Pharmacokinetics and absolute oral bioavailability of meloxicam in guinea pigs (Cavia porcellus)

Ilse Moeremansa, Mathias Devreeseb, Siegrid De Baerce, Siska Croubelsb & Katleen Hermansa

*Department of Pathology, Bacteriology and Avian Diseases, Division of Poultry, Exotic Companion Animals, Wildlife and Experimental Animals, Faculty of Veterinary Medicine, Ghent University, Merelbeke, Belgium

bDepartment of Pharmacology, Toxicology and Biochemistry, Faculty of Veterinary Medicine, Ghent University, Merelbeke, Belgium

Correspondence: Katleen Hermans, Department of Pathology, Bacteriology and Avian Diseases, Division of Poultry, Exotic Companion Animals, Wildlife and Experimental Animals, Faculty of Veterinary Medicine, Ghent University, Salisburylaan 133, 9820 Merelbeke, Belgium. E-mail: Katleen.Hermans@ugent.be

Abstract

Objective To investigate the pharmacokinetics and absolute oral bioavailability of meloxicam in guinea pigs.

Study design Prospective crossover study.

Animals A group of six healthy male Dunkin Hartley guinea pigs.

Methods A single dose of meloxicam (1.5 mg kg⁻¹) was administered orally and intravenously (IV) to six healthy male guinea pigs. A wash-out period of 48 hours was taken into account between administrations (oral and IV) in the same animal. Blood was sampled through a central venous catheter before administration (t = 0 hours) and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24 and 28 hours post administration. After centrifugation, plasma concentrations of meloxicam were measured by high-performance liquid chromatography with UV detection, and pharmacokinetic parameters were calculated using noncompartmental analysis.

Results Meloxicam in guinea pigs exhibited a moderate absorption rate after oral dosing (time to maximal plasma concentration 3.7 ± 1.7 hours) and maximal plasma concentration was 0.92 ± 0.30 µg mL⁻¹. After IV administration, total body clearance and volume of distribution were 0.13 ± 0.04 and 0.72 ± 0.36 L kg⁻¹, respectively. Terminal half-life was 3.7 ± 0.7 hours and 3.5 ± 1.1 hours after IV and oral administration, respectively. Body extraction ratio was 0.0087 and mean absorption time was 3.8 ± 1.7 hours. The absolute oral bioavailability was 0.54 ± 0.14 in unfasted guinea pigs.

Conclusions and clinical relevance This study reported the pharmacokinetics of meloxicam in guinea pigs. Studies concerning efficacy and safety are the next step towards a rational use of this drug in guinea pigs.

Keywords bioavailability, Cavia porcellus, guinea pig, meloxicam, nonsteroidal anti-inflammatory drug, pharmacokinetics.

Introduction

Small mammals such as rabbits and guinea pigs are increasingly kept as pets, and thus seen more often by veterinary practitioners. In small-mammal practice, pain and inflammation can have far-reaching consequences as those species tend to develop potential life-threatening complications, such as anorexia, paralytic ileus and possible fatal dysbacteriosis. Guinea pigs regularly suffer from infections and painful dental conditions. Veterinarians are faced with the challenge of relieving pain, alleviating inflammatory effects, and at the same time, avoiding systemic side effects. Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in veterinary practice given their distinct analgesic, antipyretic and/or anti-inflammatory properties.

Meloxicam is a widely used NSAID of the oxicam group that preferentially inhibits cyclooxygenase (COX)-2 enzyme (Türck et al. 1996). The extent of the preference of NSAIDs for COX-2 varies between species because they express COX differently (Brideau et al. 2001). In humans, for example, meloxicam is from three to 77 times more specific for COX-2 compared to COX-1 and is categorized as preferential and not specific (Hawkey 1999). In horses and cats, data show that meloxicam is also COX-2 selective, but at higher concentrations the selectivity decreases (Beretta et al. 2005; Giraudel et al. 2005b). This is consistent with the observation that in horses COX-1 is inhibited for a significant amount of time when given a higher dose of 0.6 mg kg⁻¹ IV (Lees et al. 1991). However, due to the relative preferential inhibition of COX-2, meloxicam is still considered to have a potent anti-inflammatory effect and is better tolerated with fewer adverse effects on the stomach mucosa and renal blood flow. As a
result, meloxicam has a greater therapeutic range than non- or less-selective COX inhibitors, as demonstrated in humans by Ogino et al. (1997). The drug is registered in several countries of the European Union, such as Belgium, for use in humans, dogs, cats, horses, cows, and pigs (EPAR 2018).

