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Gastrointestinal parasitism reduces the plasma availability of doramectin in lambs

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Abstract

A study was undertaken to investigate the effect of parasitism on plasma availability and pharmacokinetic behaviour of doramectin (DRM) in lambs. Fourteen parasitised grey face Suffolk lambs (26.9 ± 1.5 kg bodyweight) were selected for the study. Seven pairs of lambs were allocated to two groups to obtain an approximately even weight distribution. Group I (non-parasitised) was pre-treated with three repeated administrations of 5 mg/kg fenbendazole to maintain a parasite free condition. In group II (parasitised), the lambs did not receive any anthelmintic treatment. After the 85-day pre-treatment period, both groups of animals were treated with DRM by subcutaneous (SC) injection in the shoulder area at 200 μg/kg. Throughout the experimental period, both groups were maintained together under similar feeding and management conditions. Blood samples were collected by jugular venepuncture at different set times between 0.5 h and 60 days post-treatment. After plasma extraction and derivatisation, samples were analysed by high performance liquid chromatography (HPLC) with fluorescence detection. A computerised kinetic analysis was performed and the data were compared using the Student's paired *t* test.

The parent molecule was detected in plasma between 30 min and either day 20 (parasitised) or day 35 (non-parasitised) post-DRM treatment. The AUC values of the parasitised group (143.0 ± 18 ng d/mL) were significantly lower ($P < 0.05$) than those observed in the parasitically naïve animals (229.6 ± 21.7 ng d/mL). The mean residence time (MRT) in the parasitised group (3.4 ± 0.3 days) was significantly shorter ($P < 0.05$) than in the healthy group (6.6 ± 0.6 days). Study results have shown that parasitic disease, through alteration in the body condition, can produce significant changes in the plasma disposition of DRM when administered SC to parasitised lambs.

Keywords: Doramectin; Pharmacokinetics; Anthelmintics; Parasitised lambs

1. Introduction

Verminous gastroenteritis is an endoparasitosis that principally affects young ruminant animals by reducing their ability to absorb and efficiently utilise nutrients causing anorexia and weight loss (Garriz et al., 1987). Nematode infections are a major cause of economic loss in ruminants throughout the world (Holmes, 1987) and the administration of anthelmintics is the most common method used by farmers to control endoparasites. Recent developments for use in cattle include various forms of slow-release boluses and dermal and injectable preparations, although oral drenches are still used to treat a large percentage of cattle and are still almost exclusively used in sheep (Taylor et al., 1992). Chemotherapy continues to serve as the cornerstone of parasite control, but anti-parasitic compounds constitute a

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limited resource and their future will be impacted by a variety of factors including the development of parasite resistance.

Macrocyclic lactones, commonly referred to as endectocides, have been used to treat parasitism in livestock for almost two decades. During this period, there has been significant improvement in their chemistry resulting in increasing potency and duration of action. The combination of low dose rate, convenient formulation, high potency, unique biochemical action and pharmacokinetic behaviour, all conductive to prolonged availability in the parasitised animal, make macrocyclic lactone endectocides a very attractive "*drug of choice*" (Hennessy, 1999).

Doramectin is a broad-spectrum macrocyclic lactone endectocide belonging to the avermectin class family of compounds. In ewes, the injectable doramectin solution is indicated for the treatment and control of several species of gastrointestinal roundworms, lungworms, eyeworms, sucking lice and mange mites following a subcutaneous (SC) or intramuscular (IM) administration of 200 μg/kg (Taylor, 1999; Dorchies et al., 2001; Simon and Fergusson, 2004). The persistent anti-parasitic efficacy of doramectin has been attributed to the combination of inherent potency and an extended plasma pharmacokinetic profile (Owens and Schneider, 2000).

Anthelmintics are thoroughly tested before licensing, and consequently their pharmacokinetic behaviour, plasma concentrations after administration of therapeutic doses and tissue residues are known. Most pharmacokinetic experiments are performed on housed animals that are fed hay and, if necessary, a small additional concentrate ration, to facilitate the frequent blood sampling required. The pharmacokinetic data obtained are assumed to indicate what will happen with the same dose under field conditions, where most parasitological trials take place (Taylor et al., 1992). However, parasitism, through the changes induced in the nutritional status of host animals, may induce changes in adipose tissue deposition and in body fluid dynamics. Such changes are likely to affect the distribution pattern, plasma protein binding, and the efficacy of anthelmintic compounds (Lanusse and Prichard, 1993).

