PHARMACOKINETICS OF FLUNIXIN-MEGLUMIN FOLLOWING INTRAVENOUS ADMINISTRATION IN ANGORA RABBITS

MUAMMER ELMAS, KAMIL UNEY, AYSE KARABACAK AND ENVER YAZAR

Department of Pharmacology and Toxicology, Faculty of Veterinary Medicine, University of Selcuk, 42031, Konya, Turkey
e-mail: melmas@selcuk.edu.tr

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Abstract

The pharmacokinetics of flunixin-meglumin were determined after intravenous bolus injection at two different doses (1.1 and 2.2 mg/kg body weight) in rabbits. Six healthy adult Angora rabbits were used in the experiment. Blood samples were collected at 10, 20, 30, 45 and 60 min, 2, 4, 6, and 8 h after injection. Concentrations of drug in plasma were determined by HPLC. Pharmacokinetics were described by a two-compartment open model. The area under the curve, contrary to other pharmacokinetic parameters, showed statistically significant differences between the two doses used (P<0.05). The data obtained for the low and high doses were as follows: the elimination half-lives were 1.4 and 1.7 h, the volume of distribution - 0.6 and 0.8 L/kg, and total body clearance - 0.32 and 0.37 mL/h/kg body weight, respectively. The present study has shown that the pharmacokinetic variables of flunixin-meglumin in Angora rabbits are dose independent in the dose range of 1.1-2.2 mg/kg body weight.

Key words: rabbits, flunixin-meglumin, pharmacokinetics.

Flunixin-meglumin (FM) belongs to potent non-steroid anti-inflammatory drugs (NSAID). These drugs act by inhibiting the synthesis of cyclooxygenase derived eicosanoid inflammatory mediators including prostaglandins and thromboxanes (7, 13,17). As FM has anti-inflammatory, analgesic and antipyretic properties, it has been used extensively to treat a number of conditions in various species viz.; mastitis in cow (1, 22), endotoxaemia in calves and mares (8,16), and fever in cows (1). Characterisation of pharmacokinetics of FM has been established in horses (23, 24, 26), cattle (2, 10, 21), dogs (11), cat (15), sheep (6, 29), llamas (20), camel (28), rabbit (19), broilers (3) and birds (4). Toxicity, however, restricts its use to the short term therapy (7).

The angora rabbit is a very old and commercially valuable breed of rabbit, believed to have originated from Turkey from Ankara town. Angora fibre production is the third largest animal fibre production in the world, after wool and mohair (14). Until today, Angora rabbits have been overlooked in terms of pharmacological research. Also newer anti-inflammatory agents, such as FM, may offer possibilities for treatment of various conditions in this species. For the NSAIDs, it is important not to extrapolate kinetic data from one species to another (18).

To our knowledge, the clinical use and the pharmacokinetics of FM have not been studied in Angora rabbits. The purpose of this investigation was to determine the pharmacokinetics of FM in Angora rabbits after a single intravenous (IV) administration at two different doses.

Material and Methods

Six male French Angora rabbits (age, 6-8 months; body weight 3.1± 0.15 kg, Faculty of Veterinary Medicine, Erciyes University, Kayseri, Turkey) were used. All the animals were clinically normal and had not received any drugs within 2 months prior to the beginning of the study.

As there is lack of pharmacokinetic data for FM in Angora rabbits, it was chosen to apply the manufacturer’s recommended dose of FM in horses (1.1 mg/kg) and in cattle (2.2 mg/kg). In this study, a crossover pharmacokinetic design was performed. The withdrawal interval between the phases of the study was 2 weeks. FM (Fluvil® Inj., 50 mg/ml, Vilsan, Ankara, Turkey) was given as a bolus intravenous (IV) injection (V. auricularis) at a dose of 1.1 mg/kg body weight. After the withdrawal period, FM was administered as a bolus IV injection at a dose of 2.2 mg/kg body weight.
Blood samples (app. 2 ml) were collected into tubes with EDTA from the catheterised *A. auricularis* at 0, 0.17, 0.33, 0.5, 0.75, 1, 2, 4, 6 and 8 h after injections. Samples were centrifuged within one hour after collection and plasma samples were stored at -20 °C until analysis.

