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Short note

Plasma profile study of moxidectin in a cow and its suckling calf

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Summary — The plasma concentration of moxidectin, a macrocyclic lactone endectocide, was investigated in a cow and its suckling calf, using a new chemical assay, following subcutaneous injection (0.2 mg/kg) in the cow. The most striking result was the persistence of moxidectin in the plasma of the cow (mean residence time: 25.66 days). Moxidectin was also detected in the plasma of the calf as a result of the excretion of the drug in the cow's milk and its ingestion by the calf. The cow and calf plasma concentrations and pharmacokinetic parameters showed parallel disposition of the drug. The suckling calf received about 5% of the dose from the cow via the milk.

moxidectin / cow / calf / plasma / milk

Résumé — Étude pharmacocinétique de la moxidectine chez la vache allaitante et son veau. *Les concentrations plasmatiques de moxidectine (endectocide de la famille des lactones macrocycliques) ont été mesurées chez une vache et son veau après une injection sous-cutanée (0,2 mg/kg) à la vache. Le résultat le plus important de cette étude concerne la rémanence importante de la moxidectine dans le plasma (temps moyen de résidence : 25,66 jours). De plus, la présence de moxidectine dans le plasma du veau révèle à la fois l'excrétion mammaire de la moxidectine, et son absorption par le veau. La comparaison des paramètres pharmacocinétiques de la vache et du veau démontre un devenir parallèle du médicament ; la quantité de moxidectine reçu par le veau représente environ 5 % de la dose totale administrée à la vache.*

moxidectine / vache / plasma / lait

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INTRODUCTION

The macrocyclic lactone moxidectin is an endectocide which is closely related to the milbemycins. It originates from the actinomycete *Streptomyces cyaneogriseus non cyanogenus*. Developed by American Cyanamid Company it is proposed as an endectocide for livestock (Craig et al, 1992; Steel, 1993; Uriarte et al, 1994). Moxidectin metabolism in cattle has been reported (Zulalian et al, 1994), however there remains a lack of information regarding its pharmacokinetics parameters in cattle. The present study was undertaken in order to determine the plasma profile of moxidectin using a newly-developed chemical assay (Alvinerie et al, 1995) which allows the detection and quantitation of the drug at low concentrations (0.1 ng/mL). The persistence of the drug in plasma in a cow and its suckling calf was investigated over a period of three months.

MATERIALS AND METHODS

Animals and drug administration

A nursing cow of French Limousine breed, weighing approximately 550 kg, and its suckling calf (one month, 70 kg) were selected and maintained indoors. The cow (a three-year-old) was fed on a hay and concentrate diet; the calf was fed by milk from suckling (10–15 L per day). A commercial solution of moxidectin (Cydectin®, American Cyanamid Company, Paris, France) was administered to the cow according to the manufacturer's recommendations; ie, 0.2 mg/kg as a single subcutaneous injection.

Blood samples for analyses were collected from the cow 1, 2, 3, 4, 6, 8, 10, 13, 16, 20, 26, 30, 35, 40, 44, 50, 55, 62, 68, 76, 82, 90, 100, 110 and 120 days after injection, and from the calf after 6, 16, 26, 35, 44, 55, 68, 76, 82 and 90 days. Blood was collected in heparinized tubes, by tail vein puncture of the cow and by jugular vein puncture of the calf. Centrifugation was performed within 1 h of sampling, and plasma samples were stored at –18 °C until chromatographic analysis.

Analytical method

Plasma samples were analyzed for moxidectin concentration using a newly-described method (Alvinerie et al, 1995). Briefly, 1 mL acetonitrile and 0.25 mL water were added to 1 mL plasma. After mixing for 20 min, the samples were centrifuged at 2000 *g* for 2 min, and the supernatant applied to a Supelco C18 cartridge. After washing with water, moxidectin was eluted with 1.0 mL MeOH. The eluate was evaporated to dryness under a gentle stream of nitrogen, and the residue was dissolved in 100 µL *N*-methylimidazole solution in acetonitrile (1:2, 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 and acetonitrile (4:15:50, v/v/v) 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 exitation wavelength of 383 nm and an emission wavelength of 447 nm (RF.551 Fluorescence detector, Shimadzu, Kyoto, Japan). The limit of quantification of the method was 0.1 ng/mL of plasma with a coefficient of variation of 6.95% (inter-day variability).

Data analysis

The following triexponential equation was fitted to the plasma concentration versus time data using a program adapted from Multi (Yamaoka et al, 1981):

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

in which A_1, A_2 and A_3 are the intercepts, C the plasma concentration at time t, k_a is the first order rate constant of moxidectin absorption and α and β are the first-order rate constants for moxidectin distribution and elimination respectively. The mean residence time (MRT) was calculated by the linear trapezoidal rule without extrapolation to infinity.

RESULTS AND DISCUSSION

Following a subcutaneous administration of 0.2 mg/kg of moxidectin, the parent drug was detected in the plasma of the cow over a period of 120 days (fig 1). The calculated pharmacokinetic parameters are listed in table I. After reaching a peak (1.56 days, 18.25 ng/mL), plasma concentrations decreased slowly according to intermediate and terminal phases characterized by half-lives of 4 and 25 days respectively. A mean residence time of 25.4 days and an area under the curves of 279.96 ng.days/mL were calculated.

Plasma concentrations in the cow obtained after 1, 6–8 and 13–16 days are in good accordance with levels of blood radioactivity reported by Zulalian et al (1994) in steers receiving a similar administration of radiolabeled moxidectin. Concentrations obtained for the first three days are similar to those found in the serum of cattle treated with a single subcutaneous injection of 0.2 mg/kg of moxidectin (Miller et al, 1994).