Pharmacodynamics may be thought of as the nexus of efficacy and pharmacokinetics. Attaining a therapeutic effect requires that a drug be in the right place for an adequate time and in a sufficient concentration to exert the desired response (Geary et al., 1999). There is evidence that changes in the pharmacokinetic behaviour and metabolism of anthelmintics may result in reduced clinical efficacy and facilitate selection for resistant strains. The understanding of factors affecting the pharmacology of anthelmintics in animal production is crucial for parasitic control optimisation (Lanusse and Prichard, 1993).

Like other avermectins, doramectin disposition is due to its high lipophilicity characterised by a long residence time and large distribution volume due to drug accumulation in fat and other tissues. The aim of the present study was to elucidate the effect of gastrointestinal parasitism on the pharmacokinetic behaviour of doramectin when administered SC to lambs.

2. Materials and methods

Fourteen grey-face Suffolk lambs, aged between 3 and 4 months and 26.9 ± 1.5 kg bodyweight, were selected for the study. During the experimental period the lambs were maintained together, outdoors during the day and housed at night. They were fed daily with a rye grass and clover hay mix and a supplementary concentrate. Water and hay were provided ad libitum. They also had access to a paddock with a natural grass pasture. All lambs were weighed before the treatments by a digital scale. A serum clinical biochemistry panel including hepatic function tests was performed to evaluate the animals' health, and all values were within the normal ranges described for the ovine species under basal conditions (Meyer et al., 1992).

To identify the natural infection level, faecal examinations were performed on all lambs to determine faecal egg counts (FEC). Quantitative pre- and post-treatment FEC were performed using a modified McMaster technique (Zajac, 1994) during a 90-day period prior to and a 70-day period after ivermectin treatment. All faecal samples were obtained from the rectum during the 7-day interval between the two periods. A minimum of 200 eggs per gram (epg) of faeces was established for lamb incorporation into the experimental groups.

Seven pairs of lambs were allocated into two groups equally balanced by body weight and sex. Once the animal pairs were established, their distribution to the experimental groups was performed according to nematode faecal egg count so as to place animals with higher values in the parasitised group. In group I, the animals were treated three times with an oral (PO) administration of 5 mg/kg fenbendazole (Panacur, Intervet) in order to maintain a healthy, parasite-free condition for an 85-day period. As well as good efficacy with the main gastrointestinal sheep nematodes, fenbendazole was selected due to its faster elimination rate and short persistence of their active metabolite concentrations in plasma after oral administration in sheep (Lanusse et al., 1995). Considering these characteristics, we assumed that fenbendazole would not produce any effect on the pharmacokinetics of doramectin. In group II (parasitised), infection was sustained by oral inoculation with nematode cultures in the infective stage. A mixed larval inoculum containing approximately 5000 third-stage strongyle larvae (40% *Ostertagia*, 28% *Trichostrongylus*

and 22% *Cooperia*) was orally administered once a week for three weeks. This type of larvae is the most common type of gastrointestinal nematodes in Central-southern Chile. In each inoculation, the same inoculum was used for all animals. This group did not receive any anthelmintic treatment in order to maintain their parasitised condition for the period.

After the 85-day pre-treatment period, both lamb groups were treated with doramectin by SC injection in the shoulder area at 200 μg/kg using a commercially available formulation (Dectomax, Pfizer). During the entire experimental period, both groups were maintained together under similar feeding and management conditions.

2.1. Sampling

Blood samples were collected from the jugular vein into heparinised tubes prior to the treatments and at 0.5, 1.0, 2.0, 4.0, 8.0, 12.0, and 24.0 h and 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 14.0, 16.0, 20.0, 25.0, 30.0, 40.0, 50.0 and 60.0 days post-treatment. Plasma was separated by centrifugation and stored at −18 °C until analysed.

After the treatments, the animals were observed continuously for any sign of adverse reaction during a 4 h period and at least twice daily on the two days following treatment.

2.2. Analytical procedures

Doramectin was assayed by high performance liquid chromatography (HPLC) with fluorescence detection after solid phase extraction according to procedures previously described by Nowakowski et al. (1995).

