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The pharmacokinetics of moxidectin after oral and subcutaneous administration to sheep

Michel Alvineriea*, Elisa Escudero b, Jean-François Sutra a, Claudine Eeckhoutte a, Pierre Galtier a

a Laboratoire de pharmacologie-toxicologie, Inra, 180, chemin de Tournefeuille, BP 3, 31931 Toulouse cedex 9, France
b Department de Farmacología y Terapéutica, Facultad de Veterinaria, 30071 Espinardo, Murcia, Spain

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Abstract – The pharmacokinetic parameters of moxidectin were determined in ten sheep following a single subcutaneous or oral drench at a dose of 0.2 mg·kg−1. The plasma kinetics were best fitted by a two-compartment model. Moxidectin was detected in the plasma at the first sampling time (1 h) and thereafter for at least 60 d. The AUC were similar after both treatments indicating the same bioavailability for the two routes of administration. The oral route was characterized by a higher Cmax value (28.07 ng·mL−1) than after subcutaneous injection (8.29 ng·mL−1) and by significantly faster absorption as indicated by Tmax of 0.22 d and 0.88 d for oral and subcutaneous administrations, respectively. The most striking result of this experiment was the longer mean residence time reported for the subcutaneous route, i.e. 16.80 d as compared to 12.55 d for the oral drench. This difference is in agreement with previous studies demonstrating the longer anthelmintic efficacy of the subcutaneous route in comparison with oral administration. © Inra/Elsevier, Paris

moxidectin / sheep / pharmacokinetic / efficacy / persistence

Résumé – Étude pharmacocinétique de la moxidectine après administration orale ou sous-cutanée chez le mouton. Les paramètres pharmacocinétiques de la moxidectine ont été déterminés chez dix moutons recevant une même dose de 0,2 mg·kg−1 par voie sous-cutanée ou par voie orale. L’analyse pharmacocinétique a été réalisée grâce à un modèle bicompartimental. La moxidectine a été détectée dans le plasma lors du premier prélèvement (1 h) et jusqu’à 60 j après l’administration. Les aires sous la courbe sont similaires pour les deux voies d’administration indiquant une biodisponibilité comparable. La voie orale est caractérisée par une concentration maximale (28,07 ng·mL−1) plus élevée que celle obtenue par voie sous-cutanée (8,29 ng·mL−1) ainsi
que par une absorption plus rapide illustrée par les valeurs des Tmax qui sont respectivement de 0,22 et 0,88 j pour la voie orale et la voie sous-cutanée. Le résultat le plus surprenant de cette étude réside dans la plus longue rémanence de la voie sous-cutanée (MRT = 16,8 j) comparée à celle de la voie orale (MRT = 12,6 j). Cette différence est en accord avec des études antérieures démontrant une plus longue efficacité des anthelmintiques lors d'une administration sous-cutanée comparativement à la voie orale. © Inra/Elsevier, Paris

moxidectine / mouton / pharmacocinétique / efficacité / rémanence

1. INTRODUCTION

Moxidectin is a macrocyclic lactone produced by the non-cyanogenous species *Streptomyces cyanogriseus* and modified by chemical synthesis to give a broad spectrum antiparasitic drug for the control of both internal and external parasites of domestic animals [4, 7]. Moxidectin is chemically related to milbemycin; the molecular structure includes a fused cyclohexane tetrahydrofuran ring, a bicyclic 6,6-membered spiroketal and a cyclohexene ring fused to the 16-membered macrocyclic ring. Moxidectin is the 23-(O-methyloxime) derivative of nemodectin and differs structurally from ivermectin in having no sugar moiety at the C-13 position and in having an unsaturated side-chain at the C-25 position. These differences confer significantly different physical and pharmacological properties in the two drug types. Moxidectin is much more lipophilic in nature than avermectin and is mainly stored in the fat. This appears to have an accumulatory effect and results in a longer mean residence time for the drug in the body, as has been demonstrated in cows [3, 10]. There is no information regarding its pharmacokinetic parameters in sheep, although it is licensed as an oral drench or an injectable formulation in this species.

