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Comparative plasma disposition, bioavailability and efficacy of ivermectin following oral and pour-on administrations in horses

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ABSTRACT

Pour-on formulations of endectocides decrease the risk of injury for both user and animal, and are particularly convenient for animal owners who can apply the product. This study was designed to investigate the plasma disposition and efficacy of ivermectin (IVM) following pour-on, *per os* and intravenous administrations. Eighteen female horses weighing 510–610 kg were used in this study. The animals were allocated into three groups (*per os*, pour-on and intravenous groups). The equine paste, bovine pour-on and bovine injectable formulations of IVM were administered orally, topically and intravenously at the dose rates of 0.2, 0.5 and 0.2 mg/kg bodyweight, respectively. Heparinized blood samples and hair samples were collected at various times between 1 h and 40 days. The samples were analysed by high performance liquid chromatography with fluorescence detector. Faecal strongyle egg counts (EPG) were performed by a modified McMaster's technique before and at weekly intervals during 10 weeks after treatment. The results indicated that the plasma concentration and systemic availability of IVM was lower but the plasma persistence was prolonged after pour-on administration compared with *per os* route. IVM (paste) reduced the EPG by >95% for 10 weeks, whereas the reduction in pour-on group varied from 82 to 97%. EPG reduction in pour-on group was lower than that of *per os* group. Degradation on the application site, cutaneous biotransformation, binding of IVM to the haircoat and/or sebum are probably responsible for the relatively lower bioavailability of IVM in horses after pour-on administration. In conclusion, the poor plasma availability observed after pour-on administration could result in subtherapeutic plasma concentrations, which may promote the development of drug resistance in parasites.

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1. Introduction

Ivermectin (IVM) was the first macrocyclic lactone anthelmintic, introduced as a veterinary antiparasitic agent in France in 1981. The pharmacokinetic behaviour of IVM has been investigated more extensively than that of the other members of the endectocides and IVM is so far the most widely used endectocide across animal species. IVM is currently marketed as injectable, pour-on (cattle) and oral (sheep, goats, horses) formulations to control endo- and ectoparasites in livestock worldwide.

Ivermectin was first marketed for horses as a micellar formulation containing 20 mg of IVM per ml of sterile

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aqueous solution (2%, w/v) for intramuscular injection. After parenteral administration, rare adverse reactions such as, *Clostridia* spp. infections and anaphylaxis were observed and these undesirable effects were responsible for the withdrawal of the parenteral preparation of IVM for use in the horse in 1984 (Randi, 1984; Campbell et al., 1989). An oral paste formulation of IVM (1.87%) in titanium dioxide and propylene glycol is available in graduated delivery syringes of which each part is designed to administer sufficient IVM (200 μg/kg) for 100 kg of body weight. A liquid formulation of IVM is also marketed for administration by nasogastric intubation in some countries.

Pour-on formulations of anthelmintics decrease the risk of injury for both user and animal and are particularly convenient for farmers who can apply the product easily (Hennessy, 1997). On the other hand, it has been reported that endectocides occasionally cause local irritation, swelling and/or pain at the injection site in different animal species following subcutaneous administration (Geurden et al., 2003; Mavrogianni et al., 2004; Gokbulut et al., 2008). For these reasons, pour-on administration has widely replaced injectable routes in cattle farming practice and has been routinely used to treat many animals worldwide. Thus, this study was designed to determine the potential of pour-on administration as an alternative treatment route in horses. The aim of the study was to investigate the plasma disposition, availability and efficacy of IVM in horses after pour-on and *per os* administrations. Moreover, the hair depletion of IVM at the application and far from the application sites was also examined following pour-on administration.

2. Materials and methods

2.1. Experimental animals

Eighteen female horses weighing 510–610 kg were used in this study. The animals were allocated into three groups (*per os*, pour-on and intravenous groups) of six such that the pre-treatment mean egg count and mean weight of animals in each group was similar. They were housed and fed with wheat straw and barley. Water was supplied *ad libitum*. This study was approved by Animal Ethic Committee of Uludag University.

