Parasitol Res (2003) 89: 120–122
DOI 10.1007/s00436-002-0727-z

ORIGINAL PAPER

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Eprinomectin in goat: assessment of subcutaneous administration

Received: 12 July 2002 / Accepted: 2 August 2002 / Published online: 24 September 2002

Abstract Eprinomectin is only available as a topically applied anthelmintic for dairy cattle. To determine whether eprinomectin can be administered in the goat as an injectable formulation, it was subcutaneously delivered to six goats and measured in the plasma at different times after administration. The area under the concentration-time curve (AUC) reported after subcutaneous administration of 0.2 mg kg^{-1} eprinomectin (68.5 ± 23.2 ng day^{-1} ml^{-1}) was similar to the AUC previously reported for goats after a pour-on administration of 0.5 mg kg^{-1} eprinomectin. Thus, our results clearly show that subcutaneous administration is 2.5 times more effective than pour-on administration, in terms of amount of drug present in the organism. This work should encourage the development of a subcutaneous formulation of eprinomectin and should contribute to defining optimal therapeutic conditions for goat anthelmintic treatment.

Introduction

Among the macrocyclic lactones, eprinomectin (4′-(epiacetylamino)-4′-deoxyavermectin B1) provides an attractive opportunity (Shoop et al. 1996). Because of its partitioning profile between serum and milk (Alvinerie et al. 1999b), it is the only endectocide approved for use during lactation with a zero milk-withdrawal period. However, it is only available as a pour-on formulation marketed for beef and dairy cattle at a dose of 0.5 mg kg^{-1}.

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Resistance to anthelmintics in nematodes is of major concern in small ruminants. Benzimidazole-resistant nematodes have emerged in dairy goats (Chartier et al. 2001), certainly due to the extensive off-label use of benzimidazole in goat at a standard ovine dosage. The requirement for a new anthelmintic with good efficacy for grazing goats caused farmers to use eprinomectin off-label, as they have previously used other anthelmintics. Under-dosage is one of the factors which contribute to the selection of anthelmintic-resistant parasites.

The pharmacokinetic approach provides an efficient and accurate tool to ascertain the presence of the drug in the organism at a concentration and during a time-period compatible with optimal efficacy. Indeed, the therapeutic efficacy of endectocides depends upon the formulation of the dosage form, route of administration, bioavailability, pharmacokinetic behaviour and metabolism patterns. Moreover, subcutaneous administration of endectocides led to higher bioavailability of the drug, compared with a pour-on application (Alvinerie 2001). In addition, a recent study revealed the tremendous anthelmintic potential of eprinomectin against gastrointestinal nematodes in cattle when used as an injectable product (Shoop et al. 2001).

Because until now no pharmacokinetic data have been available concerning injectable eprinomectin, we describe here the eprinomectin disposition in goats after subcutaneous administration.

Materials and methods

Animals and treatment

Six non-lactating female Saanen goats, weighing 46–73 kg, were treated with eprinomectin formulated in a propylene glycol/glycerol formal (60:40) vehicle as described by Shoop et al. (2001), injected subcutaneously (0.1 ml kg^{-1}) at a dosage of 0.2 mg kg^{-1}. Plasma samples were prepared from blood collected from the jugular vein into heparinized vacutainer tubes at 0 (pre-treatment) 0.04, 0.08, 0.16, 0.33, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 13, 15, 20 and 26 days after drug administration.

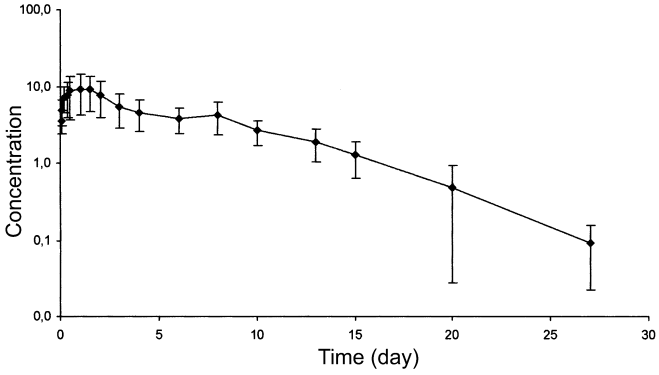

Fig. 1 Concentration-time profile of eprinomectin in the plasma of goats ($n=6$), following subcutaneous administration of eprinomectin at 0.2 mg kg^{-1}