2.3. Drug extraction and derivatisation

Drug-free plasma samples (1 mL) were fortified with doramectin to reach the following final concentrations of 0.1, 0.5, 1.0, 5.0, 10.0, 25.0 and 50.0 ng/mL. Fortified and experimental plasma samples were homogenised and solid phase extraction was performed after 15 min of incubation at room temperature. Briefly, 1 mL of acetonitrile and 0.25 mL of water were added to 1 mL of plasma. After mixing for 20 min, the samples were centrifuged at 2000*g* for 5 min, and the supernatant transferred to a Supelco C18 cartridge. After washing with water, doramectin was eluted with 1.0 mL MeOH. The eluate was evaporated to dryness under a gentle nitrogen stream, and the residue dissolved in 100 μL of *N*-methylimidazole solution in acetonitrile (1:2 v/v). To initiate the derivatisation, 150 μL of trifluoroacetic anhydride solution in acetonitrile (1:2 v/v) were added. Once the reaction was complete (<30 s), an aliquot (100 μL) of this solution was injected directly into the chromatograph. To avoid photoisomerisation of the derivatives under ambient light conditions (Sklavounos et al., 1994), solutions were stored in amber glassware during HPLC analysis (Nowakowski et al., 1995).

2.4. Chromatographic conditions

The mobile phase consisted of acetic acid (0.2% in water), methanol and acetonitrile (4:32:64, v/v/v) at a flow rate of 1.5 mL/min through a Supelcosil C18 column (3 μm; 4.6 mm i.d. × 150 mm) with fluorescence detection at an excitation wavelength of 383 nm and an emission wavelength of 447 nm (RF .551 Fluorescence detector, Shimadzu).

2.5. Method of calibration

Calibration graphs for doramectin in the range 0.1–50 ng/mL were prepared using drug-free plasma from non-treated lambs. Pooled plasma samples were taken through the procedure, and calibration graphs were plotted using the peak area as a function of analyte concentration. Linear regression analysis was used to determine the slopes and correlation coefficients of the different calibration curves. The extraction efficiency of the drug under study was measured by comparing the peak area from the spiked plasma samples with the peak area resulting from direct injections of standard in methanol carried through the derivation procedure. The inter-assay precision was evaluated by processing replicate aliquots of plasma samples containing known amounts of the drug on different days.

The analytical method used to extract, derivatise and quantify the plasma concentration of doramectin by chromatographic analysis using the fluorescence detector was adequately validated. The regression lines between peak areas and drug concentrations presented correlation coefficients ranging between 0.9973 and 0.999. The mean extraction recovery from plasma was 92.2 ± 2.5% at the spiked concentrations between 0.1 and 50 ng/mL. The inter-assay precision showed variation coefficients of 5.3 ± 1.2%. The method's quantification limit was defined as the lowest concentration that would have a coefficient of variation of <20%, and was found to be 0.1 ng/mL.

2.6. Data analysis

The plasma concentration vs. time curve obtained after treatment in each individual animal was fitted using the PK Solutions computer program (Farrier, 1997) (goodness of fit was evaluated by comparing observed concentration with calculated concentration and residue repartition). A tri-exponential equation resulted in the best-fitting concentration–time curves and was used to describe the plasma disposition kinetics of doramectin:

$$Ct = A_1^{-\alpha t} + A_2^{-\beta t} - A_3^{-k_a t},$$

where A_1, A_2 and A_3 are the zero-time intercepts, C is the plasma concentration at time t, k_a is the first-order rate constant of doramectin absorption, and α and β are the first-order rate constants for distribution and elimination, respectively. The terminal (elimination) half-life ($t_{1/2\beta}$) and absorption half-life ($t_{1/2}k_a$) were calculated as $\ln 2/\beta$ and $\ln 2/k_a$, respectively. The peak concentrations (C_{max}) and time-to-peak concentrations (T_{max}) were read from the plotted concentration–time curve of each drug in each individual animal. The area under the plasma concentration–time curves (AUC) from time zero to the last time t with a measurable concentration (C_p) was calculated using linear trapezoidal approximation. The mean residence time (MRT) was calculated by the linear trapezoidal rule without extrapolation to infinity, using the formula (Riviere, 1999)

$$\mathrm{MRT} = \frac{\mathrm{AUMC}}{\mathrm{AUC}},$$

where AUMC is the area under the first moment curve and AUC is the area under the plasma concentration time curves, as previously defined. Total body clearance (Cl_B) was calculated by: $Cl_B = \mathrm{dose/AUC}$. Since the intravenous (IV) route was not used, the Cl_B values represent their true values divided by availability and expressed as Cl_B/F (bioavailability (F) values were not estimated and the Cl_B values are expressed with respect to systemic bioavailability (Lanusse et al., 1997).

The pharmacokinetic parameters are reported as means ± SEM and were statistically compared using Student's paired t test. Prior to the statistical analysis, the AUC values were transformed to a Neperian logarithm. Mean values were considered significantly different at $P < 0.05$.

