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► **To cite this version:**

M Alvinerie, Jf Sutra, P Galtier. Ivermectin in goat plasma and milk after subcutaneous injection. *Veterinary Research*, 1993, 24 (5), pp.417-421. <hal-00902156>

HAL Id: hal-00902156

<https://hal.science/hal-00902156v1>

Submitted on 11 May 2020

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Original article

Ivermectin in goat plasma and milk after subcutaneous injection

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(Received 18 February 1993 ; accepted 17 June 1993)

Summary — The pharmacokinetics and mammary excretion of ivermectin were determined in goats following a single sc administration (0.2 mg/kg). Kinetic analysis of plasma and milk levels was performed using a 1-compartment model. The maximum plasma concentration of 6.12 ng/ml occurred at 2.85 d ; the half-life of 4.03 d was similar to the value in sheep (3.68 d). Ivermectin was detected in the milk at the first sampling time and thereafter for at least 25 d. Comparison of the milk and plasma data shows the parallel disposition of the drug in milk and plasma with a milk-plasma concentration ratio of 1.08 ± 0.23 . In conclusion, the persistence of the drug in plasma is reflected in the duration of the presence of ivermectin in milk.

ivermectin / plasma / milk / goat

Résumé — Ivermectine dans le plasma et le lait de chèvre après une injection sous-cutanée. La pharmacocinétique et l'excrétion mammaire de l'ivermectine ont été déterminées chez la chèvre après une injection sous-cutanée du médicament (0,2 mg/kg). L'analyse de l'évolution des concentrations dans le plasma et le lait a été réalisée selon un modèle monocompartimental. La concentration maximale plasmatique était de 6,12 ng/ml obtenue 2,85 j après l'injection, la demi-vie était de 4,03 j, ie une valeur comparable à celle obtenue chez le mouton (3,68 j). L'ivermectine a été détectée dans le lait depuis le premier prélèvement et pendant au moins 25 j. La comparaison des paramètres pharmacocinétiques démontre l'évolution parallèle des concentrations dans le lait et le plasma, avec un rapport de $1,08 \pm 0,23$. En conclusion, la lente élimination plasmatique de l'ivermectine est largement reflétée dans la durée de sa présence dans le lait.

ivermectine / plasma / lait / chèvre

INTRODUCTION

Ivermectin (22, 23-dihydroavermectin B1a) is a semi-synthetic derivative of a macrocyclic lactone produced by *Streptomyces avermitilis*. Ivermectin is an exceptionally potent drug with a broad spectrum of activity against gastrointestinal nematodes and lungworms in cattle, horses, goats, dogs and swine (Campbell and Benz, 1984). The pharmacokinetics of the drug differ according to the animal species, formulation and route of administration (Lo *et al*, 1985; Wilkinson *et al*, 1985). It is essential, for a drug that is used so extensively, to assess possible health hazards due to residues. Although ivermectin is not recommended for administration to lactating goats, unconventional use is possible. The present study was designed to compare the pharmacokinetics of ivermectin in plasma and milk of goats receiving a subcutaneous administration. The findings are compared with results obtained by using other routes of administration (Scott *et al*, 1990). In addition, the consequences of the mammary excretion of ivermectin are discussed.

MATERIALS AND METHODS

Animals

Five cross-bred lactating goats (40–59 kg) considered at the end of the lactating period (344–696 ml milk per day) were maintained indoors, and administered ivermectin according to the manufacturer's recommendations (IVOMEC, ovins, MSD, Paris, France) *ie* 0.2 mg/kg injected sc. Samples of blood and milk were collected from each animal at 0.3; 1–7; 9; 11; 13; 15; 17; 19; 21; 23 and 25 d after drug administration. Following centrifugation of blood samples, the plasma was removed and stored at –20°C until analysis. Milk aliquots were collected each morning in glass bottles and transferred to 5-ml tubes stored at –20°C before analysis.