The present study was, therefore, undertaken to determine the plasma profile of moxidectin in plasma when given by the oral route and by subcutaneous injection in sheep and to correlate the pharmacokinetic parameters with the persistence of activity noted in previously described studies [9].

2. MATERIALS AND METHODS

2.1. Animals and drug administration

Ten young adult Lacaune sheep weighing 23 ± 2 kg were obtained from a flock which had been reared under parasite-free conditions from birth. They were allocated into two groups of five and provided with hay, concentrates and water ad libitum. Each group received moxidectin (cydectin®, Fort Dodge International, Paris, France) either subcutaneously as a 1% injectable cydectin solution or as a 0.1% oral cydectin drench at a dose rate of 0.2 mg·kg⁻¹ according to the manufacturer’s recommendations.

Blood samples for analyses were collected from the sheep at 1, 2, 4, 8, 12 and 24 h and 1.5, 2, 3, 4, 5, 6, 8, 10, 15, 21, 25, 30, 35, 40, 50 and 60 d after injection. Blood was collected in heparinized tubes, by jugular vein puncture. Centrifugation was performed within 1 h of sampling, and the plasma samples stored at −18 °C until chromatographic analysis.

2.2. Analytical method

The plasma samples were analyzed for moxidectin concentration using a newly described method [2]. 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 2 000 g for 2 min, and the supernatant applied to a Supelco C18
cartridge. After washing with water, the moxidectin was eluted with 1.0 mL of methanol. The eluate was evaporated to dryness under a gentle nitrogen stream, and the residue dissolved in 100 μL N-methylimidazole solution in acetonitrile (1:1, v/v). Here, 150 μL trifluoroacetic anhydride solution in acetonitrile (1:2, v/v) was added to initiate the derivatization. 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⁻¹ 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, Kyoto, Japan). The quantification limit of the method was 0.1 ng·mL⁻¹ of plasma with a coefficient of variation of 6.95 % (inter-day variability).

2.3. Data analysis

The following triexponential equation was fitted to the plasma concentration versus time data using a program adapted from Multi [16]:

\[ C(t) = A_1 e^{-\alpha t} + A_2 e^{-\beta t} + A_3 e^{-\gamma t} \]

in which \( A_1, A_2 \) and \( A_3 \) are the intercepts, \( C \) the plasma concentration at time \( t \), \( k_a \) is the estimated first order rate constant of moxidectin absorption and \( \alpha \) and \( \beta \) 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.

3. RESULTS AND DISCUSSION

Following a subcutaneous or oral administration of 0.2 mg·kg⁻¹ of moxidectin, the parent drug was detected in the plasma of sheep over a period of 60 days (figure 1). The calculated pharmacokinetic parameters are listed in table 1. Moxidectin was detected at the first sampling time, 1 h post treatment in plasma of both orally and subcutaneously dosed sheep. However after oral administration the Cmax (28.07 ng·mL⁻¹) and Tmax (0.22 d) reflected a faster and higher rate

![Figure 1](image-url). Concentration time profile of moxidectin in plasma of sheep, following subcutaneous injection (×) or oral drench (●) at a dose rate of 0.2 mg·kg⁻¹.
of absorption compared to subcutaneous administration with lower values of Cmax (8.29 ng·mL⁻¹) and a longer value of Tmax (0.88 d). All plasma concentrations decreased progressively thereafter during the intermediate and terminal phases characterized by similar half-life values.