3. Results

Faecal eggs counts (FEC) for the lambs are shown in Fig. 1. At the beginning of the assays, both animal groups presented similar faecal egg count values. The effect of anthelmintic pre-treatment with fenbendazole was effective and significantly reduced the FEC in lambs of group I in comparison with group II animals, in which an increase in the number of parasite eggs in faeces was observed (Fig. 1).

At the beginning of the experimental period, the mean body weight of lambs was 26.9 ± 1.5 kg in group I, and 27.2 ± 1.4 kg for group II. A significant increase in body weight was observed in group I lambs (34.8 ± 1.8 kg), which were maintained parasite-free throughout the pre-treatment with fenbendazole, in comparison to the body weight observed in the group II (28.7 ± 1.8 kg) of the parasitised animals. These differences were maintained after a 60-day period of

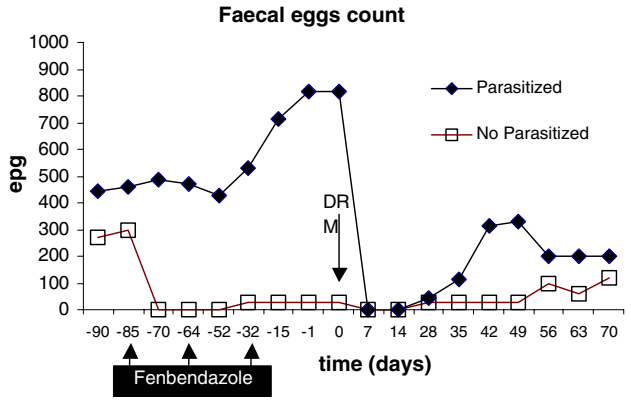

Fig. 1. Geometric mean of faecal egg counts in the two lamb groups before and after subcutaneous administration of doramectin (DRM).

doramectin treatment, where values of 44.6 ± 1.6 and 41.6 ± 1.9 kg were observed in group I and the parasitised lambs, respectively.

The mean plasma concentrations of doramectin obtained in the two lamb groups are shown in Fig. 2. Concentrations >0.1 ng/mL (quantification limit) were detected in plasma between 0.5 h and either 35 (group I) or 20 (group II) days post-doramectin treatment. The comparison of the time period during which doramectin plasma concentrations remained above 1 ng/mL is shown in Fig. 3.

The pharmacokinetic parameters that describe doramectin disposition after SC administration of 200 μg/kg in both lamb groups are shown in Table 1. A slower absorption rate was observed in the parasite-free lambs of group I, and these differences were significant ($P < 0.05$). However, no significant differences were observed for the values of C_{max}.

Parasitism induced clear modifications in doramectin disposition, which is reflected in the shape of the time

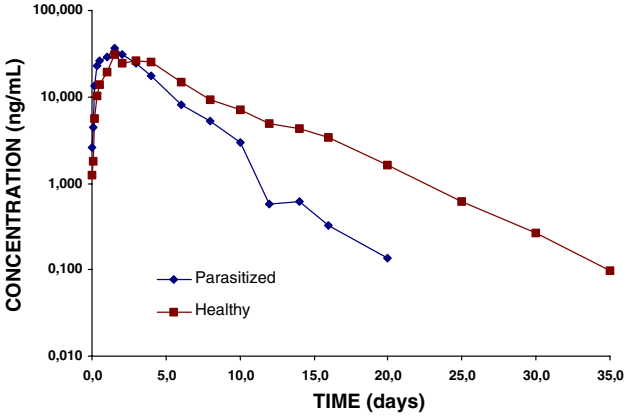

Fig. 2. Means ± SEM) plasma doramectin concentrations (ng/mL) following subcutaneous administration in healthy and parasitised lambs.

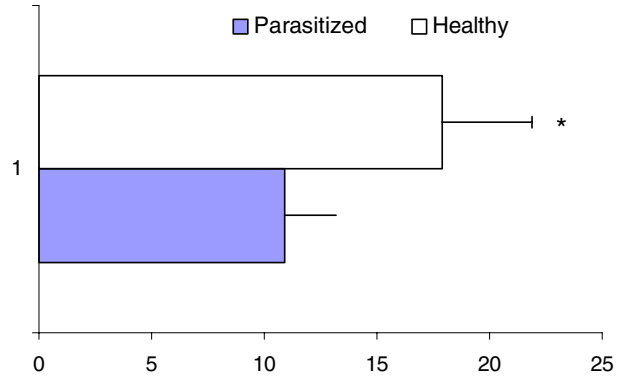

Fig. 3. Comparative time periods in which the plasma doramectin concentrations (ng/mL) remained >1 ng/mL following subcutaneous administration in healthy and parasitised lambs; $^{*}P < 0.05$.