Analysis

Both the plasma and milk samples were analyzed for ivermectin concentration using a previously described method (De Montigny *et al*, 1990). One ml acetonitrile was added to 1 ml plasma or milk. After mixing for 20 min, the solutions were centrifuged at 2 000 *g* for 2 min and the supernatants applied to an Absorbex C18 cartridge pretreated with methanol (2 ml) and water (2 ml). The column was washed with 2 ml H₂O/Me OH (75:25) and ivermectin eluted with 1 ml MeOH. This eluate was evaporated to dryness under a gentle stream of nitrogen, and the dry residue was dissolved in 100 µl *N*-methylimidazole solution in acetonitrile (1:1, v/v). To initiate the derivatization, 150 µl trifluoroacetic anhydride solution in acetonitrile (1:2, v/v) was added. After completion of the reaction (< 30 s), an aliquot (100 µl) of this solution was injected directly into the chromatograph. The mobile phase consisted of acetic acid (0.2% in water) methanol acetonitrile (4:32:64; v/v/v) pumped at a flow rate of 1.5 ml/min through a supelcosil C18 column (3 µm, 4.6 mm id x 150 mm) with fluorescence detection at an excitation wavelength of 365 nm and an emission wavelength of 475 nm (RF 551 fluorescence detector, Shimadzu, Kyoto, Japan).

The limit of quantification of the method was 0.05 ng/ml in plasma and milk, with a coefficient of variation of 4.0% (inter-day variability).

Data analysis

Equation [1] corresponding to a 1-compartment model with an absorption phase was separately fitted to the plasma and milk data.

$$C_{(t)} = A_1^{-\beta t} - A_2^{-ka t} \quad [1]$$

In this equation, A_1 and A_2 are the intercepts, C is the plasma or milk concentration at time t , ka (per min) is the first order rate constant of ivermectin absorption and β (per min) is the first order rate constant for ivermectin elimination.

Pharmacokinetic analysis of the individual animal data were carried out using a program for nonlinear regression analysis adapted for Multi (Yamaoka *et al*, 1978) Statistical comparisons between plasma and milk data were made

by Wilcoxon's test for paired data. P values < 0.05 were considered to be significant.

RESULTS

The mean concentrations of ivermectin in plasma and milk of the 5 goats administered the drug sc are shown in figure 1. Ivermectin increased slowly to reach, after 2.8 d, maximal concentrations of 6.12 and 7.26 ng/ml in plasma and milk, respectively (table I). All concentrations decreased progressively thereafter. The milk/plasma ivermectin ratio determined by using area under the curve (AUC) values was 1.08 ± 0.23 .

Calculated pharmacokinetic parameters are shown in table I. There were no significant differences between plasma and milk parameters. The absorption half-life was 1.2 d, whereas the elimination half-life was ≈ 4 d. Similar values for mean residence

time were obtained in the 2 fluids (7–7.8 d), and the AUC values were similar as well ($60 \text{ ng}\cdot\text{d}\cdot\text{ml}^{-1}$).

DISCUSSION

The results confirm the prolonged persistence of the drug in the plasma. The value of the half-life (4.03 d) is similar to those previously reported (Prichard *et al*, 1986) in sheep (3.68 d) and horses (3.66 d) following a similar sc dose. Concerning the AUC calculation, our value ($57 \text{ ng}\cdot\text{d}\cdot\text{ml}^{-1}$ or $1368 \text{ ng}\cdot\text{h}\cdot\text{ml}^{-1}$) appears 2.8-fold higher than that previously determined in goats following *po* administration of the same dose (Scott *et al*, 1990). Such a difference in the systemic availability of the drug between sc and oral administration has already been described in sheep with a ratio of 2.64 (Marriner *et al*, 1987). This difference in availability of ivermectin was attrib-