The shorter MRT obtained following oral administration (12.55 d) when compared to subcutaneous administration (16.8 d) suggest that the slower absorption process characterizing subcutaneous absorption could participate in the longer remanence of the drug in the animal organism. Similar results were reported for ivermectin in sheep [6]. This difference results in a substantial broadening of the plasma concentration and persistence of the drug in the case of the subcutaneous route. In our results, subcutaneous administration for example resulting in plasma concentrations exceeding 2 ng·mL⁻¹ for 18 d and compared to 8 d for the oral route. The AUC of moxidectin following SC (112 ng·d·mL⁻¹) or oral administration (99 ng·d·mL⁻¹) were observed to be similar for both routes of administration due to the faster oral absorption process by using oral route. This result differs from that obtained for ivermectin [1] where it showed a 59 % lower bioavailability for the oral route than for subcutaneous administration. The reasons for such differences are still unclear – the stronger lipophilic properties of moxidectin may increase oral absorption [5].

Interestingly, whatever the route of administration, moxidectin has a longer mean residence time in sheep than ivermectin – 7.8 d [11]. A similar difference was observed by others in cows [10] and horses [14]. It has been suggested that such a difference could be related to differences in the liposolubility of the two drugs, resulting in a longer half life of moxidectin in fat, which may then act as a drug reservoir that contributes to the long persistence of this drug in the body [3]. The kinetic parameters obtained for moxidectin in sheep in the current trial agreed well with those obtained in cows and horses and clearly demonstrated the longer persistence of this drug when compared to ivermectin.

The duration of efficacy of moxidectin against parasites in sheep [13] may originate from the fact that it remains longer in the plasma. Even though the anthelmintic efficacy was not evaluated during the course of this study, the pres-

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Oral (n = 5) (mean ± SD)</th>
<th>Subcutaneous (n = 5) (mean ± SD)</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng·mL⁻¹)</td>
<td>28.07 ± 10.06</td>
<td>8.29 ± 3.14</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Tmax (d)</td>
<td>0.22 ± 0.04</td>
<td>0.88 ± 0.24</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>t1/2 α (d)</td>
<td>0.82 ± 0.14</td>
<td>4.40 ± 3.21</td>
<td>NS</td>
</tr>
<tr>
<td>t1/2 β (d)</td>
<td>21.04 ± 2.01</td>
<td>29.94 ± 9.00</td>
<td>NS</td>
</tr>
<tr>
<td>MRT (d)</td>
<td>12.55 ± 1.45</td>
<td>16.80 ± 1.80</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>AUC (ng·d·mL⁻¹)</td>
<td>98.89 ± 34.90</td>
<td>112.33 ± 46.50</td>
<td>NS</td>
</tr>
</tbody>
</table>

Cmax: maximal concentration; Tmax: time of maximal concentration; t1/2 α and t1/2 β: time of half lives of intermediate and terminal elimination phases; MRT: mean residence time; AUC: area under the curve.
ence of measurable drug plasma concentrations for 2 months is of interest. 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 [12]. The ability of pharmacokinetic studies to assess the anthelmintic efficacy of drugs 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 [15] and estimated with relative certainty for moxidectin.

The comparative efficacies of the two routes of administration have been studied in sheep by several authors [8, 9]. It is interesting to note the longer duration of anthelmintic efficacy of the subcutaneous administration. Although both formulations of moxidectin showed excellent activity against *T. circumcita* and *H. contortus* with almost 100% efficacy against the abdominal parasites for up to 35 d after treatment, the efficacy of moxidectin 1% injectable against *T. colubriformis* was much higher (> 99%) than the oral drench. It was highly effective up to 21 d after treatment and produced a moderate reduction in worm burden for up to 35 d after treatment [9]. Having established a link between the plasma concentration of moxidectin and its efficacy, it is easy to see that during this period the plasma concentrations obtained by subcutaneous route were 4–1 ng·mL⁻¹, i.e. two-fold higher than those obtained by oral route (2.5–0.6 ng·mL⁻¹). This correlation clearly demonstrated the relationship between plasma concentration and moxidectin efficacy.

In conclusion, this study demonstrated that both subcutaneous or oral routes of moxidectin administration in sheep generated the same quantity of the drug in the body. Nevertheless the persistence of the drug was higher with the subcutaneous administration. This longer persistence was in agreement with the comparative efficacy of this route.

This is a good example of the usefulness of pharmacokinetic investigations in order to improve therapeutic treatments.

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