Table 1
Plasma pharmacokinetic parameters (means ± SEM) of doramectin, at 200 μg/kg body weight after subcutaneous administration in healthy and parasitised lambs

Parameter	Non-parasitised	Parasitised	*P* value
Body weight (kg)	34.8 ± 1.8	28.7 ± 1.4	0.036*
Dose (μg/kg)	200	200	
$t_{1/2}k_a$ (h)	32.5 ± 4.9	15.9 ± 2.2	0.034*
C_{max} (ng/mL)	33.9 ± 2.0	38.4 ± 0.8	0.433
T_{max} (d)	2.7 ± 0.4	1.64 ± 0.2	0.067
$t_{1/2\beta}$ (days)[a]	4.0 ± 0.5	2.0 ± 0.3	0.01**
AUC-C-last (ng d/mL)	229.6 ± 21.7	143.0 ± 18.0	0.011*
AUMC (ng d^2/mL)	1540 ± 254	442.5 ± 31	0.004**
MRT-C-last (days)	6.6 ± 0.6	3.4 ± 0.3	0.005**
Cl_B/F (mL/kg d)	913 ± 82	1347 ± 119	0.046*

$t_{1/2}k_a$, absorption half-life; C_{max}, peak plasma concentration; T_{max}, time to peak plasma concentration; AUC-C-last, area under the concentration time curve from t_0 to the last measurable concentration (C-last); $t_{1/2\beta}$, terminal half-life; Cl_B/F, body clearance.
MRT-C-last, mean residence time from t_0 to the last measurable concentration.
[a] Values represent the arithmetic mean for $t_{1/2}k_a$ and $t_{1/2\beta}$ (days).
* Significant at $P < 0.05$.
** Significant at $P < 0.01$.

concentration curve (Fig. 2) and in the principal pharmacokinetic parameters (Table 1). The AUC values of the parasitised group (143.0 ± 18 ng d/mL) were significantly lower ($P < 0.05$) than those observed in the parasite naive group (229.6 ± 21.7 ng d/mL). These changes were associated with a higher body clearance ($P < 0.05$) and a twofold decrease in the elimination half-life ($t_{1/2\beta}$) in the parasitised group. The mean residence time (MRT) in the parasitised group (3.4 ± 0.3 days) was significantly ($P < 0.05$) shorter than in the healthy group's MRT (6.6 ± 0.6 days).

4. Discussion

It is well known that a common feature of gastrointestinal nematode infections is a reduction in voluntary food intake, which is widely recognised as a major factor in the pathogenesis of such infections (Holmes, 1987). Gastrointestinal parasitosis is responsible for serious decreases in individual growth efficiency and protein metabolism in growing animals most affected by this disease with muscle mass and, to a lesser extent, fat seriously reduced in affected animals (Entrocasso, 1987).

The results of the current study indicate that while the non-parasitised group increased significantly in their body weight, the parasitised lambs remained at values similar to those observed previously at the beginning of the assay (day – 85). Probably, these body weight differences indicate important differences in the body composition of parasitised lambs. Indeed, it is probable that the body weight changes observed in parasitised lambs can have a significant influence on doramectin's pharmacokinetic profile, considering that avermectins are highly lipophilic drugs with a high affinity for body fat.

Doramectin is a highly lipid-soluble drug that is formulated as an oil-based preparation containing sesame oil/ethyl oleate (90:10) that produces lower and later peak concentrations with more persistent plasma levels when the formulation is injected by the SC route in cows, than with a micelle aqueous solution by the same route (Wicks et al., 1993).

A significant decrease in the absorption half-life was observed in the parasitised lambs indicating a faster absorption rate in these animals. It has been demonstrated that the low solubility of the avermectin anthelmintic group in water and its deposition in SC fat favour slow absorption from the injection site and provide a prolonged duration in the bloodstream (Lanusse et al., 1997). The slow absorption process from the injection site is pivotal to the persistence of doramectin administered in oil vehicles (Nowakowski et al., 1995). Thus, the absorption rate from the SC space appears to be the rate-limiting step in the disposition of doramectin after SC administration of the commercial formulation (Atta and Abo-Shihada, 2000). Consequently, it is possible that the low SC fat content in the parasitised lambs reduced the time of doramectin's persistence at the injection site. These results agree with those described by Craven et al. (2002) who found a faster absorption rate and a lower systemic availability of ivermectin in thin pigs when compared to fat pigs. Similarly, the persistent efficacy of moxidectin against *Ostertagia circumcincta* injection was reduced in sheep with low body fat reserves (Rolfe et al., 1995).

