ABZSO depends mainly on CYP3A activity, whereas synthesis of (+)-ABZSO depends on FMO (Delatour et al., 1991; Moroni et al., 1995). The ratios of ABZSO enantiomers represent sensitive indicators of inter-species differences in activities of both ABZ oxidizing systems and these ratios significantly differed in cattle, sheep, pig and deer species (Velík et al., 2005a; Virkel et al., 2004). Sulfonation, the second step of ABZ oxidation, is mediated by CYP1A. In accordance with the high CYP1A activity in bovine liver, the formation of $ABZSO_2$ was significantly faster in cattle than in sheep or pig (Velík et al., 2005a).

All documented studies proved relatively high differences in pharmacokinetics of anthelmintics, not only among dissimilar species, but also among related species. These facts emphasize the importance of detailed pharmacokinetic studies of anthelmintics in all target species.

3. Sex-differences in pharmacokinetics of benzimidazole anthelmintics

In animal organisms, all biochemical pathways are controlled by hormones, including sex hormones. Therefore, certain differences between males and females in drug pharmacokinetics