Table 1 Selected pharmacokinetic parameters for eprinomectin after subcutaneous administration in goats. Goats received eprinomectin subcutaneously at 0.2 mg kg^{-1}. The drug was analysed in plasma at different times. *AUC* area under the plasma concentration vs time curve, C_{max} Observed peak plasma concentration, *MRT* mean residence time, T_{max} time to reach C_{max}. Pour-on application data are from Alvinerie et al. (1999a, b). All values are means ± SD for six animals

Parameters	Subcutaneous administration (0.2 mg kg^{-1})	Pour-on application (0.5 mg kg^{-1})
C_{max} (ng ml^{-1})	9.96 ± 4.54	5.60 ± 1.01
T_{max} (days)	0.94 ± 0.70	2.55 ± 0.85
AUC units: ng day ml^{-1}	68.50 ± 23.18	72.31 ± 11.15
Tmax and MRT: day	6.61 ± 1.31	9.42 ± 0.43

Drug analysis

Eprinomectin concentration was measured in plasma by HPLC with fluorescent detection, according to the method set up by Sutra et al. (1998).

Pharmacokinetic analysis

The data were subjected to non-compartmental analysis, using the statistical moment approach (Perrier and Mayersohn 1982). The area under the concentration-time curve (AUC) and the mean residence time (MRT) were calculated from $t=0$ to the last measurable concentration (t_{last}), using the arithmetic trapezoidal rule. The peak plasma concentration (C_{max}) and time of peak plasma concentration (T_{max}) were read from the plotted concentration versus time for each animal.

Results and discussion

It is now generally accepted that the effect of drugs administered by the extra-vascular route is better represented by the systemic area under the plasma AUC than by the administered dosage (Gayrard et al. 1999). The mean eprinomectin plasma AUC after subcutaneous injection of 0.2 mg kg^{-1} is reported in Fig. 1. Eprinomectin was detected at the first sampling time (1 h) at a concentration of 0.53 ± 0.42 ng ml^{-1}. In this study performed with non-lactating goats, the systemic AUC calculated was 68.5 ± 23.2 ng day ml^{-1}. A similar AUC value (72.31 ± 11.15 ng day ml^{-1}) was previously reported for non-lactating goats after a pour-on administration of eprinomectin at 0.5 mg kg^{-1} (Alvinerie et al. 1999a). The C_{max} obtained with subcutaneous administration was higher and appeared earlier than with the pour-on application. The MRT was 6.6 ± 1.3 days, not significantly different from the one obtained for pour-on application (Table 1).

Thus, our results clearly show that subcutaneous administration is 2.5-fold more efficient than pour-on administration, in terms of bioavailability. These results are in good agreement with the high anthelmintic potential of the subcutaneous administration of eprinomectin recently reported in cattle. In this study, the lowest efficient dose tested was 0.056 mg kg^{-1}, ten times less than a pour-on dosage (Shoop et al. 2001).

Pour-on administration represents an additional confusing factor that can alter animal exposure to the drug. Pharmacokinetic studies performed in goats using topical administration with eprinomectin at a bovine dose rate revealed a low level of exposure to the drug (Dupuy et al. 2001), with limited efficacy against *Trichostrongylus colubriformis*, a major intestinal nematode in goats (Chartier et al. 1999). Moreover, recent studies performed in cattle have shown that grooming makes the systemic availability for a topical endectocide low and unpredictable (Laffont et al. 2001). The resulting undesirable sub-therapeutic concentrations in both treated and untreated cattle may contribute to the development of drug resistance.

This work provides evidence to encourage the development of a subcutaneous formulation for eprinomectin. In addition, it contributes to defining the optimal therapeutic conditions for goats when treated with eprinomectin.

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