Pharmacokinetics and oral bioavailability of enrofloxacin in faunated and defaunated Angora goats

M. ELMAS, E. YAZAR, B. TRAŞ, A.L. BAŞ and A. ERYAVUZ

1. Introduction

Enrofloxacin is the first fluoroquinolone introduced into veterinary medicine [22, 25]. Enrofloxacin has broad-spectrum activity against gram-negative and gram-positive bacteria and mycoplasma spp and has efficacy against organisms that are resistant to other antibacterial agents [1, 2]. Pharmacokinetic studies have indicated that enrofloxacin is rapidly absorbed after oral and parenteral administration, has a large volume of distribution, with low plasma protein binding, and penetrates well into tissue and cells [6, 19, 23, 25, 27]. In addition, fluoroquinolones have a long serum elimination half-life, making them suitable for once or twice a day administration. The pharmacokinetic characteristics of enrofloxacin after intravenous (IV) and intramuscular (IM) administration to Angora goats were determined in a previous study [10]. Enrofloxacin was rapidly and almost completely absorbed after IM administration. Although enrofloxacin is given by oral route in adult ruminants, the oral absorption of this drug in these species is only approximately 10-35 % [8, 25].
Defaunation, which consist in an elimination of ciliate protozoa from the rumen, was reported to be beneficial for the growth of young ruminants and for wool and mohair production of sheep and Angora goats, when diet deficient in rumen-undegradable protein and rich in soluble sugar were used [3, 11]. While defaunation also causes an increase in the total number of bacteria in the rumen, the total number of protozoa in the rumen is approximately rendered [4, 16, 21]. HSU et al.[13] observed an double increase in numbers of ruminal bacteria and fungal zoospores in defaunated animals compared with the faunated controls. Inconsequence, defaunation influences the intensity of fermentation and its qualitative evolution.

The objectives of this present study were to determine some pharmacokinetic variables after oral administration, and to evaluate the effect of defaunation on oral bioavailability in Angora goats.

2. Materials and methods

A) ANIMALS AND GROUPS

Ten Angora goats (male, healthy, approximately 18 months of age and 22.25 ±1.125 kg) were used. The goats were equally divided into two groups [faunated (control group) or defaunated (experiment group)] as similar as possible with regard to their body weight at the beginning of the experiment. The goats in the experiment group were defaunated with solution (150 ml to each animal) of dioctyle sodiumsulphosuccinate (DSS) (3 % w/v) delivered directly into the rumen through a polyethylene tube inserted down the esophagus. These were given on each of three consecutive days. Feed was not provided during this period. In the first day of following weeks, 100 ml solution of DSS (0.1% w/v) was infused into rumen of each goat in the experiment group (without fasting the goats) to ensure a protozoa-free environment throughout the rest of experiment period. Samples of rumen contents from defaunated goats were continuously examined for ciliates microscopically every other weeks. The defaunated goats were housed in a room isolated from other ruminants to prevent refaunation. The faunated goats were also housed in an adjacent room with identical environmental conditions. The goats in each two groups were fed ad libitum with same diet. All animals were clinically normal and had not received antibiotics within 1 month of beginning the study.

B) DRUG ADMINISTRATION AND SAMPLING

Enrofloxacin (Baytril 2.5 % sol., Bayer AG, Istanbul, Turkey) at dose of 5 mg/kg body weight (bw) was administered orally (PO) by a polyethylene tube to all goats. Blood samples were collected into tubes with EDTA from the left jugular vein at 0.33, 0.66, 1, 1.5, 2, 4, 8, 12 and 24 h after oral administration. Samples were centrifuged within one hours of collection, and stored -20° C until analysis.

C) ENROFLOXACIN ASSAY

Plasma concentrations of enrofloxacin were determined by high performance liquid chromatography (Shimadzu Corp, Analytical Instrument Plant, Kyoto, Japan) as described by ANADON et al [1]. Enrofloxacin was extracted from plasma, using dichloromethane (Merck), and analysed by reverse-phase chromatography. The mobil phase was a mixture (pH : 2.2) of buffer and acetonitril (80 : 20/V). Heptane sulfonic acid-Na (1.1 g/L) was added as ion-pairing reagent. Ultraviolet absorbance (set at 278 nm) was used for detection with flow rate maintained at 2 ml/min. Linearity of the method was examined by linear regression analysis of calibration curves in plasma from goats. The method was found to be linear and reproducible in the concentration range of drug. The recovery was > 90 % for enrofloxacin. The limit of quantification of enrofloxacin was 0.01 µg/ml.