The results of the present study have demonstrated that parasitism induced significant changes in doramectin's disposition and availability, which are associated with a significantly higher drug clearance than in the non-parasitised animals. These changes were consistent with a shorter elimination half-life of the drug in the terminal phase of the concentration–time curve. As a consequence of the faster doramectin elimination rate in the

parasitised lambs, there was a significant reduction in the plasma availability measured as the AUC values. These results are similar to those found by Lespine et al. (2004) in parasitised lambs treated with SC moxidectin.

The resulting concentration–time curve and the pharmacokinetic parameters suggest that the parasite-infected animals were exposed to less drug compared to the parasite naïve animals, a conclusion that is similar to the results found by Echeverría et al. (2002) in mange-infected sheep, and by Lespine et al. (2004) for lambs with gastrointestinal parasitism. According to these authors, the low drug concentration observed during infection of parasitised animals may be the result of a higher elimination rate associated with an increase in drug biotransformation.

The clinical efficacy of anti-parasitic drugs is closely related to pharmacokinetic behaviour. The length of time during which therapeutic concentrations are maintained at the parasite location, is a relevant factor in persistent anti-parasitic efficacy (Lanusse and Prichard, 1993). The prolonged persistence of doramectin, abamectin and ivermectin contributes to the achievement of drug concentrations in target tissues, where the sustained attainment of drug levels toxic to the parasites is critical for the resulting efficacy (Lifschitz et al., 2004). There is a high correlation between doramectin concentrations measured in plasma and those achieved in the tissues where parasites are located (Lifschitz et al., 2000).

Endectocide molecules paralyse the pharyngeal pumping activity and also produce paralysing effects on the somatic musculature (Geary et al., 1993). Based on pharmacological in vitro assays (Geary et al., 1993; Gill and Lacey, 1998), the theoretical assumption that plasma concentrations >1 ng/mL would be indicative of the minimal drug concentration required for optimal anti-parasitic activity against some endoparasites may be adopted (Lifschitz et al., 2004). According to the results found in the current study, plasma concentrations >1 ng/mL were maintained for a period of 10.9 days in the parasitised group, while in the non-parasitised animals these values were maintained for 17.9 days. These results indicate greater prolonged drug persistence in non-parasitised animals, which is consistent with higher average MRT values for this group. The short residence time of the drug observed in infected animals may contribute to reducing the long-term efficacy of the endectocide. We did not perform serum clinical biochemistry panel or hepatic function tests or look at the long-term efficacy of endectocides. Consequently, reinfection may occur more rapidly when the drug is given to heavily infected animals (Lespine et al., 2004).

Avermectins are highly lipophilic drugs that are extensively distributed from the bloodstream to different tissues. A large distribution volume (7.6 L/kg) has been reported after IV administration of doramectin in sheep (Gottschall, 1997). The high lipid solubility of doramectin facilitates their deposition in adipose tissue. In sheep, the large fat reservoir may contribute to the long persistence of doramectin in plasma at low concentrations probably due to the low blood supply to the fat tissues (Atta and Abo-Shihada, 2000). Therefore, the lower plasma availability of doramectin in parasitised lambs could be attributed to reduced fat reserves of these animals in comparison with the non-parasitised lambs. These differences could explain the faster rate of drug elimination from the body of parasitised animals, based on the differences observed in the values of the elimination half-life and clearance between the two animal groups.

Large molecular weight drugs such as the endectocide compounds are excreted in bile rather than in the urine (Baggot, 1992). As has been demonstrated for sheep, a significant portion of the systemically available doramectin is secreted through bile, reabsorbed and enterohepatically recycled (Hennessy et al., 2000). Moreover, Laffont et al. (2002) proposed the possibility of an intestinal secretion mechanism for ivermectin through the gut wall. Studies performed in rats by these authors, using an intestinal closed-loop model, have demonstrated that the amount of the ivermectin parent drug actively secreted into the small intestinal lumen was five times higher than the amount eliminated in bile (Laffont et al., 2002).

