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# Pharmacokinetics of doramectin in lactating dairy sheep and suckling lambs

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**Abstract**

The aim of the present study was to estimate permeation of doramectin (DOR) into sheep's milk by following its time course in blood plasma and milk. Six Istrian Pramenka sheep in the early lactation period, each having a suckling lamb, were administered DOR in a single subcutaneous dose of 0.2 mg $kg^{-1}$ body weight. Blood plasma and milk samples were taken from days 1 to 42 following drug administration. Mean maximal DOR concentration observed ($c_{max}$) in ewes' blood plasma and milk were 22.8 and 31.1 μg $l^{-1}$, respectively, at day 3 ($t_{max}$) following drug administration. Mean elimination half-lives ($t_{1/2}$) and mean residence times (MRT) were 3.4 and 6.2 days for plasma data and 4.6 and 6.9 days for milk data, respectively. Transfer of DOR residues to suckling lambs was evaluated by determination of DOR concentration time courses in lambs' blood plasma. Mean maximal DOR concentration 2.1 μg $l^{-1}$ ($c_{max}$), was observed at 5.5 days ($t_{max}$) following drug administration to ewes, while $t_{1/2}$ and MRT were 3.8 and 9.1 days, correspondingly. Mean time in which concentrations fell below the limit of detection was >35 days for ewes' blood plasma and >37 days for milk, while residual DOR concentration in lambs' blood plasma fell below the limit of detection on day 20 following drug administration to ewes in only one out of six lambs. DOR extensively permeated into sheep's milk. Mean milk to plasma concentration ratio was 1.4. It was estimated that 1.6% of the DOR dose was excreted into milk and ingested by suckling lambs.

As DOR use during lactation is prohibited, its long lasting presence of residues in milk merits proper veterinary sanitary control. The results reported contribute to further understanding of the DOR persistence and excretion patterns in lactating sheep and implementation of evidence-based guidelines to anti parasitic treatment of dairy animals.


*Keywords:* Doramectin; Sheep; Residues; Pharmacokinetics; Milk; Suckling lambs

## 1. Introduction

Macrocyclic lactone doramectin (DOR) is the product of a mutational biosynthesis program where a mutant strain of soil actinomycete *Streptomyces avermitilis* was utilized to produce avermectins with substituents at the C-25 position. Its chemical name is 25-cyclohexyl-5-*O*-demethyl-25-de(1-methylpropyl) avermectin $B_1$ (Fig. 1). DOR is an exceptionally potent endectocide with a broad spectrum of activity against nematode and arthropod parasites acting at very low dosing rates. Commercially it is available since 1993 [1]. Injectable oil-based formulations of DOR were particularly optimized for their pharmacodynamic efficacy [2] and are

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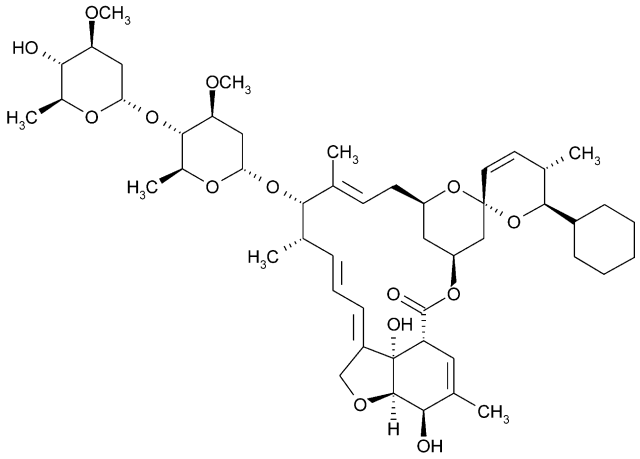

Fig. 1. Chemical structure of doramectin (DOR).

licensed for use in cattle, swine, and sheep [3,4] in many countries as well as in Slovenia. Close relationship between pharmacokinetics and the resulting clinical efficacy of antiparasitic drugs has been well documented [5,6].