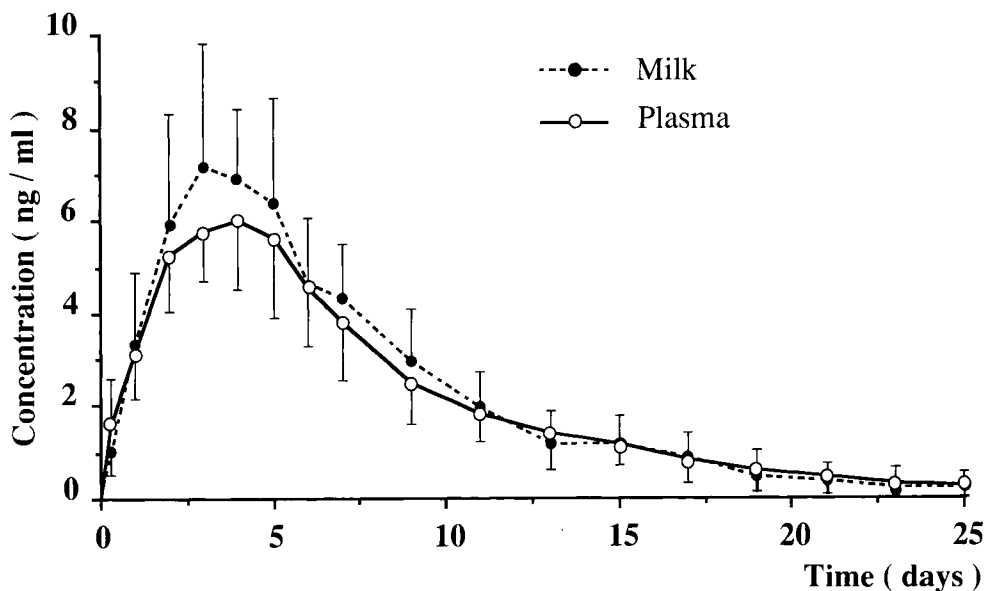


Fig 1. Concentration time profile of ivermectin in plasma (O) and milk (●) in goats following a single sc dose of 0.2 mg/kg.

Table 1. Pharmacokinetic parameters of ivermectin in plasma and milk of 5 goats (mean \pm SD) following a single sc administration (0.2 mg/kg).

Parameters	Plasma	Milk
C_{\max} (ng/ml)	6.12 \pm 1.15	7.26 \pm 1.49
T_{\max} (d)	2.85 \pm 0.89	2.82 \pm 0.36
$t_{1/2\ ka}$ (d)	1.208 \pm 0.580	1.255 \pm 0.215
$t_{1/2\ \beta}$ (d)	4.032 \pm 0.940	3.45 \pm 0.89
MRT (d)	7.85 \pm 1.42	7.06 \pm 1.02
AUC ng•d•ml ⁻¹	59.996 \pm 13.705	60.770 \pm 18.00

C_{\max} : maximal concentration; T_{\max} : time for maximal concentration; $t_{1/2\ ka}$: time of half absorption; $t_{1/2\ \beta}$: time of half elimination; MRT: mean residence time; AUC: area under the curve.

uted to degradation of the drug in the rumen according to Prichard *et al* (1986), who demonstrated that intraabomasal administration of ivermectin to sheep resulted in 100% systemic availability, whereas intraruminal administration resulted in only 25% plasma availability.

Ivermectin is a highly lipid-soluble chemical (Lo *et al*, 1985). Consequently, it is not surprising that it is excreted in milk. In studies using ewes (Marriner *et al*, 1987) or cows (Alvinerie *et al*, 1987; Bogan and Mc Kellar, 1988), the concentration of ivermectin in milk was found to be similar to the plasma concentration, which is in good accordance with our results. Following oral or pour-on administration (Scott *et al*, 1990), the excretion pattern of ivermectin is similar.

Ivermectin could be detected in the milk for 25 d after treatment. The product of ivermectin concentration and individual milk yield during the experiment amounted to an average drug recovery in milk of 0.31 \pm 0.21% of the administered dose. This result can be compared to 4% of the dose in sheep (Marriner *et al*, 1987) and 5.46% in cows (Toutain *et al*, 1988). This large dif-

ference appears to be related to differences in the volume of milk produced in the various species, or to fat content of the milk.

In conclusion, the presence and persistence of ivermectin residues in milk deserve attention. Ivermectin acts mainly on γ -amino-butyric acid (GABA)-mediated nerves which are mainly present in the central nervous system of mammals (Campbell *et al*, 1983). This drug appears to be generally safe, however, since it does not readily cross the adult blood-brain barrier. The safety margin in target species is, therefore, \approx 10-fold greater than the recommended therapeutic dose (Bennet, 1986). Nevertheless, attention must be paid to factors affecting the blood-brain barrier permeability, in terms of species (Hoy *et al*, 1990) or age differences, particularly in the newborn in which this physiological barrier is known to be poorly developed. Consequently, the potential use of ivermectin in developing countries in which prolonged breast feeding is frequent should encourage a thorough analysis of ivermectin in human milk to assess its toxicological significance.

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