Plasma concentrations of FM were determined with high performance liquid chromatography (HPLC, Model LC-6A with UV spectrophotometer detector model SPD-6A and data processor model chromatopac CR-6A, Shimadzu Corp, Analytical Instrument Plant, Kyoto, Japan) by use of procedure, which was modified after the works of Baert and De Backer (3), and Cheng et al. (6).

The plasma concentration-time data were fitted to a two-compartment open model for kinetic analysis. Pharmacokinetic variables were calculated using the computer programme (PKCALC Manual, Releasing 1987) based on equation described by Shumaker (25), and other programme (GW-Basic, 2.02) based on equation described by Wagner (27). The plasma curves of FM in each animal after IV administrations of both doses were fitted to the following exponential equations:

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

where \( C \) is plasma concentration of FM; \( A_1 \), and \( A_2 \) are mathematical coefficients; \( \alpha \) is the rate constant for distribution phase; \( \beta \) is the rate constant for terminal elimination phase; and \( t \) is time.

After IV administration, the areas under the concentration time curves (AUC) were calculated by the trapezoidal method. The mean pharmacokinetic variables were calculated for drug disposition after each administration in each rabbit. From these data, the half-life of the \( \alpha \) phase (\( t_{1/2\alpha} \)), the half-life of the \( \beta \) phase (\( t_{1/2\beta} \)), mean residence time (MRT), volume of distribution (Vd-area), volume of distribution in steady state (Vdss), total clearance (CLt), distribution rate constant for transferring the drug from the central to peripheral compartment (\( k_{12} \)), transfer rate constant from peripheral to central compartment (\( k_{21} \)) and elimination rate constant (\( k_{10} \)) were estimated. All data in this study were tabulated as mean±SEM. Differences in pharmacokinetic data and concentrations in plasma between two different doses were analysed for statistical significance by use of the paired Student \( t \)-test. Differences of \( p<0.05 \) were considered as statistically significant.

**Results**

The disposition curve for IV administered FM was best described by a biexponential equation (two-compartment open model) (Fig. 1). The results of kinetic analysis were presented in Table 1.

The area under the curve, contrary to other pharmacokinetic parameters, showed statistically significant differences between the two doses used (\( P<0.05 \)). Vd-area and half-life values after administration at the dose of 2.2 mg/kg were slightly higher than those after the lower dose, but these differences were not statistically significant (\( P>0.05 \)).

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**Fig. 1.** The semilogarithmic plot of plasma concentration time curves of flunixin-meglumin after intravenous bolus injection at two different doses (1.1 and 2.2 mg/kg body weight) in Angora rabbits (n=6).
Table 1
Pharmacokinetic variables of flunixin-meglumine after intravenous bolus injection at two different doses (1.1 and 2.2 mg/kg body weight) in Angora rabbits (n=6, mean±SEM)

<table>
<thead>
<tr>
<th>Variable</th>
<th>DOSE</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC 0-∞ (µg.h/mL)</td>
<td>1.1 mg/kg</td>
<td>3.51±0.38</td>
</tr>
<tr>
<td>t ½α (h)</td>
<td>1.1 mg/kg</td>
<td>0.15±0.02</td>
</tr>
<tr>
<td>t ½β (h)</td>
<td>1.1 mg/kg</td>
<td>1.41±0.14</td>
</tr>
<tr>
<td>k12 (h⁻¹)</td>
<td>1.1 mg/kg</td>
<td>1.93±0.36</td>
</tr>
<tr>
<td>k21 (h⁻¹)</td>
<td>1.1 mg/kg</td>
<td>0.99±0.18</td>
</tr>
<tr>
<td>k10 (h⁻¹)</td>
<td>1.1 mg/kg</td>
<td>2.48±0.33</td>
</tr>
<tr>
<td>ClT (L/h/kg)</td>
<td>1.1 mg/kg</td>
<td>0.32±0.03</td>
</tr>
<tr>
<td>Vd-area (L/kg)</td>
<td>1.1 mg/kg</td>
<td>0.55±0.22</td>
</tr>
<tr>
<td>Vd ss (L/kg)</td>
<td>1.1 mg/kg</td>
<td>0.44±0.04</td>
</tr>
<tr>
<td>MRT (h⁻¹)</td>
<td>1.1 mg/kg</td>
<td>1.46±0.16</td>
</tr>
</tbody>
</table>