At day 6 following dosing of the cow, moxidectin was detected in the plasma of the suckling calf at a concentration of 2.70 ng/mL, thus establishing the excretion of the drug in the milk. This level decreased slowly until day 90 (fig 1). A triexponential equation was fitted to the cow data; the parameters are indicated in table I. The decay of moxidectin concentration in the calf plasma was fitted to a single terminal

Table I. Pharmacokinetics parameters of moxidectin in the plasma of the cow and its suckling calf following a single subcutaneous administration (0.2 mg/kg) to the cow.

Parameter	*Cow*	*Calf*
C_{max} (ng/mL)	18.25	–
T_{max} (day)	1.56	–
$t_{1/2ka}$ (day)	0.40	–
$t_{1/2\alpha}$ (day)	4.04	–
$t_{1/2\beta}$ (day)	25.40	19.40
MRT (day)	25.66	27.50
AUC (ng.day.mL^{-1})	279.96	68.37

C_{max}: maximal concentration; T_{max}: time for maximal concentration; $t_{1/2ka}$: time of half-life absorption; $t_{1/2\alpha}$ and $t_{1/2\beta}$: time of half lifes of intermediate and terminal phases; MRT: mean residence time; AUC: area under the curve.

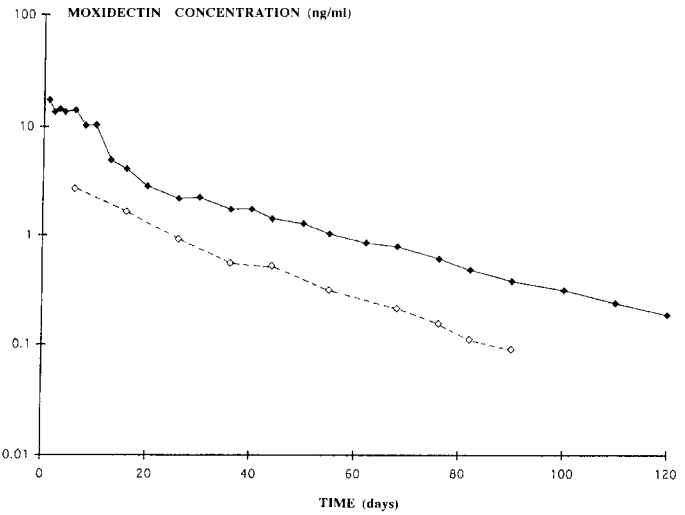

Fig 1. Semilogarithmic plot of the disposition curves of moxidectin in plasma of nursing cow (◆) and its calf (◊) following subcutaneous administration of moxidectin (0.2 mg/kg) to the cow.

elimination phase (half life: 19.4 days). The resulting mean residence time of 27.5 days was similar to that calculated for the nursing cow. The calf/cow ratio of areas under curves was 0.24. Therefore, assuming that the bioavaibility of moxidectin by the oral route is about 50%, and allowing for the weight difference between the animals, the estimated dose received by the calf through the milk represents approximately 5% of the total dose administered to the cow.

The most striking result of this experiment was the persistence of moxidectin in plasma. These data are in good agreement with a study of tissue residues of moxidectin in cattle (Zulalian et al, 1994), where the authors reported the persistence of high levels of moxidectin in fat (275 ng/g) 28 days after administration. The high efficacy of moxidectin against parasites may originate from its long terminal half-life (25 days). Even though the anthelmintic efficacy of moxidectin was not evaluated during the course of this study, the presence of measurable drug concentrations in plasma for three months is of interest in this respect. Anthelmintic activity is generally related to the presence of an active concentration of the drug at the site of action for a suitable period of time (Baggot and McKellar, 1994). The role of pharmacokinetic studies in the assessment of the efficacy of an anthelmintic drug relies on the assumption that the plasma concentration profile reflects the active concentration profile at the site of action. The link between these two parameters has been established for ivermectin (Prichard et al, 1985) and estimated with relative certainty for moxidectin. Considering the results obtained in a similar experiment with ivermectin (Alvinerie et al, 1993b), using a similar highly-sensitive analytical method, the absorption process for ivermectin appears longer than for moxidectin (the times to peak plasma concentration are 4.0 and 1.56 days respectively). Since moxidectin pharmacokinetic parameters have been previously characterized for a period of 5 days (Miller et al, 1994), this original study was designed to improve the knowledge of these parameters over an increased period of time (110 days). In addition, the mean residence time of moxidectin seems to be longer than that of ivermectin. This observation is consistent with the hypothesis of a longer exposure of parasites to the drug in the case of moxidectin treatment compared to ivermectin (Xiao et al, 1994).

The presence of moxidectin in the plasma of the calf reveals both the excretion of the drug in the milk and its transfer to the calf. Since moxidectin, like ivermectin, is a highly lipid-soluble chemical, its excretion in milk was expected. In studies using cows (Toutain et al, 1988) or goats (Alvinerie et al, 1993a), the concentration of ivermectin in milk was found to be similar to that in plasma. This resulted in a high fraction of ivermectin eliminated in the milk: around 5% of the administered dose, which is in good agreement with our results.

In conclusion, this experiment clearly demonstrates the excretion of moxidectin in milk, and provides evidence that the plasma pharmacokinetic profile of moxidectin is different from that of ivermectin. Nevertheless, further experiments are needed to confirm this preliminary result.

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