D) PHARMACOKINETIC ANALYSIS

This study was not based on a cross-over study design, because the animals in the defaunated group were being different herd. However, the five goats of our previous study [10] were used as faunated group. Oral bioavailability (F) of enrofloxacin was calculated from the ratio between the value of AUC 0-∞ po for each animal and the mean value of AUC 0-∞ iv for the five goats used in our previous study. Complete absorption was determined on the basis of AUC 0-∞ i.v., which represents the mean value (21.12 ± 0.21 µg.h/ml) of AUC 0-∞ i.v. for the five goats.

The plasma concentration-time data were fitted to a two-compartment open model with first order absorption for kinetic analysis. Pharmacokinetic variables were calculated using the computer programme (PKCALC Manual, Releasing 1987) based on equation described by SHUMAKER [24], and other programme (GW-Basic, 2.02) based on equation described by WAGNER [26]. The plasma curves of enrofloxacin in each animal after oral administrations were fitted to the following exponential equations:

\[ C = A_1 e^{-\alpha t} + A_2 e^{-\beta t} - A_3 e^{-k_{at}} \]

where C is plasma concentration of enrofloxacin; A1, A2, and A3 are mathematical coefficients; \( \alpha \) is the hybrid rate constant for distribution phase ; \( \beta \) is the hybrid rate constant for terminal elimination phase ; \( k_{at} \) is the first-order rate constant, and t is time.

After oral administration, the areas under the concentration time curves (AUC) were calculated by the polynoexponential method. The mean pharmacokinetic variables were calculated for drug disposition after each administration in each goat. From these data, the absorption half-life (t 1/2a), the half-life of the \( \alpha \) phase (t 1/2a), the half-life of the \( \beta \) phase (t 1/2b), mean residence time (MRT), volume of distribution in steady state (Vd(ss)), total plasma clearance (CL), bioavailability (F %), maximal concentration in plasma (C max) and time to reach C max (t max) were estimated.

Differences in pharmacokinetic data and plasma concentrations at same sampling time between faunated and defau- nated groups were analysed for statistical significance by use of the paired student t-test. Differences of p < 0.05 were considered significant. All data in this study were presented as mean ± SEM.
3. Results

The concentration-time curves of enrofloxacin in plasma after oral administration at the dose of 5 mg/kg bw in faunated and defaunated Angora goats are depicted in Figure 1, and the results of kinetic analysis are shown Table I. The plasma concentrations of enrofloxacin in defaunated group were higher than those of faunated group except for 8,12 and 24 hours (Figure 1), and C_max in defaunated goats was also higher than other group (p < 0.05). Enrofloxacin was reached to C_max within a long time following oral administration in both groups (Table I). Although the oral bioavailability of the drug in defaunated group (F, 30 %) was higher than faunated group (F, 23 %), there was a not significant difference (p > 0.05). After oral administration, a rapid distribution phase and a quite slower elimination phase were observed (Table I). Statistically significant differences (p < 0.05) in pharmacokinetic parameters between faunated and defaunated groups were found for MRT and C_max.

4. Discussions and conclusions

Enrofloxacin has low minimum inhibitory concentration (MIC) values ranging 0.008-0.75 µg/ml > 100 various bacterial pathogens [6, 22]. Enrofloxacin also almost penetrate all tissue, cell and lymph fluids [9, 22, 25]. In agreement with our previous work performed in Angora goats [10], plasma enro-