N.S. = not significant. AUC = area under the concentration time curve; t ½α = the half-life of the α phase; t ½β = the half-life of the β phase; k12 = distribution rate constant for transferring the drug from the central to peripheral compartment; k21 = transfer rate constant from peripheral to central compartment; k10 = elimination rate constant; ClT = total body clearance; Vd-area = volume of distribution; Vd-ss = volume of distribution in steady state; MRT = mean residence time

Discussion

The pharmacokinetics of FM after i.v. administration at two different doses fitted correctly in all rabbits (correlation coefficients was >0.98) to a two-compartment open model. Previous studies performed in rabbits (19), sheep (6), camels (28) and broilers (3) have led to the same conclusions. In this study, while the mean distribution half-lives of FM in Angora rabbits at the doses of 1.1 and 2.2 mg/kg were 0.15 and 0.16 h, the elimination half-lives were 1.41 and 1.70 h, respectively. These results indicated that the drug distribution and elimination in Angora rabbits were fast and may be related to higher clearance rate. Miyazaki et al. (19) reported that FM had a short half-life (<4 h) and a high binding percentage with plasma protein (>99%) after intravenous injection in Japanese white rabbit. Similar half-life values of FM have also been reported in other animals including birds (4), dogs (11), cats (15), horses (26) and llamas (20), but these values were lower than those noted in sheep (6, 29), cattle (2, 10, 21) and camels (28).

In this study, the total clearance values of FM in Angora rabbit following two different doses were similar, and these values were higher than other species (10, 28, 29). Miyazaki et al. (19) reported that the elimination of FM in rabbits was mainly due to non-renal routes including biotransformation in the liver. In camels and dogs, glucuronidation of the parent molecule seems to be the major metabolic pathway (5, 28). In horses, a hydroxy metabolite is formed and conjugation reactions have been suggested (12).

One of significant finding is that in the present study FM has large Vd-area in Angora rabbits (app. 0.6-0.8 L/kg). This is in agreement with the result (0.5 L/kg) of Miyazaki et al. (19). The values of Vd-area in most NSAIDs are usually less than 0.1 L/kg, because of FM high binding properties with plasma protein (>98%) (9, 19). However, some reports have shown a relatively large Vd-area for FM such as, 0.8-1 L/kg in cattle (10, 21), 0.5 L/kg in camels (28), and 0.4 L/kg in dogs (11). Moreover, the relationship between k12 and k21, was close to 2, which suggested that the drug may be retained in tissues and support large Vd-area.

The present study has shown that the pharmacokinetic variables of FM are dose independent in the dose range of 1.1-2.2 mg/kg body weight. This is in agreement with the data reported for camels (28). However, dose dependent kinetics of FM was previously reported in horses (23). When a higher dose is used in animals, dose dependent kinetics may occur. Moreover, slightly higher Vd-area and half-life values at the dose of 2.2 mg/kg obtained from the present study have supported this conclusion.

The pharmacokinetics of FM in Angora rabbits following IV dose of 1.1 and 2.2 mg/kg are similar and characterized by a short elimination half-life, high clearance and large volume of distribution. In addition, the results of the present study indicated that both doses were well tolerated by all rabbits. The therapeutic effect of FM in Angora rabbits is not known, and we did not investigate its toxicity in our study. For this reason, further studies related to pharmacokinetics, pharmacodynamics, and clinical efficacy in diseased as well as healthy angora rabbits must be performed.
References