Parasitism is also associated with increased intestinal secretions and gut motility (Lespine et al., 2004). Host physiopathological changes induced by parasitism on gastrointestinal mucosa and tissues may significantly influence the rate of drug elimination in comparison with non-parasitised animals. Diarrhoea is commonly reported in parasitised ruminants and especially in pasture-grazing ruminants. In experimental infections, increases in the faecal water content producing frank diarrhoea have been reported with moderate to heavy infections produced by all of the important gastrointestinal nematodes. In abomasal infections with *Ostertagia* spp., the onset of diarrhoea has been found to coincide with the maturation of larval into young adults (Holmes, 1987). These changes may contribute to the increased clearance of doramectin seen in the parasitised lambs in the present study.

In summary, from the pharmacokinetic point of view, the greatest difference between the two groups of animals was in the area under the plasma concentration–time curve, which was 37.7% lower for the parasitised group than for the non-parasitised lambs. The difference can be attributed to the following factors: (1) faster absorption rate; (2) increased plasma clearance; (3) reduction in the elimination half-life and, speculatively, (4) a reduction in the apparent volume of distribution.

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References

Atta, A.H., Abo-Shihada, M.N., 2000. Comparative pharmacokinetics of doramectin and ivermectin in sheep. Journal of Veterinary Pharmacology and Therapeutics 23, 49–52.

Baggot, J.D., 1992. Disposition and fate of drugs in the body. In: Booth, N.H., McDonald, L.E. (Eds.), Veterinary Pharmacology and Therapeutics, sixth ed. Iowa State University Press, Ames, pp. 38–71.

Craven, J., Bjorn, H., Hennessy, D.R., Friis, C., 2002. The effect of body composition on the pharmacokinetics of subcutaneously injected ivermectin and moxidectin in pigs. Journal of Veterinary Pharmacology and Therapeutics 25, 227–232.

Dorchies, P., Jacquiet, P., Bergaud, J.P., Duranton, C., Prevot, F., Alzieu, J.P., Gossellin, J., 2001. Efficacy of doramectin injectable against Oestrus ovis and gastrointestinal nematodes in sheep in southwestern region of France. Veterinary Parasitology 96, 147–154.

Echeverría, J., Mestorino, N., Errecalde, J., 2002. Comparative pharmacokinetics of ivermectin after its subcutaneous administration in healthy sheep and sheep infected with mange. Journal of Veterinary Pharmacology and Therapeutics 25, 159–160.

Entrocasso, C.M., 1987. Economic impact of gastrointestinal verminosis in temperate climates areas of South America with special reference to Argentina. In: Proceedings of the XXIII World Veterinary Congress, Montreal, Que., Canada, pp. 53–58.

Farrier, D., 1997. PK Solutions. Non-Compartmental Pharmacokinetics Data Analysis. User Guide. Summit Research Services, Ashland, OH, USA, pp. 1– 50.

Garriz, C.A., Touraille, C., Steffan, P., Fiel, C.A., Ambrustolo, R.R., Biondani, C.A., Zamorano, M., Bulman, G.M., 1987. Gastrointestinal parasitism: its effects on muscle, fat and bone composition of the carcass and organoleptic characteristics of meat. In: Leaning, W.H.D., Guerrero, J. (Eds.), The Economic Impact of Parasitism in Cattle. Proceedings of XXIII World Veterinary Congress, Montreal, Que., Canada, pp. 59–68.

Geary, T.G., Sims, S.M., Thomas, E.M., Vanover, L., Davis, J.P., Winterrowd, C.A., Klein, R.D., Ho, N.F.H., Thompson, D.P., 1993. Haemonchus contortus: ivermectin-induced paralysis of the pharynx. Experimental Parasitology 77, 88–96.

Geary, T.G., Sangster, N.C., Thompson, D.P., 1999. Frontiers in anthelmintic pharmacology. Veterinary Parasitology 84, 275–295.

Gill, J.H., Lacey, E., 1998. Avermectin/milbemycin resistance in trichostrongylid nematodes. International Journal for Parasitology 28, 863–877.

Gottschall, D.W., 1997. A comparison of the pharmacokinetics and tissue residues of doramectin after intravenous and intramuscular administration in sheep. In: Proceedings of 16th International Conference of the World Association for the Advancement of Veterinary Parasitology, Sun City, South Africa, 13 August, pp. 9–19.

Hennessy, J.D., 1999. Endectocides: spectrum of efficacy and mechanism of action. In: Proceedings of XXVI World Veterinary Congress, Lyon, France, 23–26 September.

Hennessy, D., Page, S.W., Gottschall, D.W., 2000. The behaviour of doramectin in the gastrointestinal tract, its secretion in bile and pharmacokinetic disposition in the peripheral circulation after oral and intravenous administration to sheep. Journal of Veterinary Pharmacology and Therapeutics 23, 203–213.