The most pronounced characteristic of macrocyclic lactones is their high lipophilicity [7]. For this reason, regardless of their route of administration, these compounds are distributed extensively throughout the body and concentrate particularly in adipose tissues. Due to high lipophilicity macrocyclic lactones also considerably partition into milk. In European Union DOR as well as ivermectin and abamectin are banned for use in animals from which milk is produced for human consumption and the only registered avermectin for use in dairy cows is eprinomectin [8]. Although an acceptable daily intake (ADI) of 0–0.5 $\mu g\,kg^{-1}$ b.w. was calculated for DOR [9], the establishment of maximum residue level (MRL) for its residues in milk was not applied, in spite of possibility for extra-label use in dairy animals [10]. Studies on DOR permeation into milk are very scant. To our knowledge, the only data available on DOR milk residues in lactating dairy sheep are from Imperiale et al. [11]. For this reason, the aims of the present study were to follow the concentration time course of DOR in blood plasma and its excretion in sheep's milk in an autochthonous Slovenian dairy breed. Additionally, transfer of DOR residues to suckling lambs was evaluated by measuring time courses of DOR concentration in blood plasma of the lambs. The information about DOR disposition in dairy animals is essential for development of reasonable guidelines to antiparasitic treatment of dairy sheep regarding withdrawal time for milk and lamb meat for consumer safety reasons.

## 2. Experimental

### 2.1. Animals

The study was performed on Istrian Pramenka sheep, an autochthonous Slovenian dairy breed [12] in the early lactation period. Eight stabled ewes, weighing between 50 and 72 kg (mean 61 kg) and aged from 3 to 6 years (mean 4.1 years), each having a suckling lamb of age of 6 weeks, were enrolled in the experiment. Lambs were kept with their mothers. Only on sampling days they were separated for 6 h in order to collect enough milk for analysis. Animals were clinically healthy and parasite free as indicated by haematological, biochemical and faecal examinations. They did not receive any avermectin drug for at least a year and any drug for at least 2 months before beginning of the experiment. The feeding regime was as follows: all animals were fed hay and mixed fodder (maize, barley and oily rape), lambs received also mothers' milk and aftermath. For all animals water was available *ad libitum*. The health status including haematological, biochemical and parasitological analyses as well as the body weight was controlled during the entire experiment.

### 2.2. Study design

Six ewes were administered a single subcutaneous dose of 0.2 $mg\,kg^{-1}$ b.w. of DOR (Dectomax*, Pfizer Animal Health S.A., Amboise, France) in the shoulder area. Individual blood and milk samples were taken on days 0 (before administration)–1, 2, 3, 4, 5, 7, 9, 11, 14, 17, 20, 23, 26, 29, 32, 36 and 42 following DOR administration to sheep. At the same times, samples from two separately kept untreated animals were taken for control. Blood samples from lambs were taken on the same days, up to day 20, at the same time of the day as from their mothers.

Blood was taken from the jugular vein in heparinized vacuum tubes. Samples were cooled to 4 °C and transported to the laboratory where blood plasma was separated by centrifugation at 2470 × g for 20 min. Until analysis plasma and milk samples were kept frozen at −20 °C.

The animal experiment was approved by the Veterinary Administration of the Republic of Slovenia (No. 323-02-187/01).

### 2.3. Analytical method for DOR determination

The concentration of DOR in individual sheep's blood plasma and milk samples was determined using a selective and sensitive liquid chromatographic (LC) method, based on previously used analytical procedure for determination of ivermectin in blood plasma and milk [13–15], which was extended for DOR and abamectin to become a so called multi method for determination of residues of most often used avermectin drugs, registered for use in Slovenia. As the aim of this manuscript is to present only DOR pharmacokinetics, only data concerning this drug will be presented.

#### 2.3.1. Chemicals

Pure reference standard of DOR was obtained as a gift from Pfizer Inc. (Groton, CT, USA). Standardized solutions were prepared in acetonitrile using previously silanized glassware.