2.2. Treatments and sampling

The paste formulation of IVM for horses (Ivomec® paste, 1.87% w/v, Merial, Germany) was administered orally as a single bolus dose on the back of the tongue of each in the *per os* group at 0.2 mg/kg bodyweight (BW). The extra label administration of pour-on and injectable formulations of IVM licensed for cattle was used in horses in the present study. The pour-on formulation of IVM (Ivomec® pour-on, 0.5% w/v, Merial, Germany) was administered topically at the dose rate of 0.5 mg/kg BW along the midline of the back of horses. The injectable formulation of IVM (Ivomec® injectable, 0.1% w/v, Merial, Germany) was administered intravenously at a dose rate of 0.2 mg/kg BW. Heparinized blood samples were collected by jugular venipuncture prior to drug administration then at 1, 2, 4, 8, 12, 16, 24, 32, 48, 72, 96 and 120 h and 6, 8, 10, 12,15, 20, 25, 30, 35 and 40 days.

Hair samples (>0.01 g) were also collected from both application site and far from the application site (from the chest of each animal) with tweezers throughout the blood sampling period in order to determine haircoat depletion of IVM. To prevent crosscontamination, gloves were used and the tweezers were washed with methanol after each hair sampling. Blood samples were centrifuged at $2000 \times g$ for 30 min and plasma was transferred to plastic tubes. All the plasma and hair samples were stored at −20 °C until the estimation of drug concentration.

2.3. Analytical procedure

A stock solution (100 μg/ml) of pure standard of IVM (Sigma, St. Louis, MO, USA) was prepared using acetonitrile (Sigma, St. Louis, MO, USA) as the solvent. This was diluted to give 5, 10, 100, 200 and 500 ng/ml and 0.5, 1, 5, 10 and 50 μg/ml standard solutions for plasma and hair samples, respectively for calibration as standard curves and to add to drug-free plasma and hair samples to determine the recovery.

The plasma concentrations of IVM were analysed by high performance liquid chromatography (HPLC) with fluorescence detection following solid phase extraction (SPE) procedure according to a previously described method Demontigny et al. (1990) and Alvinerie et al. (1995) and the hair samples were analysed by HPLC with a liquid–liquid phase extraction procedure adapted from that described by Scott and McKellar (1992).

Briefly, drug-free plasma samples (0.5 ml) were spiked with IVM standard to reach the following final concentrations: 0.25, 0.5, 1, 10, 25 and 50 ng/ml. The plasma samples (spiked and experimental) were combined with 50 μl of internal standard (moxidectin, 250 ng/ml) and then mixed with 0.5-ml acetonitrile. After mixing for 5 min, the solvent–sample mixture was centrifuged at $10\,000 \times g$ for 10 min. The supernatant was transferred to a C_{18} SPE cartridge (500 mg/6 ml, AccuBOND, Agilent, Waldron, Germany) previously conditioned with 2 ml methanol and 2 ml deionised water. The cartridge was washed with 2 ml of water/methanol (3:1) and dried under vacuum for 1 h. The analytes were eluted with 3 ml of methanol and concentrated to dryness at 45 °C in a sample concentrator (Maxi-dry plus, Heto Lab. Equipment, Denmark). The reconstitution was done using 100 ml of a solution of N-methylimidazole in acetonitrile (1:1). Derivatization was initiated by adding 150 ml trifluoroacetic anhydride solution in acetonitrile (1:2). After completion of the reaction, an aliquot (50 μl) of this solution was injected directly into the chromatograph.

The mobile phase consisted of acetonitrile and methanol (66:34, v/v) and was delivered (1100 Series QuatPump, Agilent, Waldron, Germany) at a flow rate of 1.3 ml/min. A nucleosil C_{18} analytical column (Luna, 3 μm, 150 mm × 4.6 mm, Phenomenex, Macclesfield, Cheshire, UK) with nucleosil C_{18} guard column (Phenomenex, Macclesfield, Cheshire, UK) was used for the analysis of the molecules. Fluorescence detection (1100

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