Holmes, P.H., 1987. Pathophysiology of nematode infection. International Journal for Parasitology 17, 433–451.

Laffont, C.M., Toutain, P.L., Alvinerie, M., Bousquet-Melou, A., 2002. Intestinal secretion is a major route for parent ivermectin elimination in the rat. Drug Metabolism and Disposition 30, 626–630.

Lanusse, C., Prichard, R.K., 1993. Relationship between pharmacological properties and clinical efficacy of ruminant anthelmintics. Veterinary Parasitology 49, 123–158.

Lanusse, C., Gascon, L.H., Prichard, R.K., 1995. Comparative plasma disposition of albendazole, fenbendazole, oxfendazole and their metabolites in adult sheep. Journal of Veterinary Pharmacology and Therapeutics 18, 196–203.

Lanusse, C., Lifschitz, A., Virkel, G., Alvarez, L., Sánchez, S., Sutra, J.F., Galtier, P., Alvinerie, M., 1997. Comparative plasma disposition kinetic of ivermectin, moxidectin and doramectin in cattle. Journal of Veterinary Pharmacology and Therapeutics 20, 91–99.

Lespine, A., Sutra, J.F., Dupuy, J., Alvinerie, M., Aumont, G., 2004. The influence of parasitism on the pharmacokinetics of moxidectin in lambs. Parasitology Research 93, 121–126.

Lifschitz, A., Virkel, G., Sallovitz, J., Sutra, J.F., Galtier, P., Alvinerie, M., Lanusse, C., 2000. Comparative distribution of ivermectin and doramectin to parasite location tissues in cattle. Veterinary Parasitology 87, 327–338.

Lifschitz, A., Sallovitz, J., Imperiale, F., Pis, A., Jauregui Lorda, J., Lanusse, C., 2004. Pharmacokinetic evaluation of four ivermectin generic formulations in calves. Veterinary Parasitology 119, 247–257.

Meyer, D., Coles, E., Rich, L., 1992. Veterinary Laboratory Medicine. Interpretation and Diagnosis. W.B. Saunders, Philadelphia, p. 331.

Nowakowski, M., Lynch, M., Smith, D., Logan, N., Mouzin, D., Lukaszewicz, J., Ryan, N., Hunter, R., Jones, R., 1995. Pharmacokinetics and bioequivalence of parenterally administered doramectin in cattle. Journal of Veterinary Pharmacology and Therapeutics 18, 290–298.

Owens, J., Schneider, R.P., 2000. The metabolism of doramectin in cattle microsomes. In: Proceedings of the 8th International Congress of the European Association for Veterinary Pharmacology and Toxicology, Jerusalem, Israel, July 30–August 3, p. 115.

Riviere, J.E., 1999. Comparative Pharmacokinetics: Principles, Techniques and Applications. Iowa State University Press, Ames, Iowa, pp. 148–167.

Rolfe, P.F., Loughling, J., Nichols, K., Montgomery, J., 1995. Sustained activity and use of moxidectin against intestinal parasites in sheep. In: Proceedings of the Australian Sheep Veterinary Society, Melbourne, Australia, May 1995, pp. 133–136.

Simon, A.J., Fergusson, E.G., 2004. Dectomax injectable solution for cattle and sheep. Veterinary Record 154, 341.

Sklavounos, C., Dmers, N., Lukaszewicks, Nowakowski, M., 1994. Photoisomerization of aromatic doramectin derivatives. Journal of Agricultural and Food Chemistry 42, 1228–1231.

Taylor, M., 1999. Use of anthelmintics in sheep. In Practice 21, 222–231.

Taylor, S.M., Mallon, T.R., Blanchflower, W.J., Kennedy, D.G., Green, W.P., 1992. Effects of diet on plasma concentrations of oral anthelmintics for cattle and sheep. Veterinary Record 130, 264–268.

Wicks, S.R., Kaye, B., Weatherley, A.J., Lewis, D., Davidson, E., Gibson, S.P., Smith, D.G., 1993. Effect of formulation on the pharmacokinetics and efficacy of doramectin. Veterinary Parasitology 49, 17–26.

Zajac, A.M., 1994. Fecal examination in the diagnosis of parasitism. In: Sloss, M.W., Kemp, R.L., Zajac, A.M. (Eds.), Veterinary Clinical Parasitology, sixth ed. Iowa State University Press, Ames, Iowa, pp. 3–93.