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Doramectin concentration profiles in the gastrointestinal tract of topically-treated calves: Influence of animal licking restriction

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Abstract

Endectocide compounds are extensively used for broad-spectrum parasite control and their topical administration to cattle is widespread in clinical practice. Pour-on formulations of moxidectin, ivermectin, eprinomectin and doramectin (DRM) are marketed internationally for use in cattle. However, variability in antiparasitic efficacy and pharmacokinetic profiles has been observed. Although the tissue distribution pattern for different endectocide molecules given subcutaneously to cattle has been described, only limited information on drug concentration profiles in tissues of parasite location after topical treatment is available. Understanding the plasma and target tissue kinetics for topically-administered endectocide compounds is relevant to optimise their therapeutic potential. The current work was designed to measure the plasma and gastrointestinal (GI) concentration profiles of DRM following its pour-on administration to calves. The influence of natural licking behaviour of cattle on DRM concentration in mucosal tissue and luminal content of different GI sections was evaluated. The trial was conducted in two experimental phases. In Phase I, the DRM plasma kinetics was comparatively characterised in free-licking and in 2-day licking-restricted (non-licking) calves. The pattern of distribution of topical DRM to mucosal and luminal contents from abomasum, duodenum, ileum, caecum and spiral colon was assessed in free-licking and non-licking calves restricted over 10 days post-administration (Phase II). The prevention of licking caused marked changes on the plasma and GI kinetics of DRM administered pour-on. In 2-day licking restricted calves, DRM systemic availability was significantly lower (29%) than in free licking animals during the first 9 days post-treatment. Following a 10-day long licking restriction period, DRM concentrations profiles in both mucosal tissue and luminal contents of the GI tract were markedly higher in animals allowed to lick freely. This enhancement in drug concentrations in free-licking compared to non-licking calves, was particularly pronounced in the abomasal (38-fold higher) and duodenal (six-fold higher) luminal content. As shown earlier for ivermectin, licking behaviour may facilitate the oral ingestion of topically-administered DRM in cattle. This would be consistent with the marked lower drug concentration profiles measured in the bloodstream and GI tract of the animals prevented from licking. The work reported here provides relevant information on the pattern of DRM distribution to the GI tract after pour-on treatment, and contributes to understand the variability observed in the antiparasitic persistence of topically-administered endectocides in cattle. The implications of natural licking in topical treatments are

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required to be seriously assessed to achieve optimal parasite control and to design parasitological and pharmacological studies within the drug approval process.

Keywords: Doramectin; Licking behaviour; Cattle; Transdermal absorption

1. Introduction

The macrocyclic lactone compounds from both the avermectin and milbemycin families, known as endectocides for their activity against both endo-and ectoparasites, are extensively used for broad-spectrum parasite control in livestock. Doramectin (DRM) is an avermectin endectocide compound that exhibits no activity against cestode and trematode parasites, but it is highly effective against the adult, developing and hypobiotic larvae of most gastrointestinal (GI) nematodes, lungworms and many arthropod ectoparasites at extremely low dosages (Vercruysse et al., 1993; Jones et al., 1993). Parasiticides are the most frequently used topical veterinary medications and the use of pour-on endectocide formulations in cattle is widespread (Baynes et al., 1997). DRM is marketed as injectable and topical (pour-on) formulations for use in beef cattle. Additionally, pour-on formulations of ivermectin, eprinomectin and moxidectin are internationally available for use in cattle. They offer considerable practical (less labour-intensive) and pharmacological (avoidance of liver first-pass effect and no drug residue at the injection site) advantages compared to other routes of drug administration (Baggot and Brown, 1998). However, variability in antiparasitic efficacy has been observed. Information on the plasma kinetic behaviour of topical ivermectin, doramectin (Gayrard et al., 1999; Laffont et al., 2001, 2003; Bousquet-Mélou et al., 2004), eprinomectin (Alvinerie et al., 1999a) and moxidectin (Sallovitz et al., 2002; Bousquet-Mélou et al., 2004) in cattle is available. Other studies have also investigated the tissue distribution and level of tissue drug residues after the subcutaneous administration of different endectocide molecules (Lifschitz et al., 1999a, 1999b, 2000; Afzal et al., 1994; Zulalian et al., 1994) to ruminant species. The gastrointestinal disposition of DRM has been studied after oral and intravenous administration to sheep (Hennessy et al., 2000). Other studies investigated the effect of different variables on the plasma kinetics of endectocides in cattle. Among these factors were route of administration and formulation (Herd et al., 1996; Lifschitz et al., 1999b; Alvinerie et al., 1999b), breed (Sallovitz et al., 2002), and natural licking behaviour (Laffont et al., 2001; Bousquet-Mélou et al., 2004). However, only few studies (Sallovitz et al., 2003) reported on the tissue distribution of endectocides (moxidectin) after its topical (pour-on) administration to cattle. This study was conducted without considering the effect of licking on the pattern of tissue distribution of the drug. It is well established that an optimised full antiparasitic effect can be achieved if pharmacological, parasitological and physiological variables are considered in an integrated manner. The optimisation of the antiparasitic activity of topically administered endectocides can be achieved through a thorough knowledge of their absorption pattern and tissue kinetic behaviour, particularly at those sites where parasites locate, and identification of different factors affecting the performance of the topically administered compound. Hence, the current work was designed to investigate the plasma and GI tract disposition of DRM following pour-on treatment in calves. Also, the influence of animal natural licking behaviour in cattle on DRM concentration profiles in the bloodstream and in the GI mucosas and luminal contents was assessed. The comparative DRM availability in abomasum and in different intestine sections in free-licking and licking-restricted calves topically-treated at recommended dose rates is reported here.

2. Materials and methods

The present experiment was conducted in two experimental phases. In Phase I, DRM plasma kinetics was comparatively characterised in free-licking and in 2-day licking restricted (non-licking) calves. In Phase II, the pattern of DRM concentrations in mucosal