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![Figure 1. — Plasma concentrations of enrofloxacin (5 mg/kg bw) in faunated and defaunated Angora goats after oral administration.](image)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Faunated</th>
<th>Range</th>
<th>Defaunated</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>t_1/2α (h)</td>
<td>0.16±0.06</td>
<td>0.07-0.36</td>
<td>0.14±0.02</td>
<td>0.08-0.19</td>
</tr>
<tr>
<td>t_1/2β (h)</td>
<td>2.37±0.25</td>
<td>1.94-3.07</td>
<td>1.48±0.47</td>
<td>0.81-3.35</td>
</tr>
<tr>
<td>t_1/2a (h)</td>
<td>9.26±0.65</td>
<td>7.53-11.55</td>
<td>8.15±0.18</td>
<td>7.52-8.56</td>
</tr>
<tr>
<td>AUC_0-∞ (µg.h/ml)</td>
<td>4.92±0.52</td>
<td>3.52-6.95</td>
<td>6.39±0.43</td>
<td>5.76-8.08</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>15.36±0.81*</td>
<td>13.63-18.08</td>
<td>13.07±0.34</td>
<td>12.07-14.17</td>
</tr>
<tr>
<td>Vd (ss) (l/kg)</td>
<td>3.27±0.12</td>
<td>2.93-3.96</td>
<td>2.92±0.11</td>
<td>2.72-3.32</td>
</tr>
<tr>
<td>CL (l/h/kg)</td>
<td>0.24±0.01</td>
<td>0.23-0.25</td>
<td>0.24±0.01</td>
<td>0.23-0.24</td>
</tr>
<tr>
<td>C_max (µg/ml)</td>
<td>0.25±0.03*</td>
<td>0.22-0.36</td>
<td>0.42±0.06*</td>
<td>0.33-0.60</td>
</tr>
<tr>
<td>t_max (h)</td>
<td>5.20±1.20</td>
<td>2.00-8.00</td>
<td>3.50±0.50</td>
<td>1.50-4.00</td>
</tr>
<tr>
<td>F (%)</td>
<td>0.23±0.03</td>
<td>0.17-0.32</td>
<td>0.30±0.02</td>
<td>0.27-0.38</td>
</tr>
</tbody>
</table>

* P < 0.05 (values with same symbol are significantly different)

Table I. — Pharmacokinetik parameters (Mean ± SEM, minimum-maximum) obtained after single oral administration of enrofloxacin (5 mg/kg b.w.) in faunated and defaunated goats.

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PHARMACOKINETICS AND ORAL BIOAVAILABILITY OF ENROFLOXACIN IN FAUNATED AND DEFAUNATED ANGORA GOATS
fluoroquinolones are concentration-dependent antimicrobials which have also a post antibiotic effect [7], and enrofloxacin is metabolised ciprofloxacin which has also antimicrobial activity. Thus, it is not necessary to maintain antimicrobial activity above MIC during whole dosage interval [18].

Pharmacokinetic of enrofloxacin after oral administrations in Angora goats could be described adequately by a two-compartment open model. Studies performed by others in birds [12], chickens [1], rabbits [5,6], dogs [27], sheep [9] and Angora goats [10] have led to same conclusion.

Enrofloxacin pharmacokinetic parameters in both groups were similar in terms of AUC 0-24h, t1/2α, t1/2β, CL and Vd(0ss). After oral administration of enrofloxacin at the dose of 5 mg/kg bw, the mean elimination half-lives in faunated and defaunated goats were found to be 9.8 and 8.2 h, respectively. These values were markedly longer than those of parenteral (IV and IM) administrations in same species [10]. Vd(0ss) values for ruminants after different administration routes are between 0.6 and 3 L/kg [8, 17, 20]. The large Vd(0ss) values suggest that the drug infuses into all body tissues.

Oral bioavailability of enrofloxacin in Angora goats was found to be poor (22-35 %) agreement with reported data for other different adult ruminant species [8, 25]. In present study, although the oral bioavailability of the drug in defaunated group (F; 30 %) was higher than faunated group (F; 23 %), there was a not significant difference (p > 0.05). In addition to this, the plasma concentrations of enrofloxacin in defaunated group were higher than those of faunated group except for 8,12 and 24 hours, and Cmax in defaunated goats was also higher than other group (p < 0.05). Ruminoreticul contents may have a marked effect on foreign compounds [15]. IVAN et al [14] showed that defaunated rams are more sensitive to copper toxicity than faunated ones, because protozoa stimulated the complexation of the Cu in sulphide form, making it unavailable for absorption and utilisation. The similar mechanism can play a significant role on increasing oral absorption of enrofloxacin in defaunated group.

The pharmacokinetic parameters of enrofloxacin in Angora goats following oral administration are characterised by long elimination half-life, high bioavailability and high volume of distribution. The results of this study show that oral absorption of enrofloxacin in adult angora goats was poor and oral absorption was slightly affected by defaunation. Although oral bioavailability of enrofloxacin in faunated and defaunated Angora goats are 23 and 30 %, respectively, once daily oral administration of enrofloxacin at the dose of 5 mg/kg bw may be suitable in treatment of infectious diseases caused by sensitive pathogens in Angora goats.

References


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