Meloxicam has been used off label in rabbits and guinea pigs to treat pain and inflammatory responses. The dose for rabbits and guinea pigs was initially extrapolated and set at the same dose as in cats and dogs [0.1–0.3 mg kg\(^{-1}\) body weight (BW)], although the recommended dose for rats and other small rodents is higher, namely 1–2 mg kg\(^{-1}\) BW (EPAR 2010). Pharmacokinetic data in rabbits show that the extrapolated dose might be insufficient (Carpenter et al. 2009) and that higher doses (1.0 mg kg\(^{-1}\) for 29 days and 1.5 mg kg\(^{-1}\) for 5 days) are safe (Turner et al. 2006; Delk et al. 2014). However, further safety and efficacy studies in rabbits are required before conclusions can be made (Fredholm et al. 2013).

Despite the growing popularity of guinea pigs as pets, no known conclusive studies are available on the rational use or pharmacological properties of any NSAID in this species. In order to obtain a better insight into an appropriate drug dosing regimen, the aim of this study was to assess the main pharmacokinetic parameters and absolute oral bioavailability of meloxicam in guinea pigs.

Materials and methods

Animals and experimental protocol

The protocol was examined and approved by the ethical committees of the Faculties of Veterinary Medicine and Bioscience Engineering of Ghent University, Belgium (EC2013_179). Pilot studies were performed in five animals. Only one animal had the same features as the experimental animals of the pharmacokinetic study, and the results from this animal were used to gain an idea of the general pharmacokinetic properties of meloxicam in guinea pigs. The other four animals were end-of-study animals previously used for regulatory vaccine testing, and their results were used to adapt the dose used in the pharmacokinetic study.

The experiments, for the pharmacokinetic study, were carried out in six 9-week-old healthy male guinea pigs (Cavia porcellus) of 600–700 g BW that were previously catheterized in the jugular vein (Charles River, France). Upon arrival, catheters were flushed and filled with a locking solution (heparinized glucose 30%), in accordance with the instructions of the supplier. General clinical examination showed no abnormalities. The animals were housed individually on wood shavings and were allowed to adapt for 1 day. They were fed ad libitum with commercial pelleted food (Sniff Guinea Pig, Germany) and meadow hay. Drinking water was supplemented with 1 g L\(^{-1}\) ascorbic acid. The animals were provided with a shelter box and lived in a natural day–night cycle, at a room temperature of 20–22 °C.

Animals were assigned to receive one of two treatments in a random crossover design. Animals were assigned a number based on the random opening of their transport cages prior to the study and adaptation period. Animals 1–3 and 3–6 were in the first and second groups, respectively. For intravenous administration, 1.5 mg kg\(^{-1}\) meloxicam (Metacam 2 mg mL\(^{-1}\) injection for cats; Boehringer Ingelheim s.a., Belgium) was injected as a single bolus under isoflurane anaesthesia in the saphenous or noncatheterized jugular vein. Anaesthesia was induced in a box and maintained with a mask. Anaesthetic depth was tailored, to effect, in order to facilitate the injection and avoid unnecessary stress (pain of the injection or restraint).

The second treatment was 1.5 mg kg\(^{-1}\) of the oral formulation (Metacam 1.5 mg mL\(^{-1}\) oral suspension for dogs; Boehringer Ingelheim s.a.) administered by oral gavage in the conscious animals. After oral administration, the syringe and gavage tube were flushed with 2 mL of tap water.

There was a 48 hour washout period between the oral and IV administration protocols. The dose and washout period were determined based on the results of two pilot studies.

Pilot studies

A pilot study was performed to obtain full plasma pharmacokinetic profiles in one animal (same features as the six animals used in the crossover study). A total of 0.3 and 1 mg kg\(^{-1}\) BW meloxicam was administered orally with a 48 hour washout period. The aim was to determine maximal plasma concentration (C\(_{\text{max}}\)) at both doses and time to maximal plasma concentration (t\(_{\text{max}}\)), which was 4 hours. We also defined the appropriate blood collection protocol for the pharmacokinetic study. After the experiment, the central venous catheter was removed during short anaesthesia (premedication with an intramuscular injection of buprenorphine 0.05 mg kg\(^{-1}\), 15 minutes prior to box induction with isoflurane and maintenance by mask). Afterwards, the animal was monitored for signs of discomfort, food and water intake and faecal production for 7 days. The animal received meloxicam for another 3 days (0.3 mg kg\(^{-1}\) orally once daily). After the pharmacokinetic study, it was placed in a group housing with other guinea pigs. All animals were castrated at a later time and kept in groups with a minimum of two animals at the authors’ clinic. They were reused for educational purposes for as long as they were in good health. C\(_{\text{max}}\) was low, so a second pilot study was performed in four animals administered 1.5 mg kg\(^{-1}\) BW orally. We determined the plasma concentration at 3 and 4 hours after administration through terminal cardiac blood
sampling under general anaesthesia. After blood sampling, 1 mL sodium pentobarbital (20%, 200 mg mL$^{-1}$; Kela, Belgium) was injected intracardially to kill the animals while under general anaesthesia. Plasma concentrations were highest at 4 hours after administration and were between 1.02 ± 0.06 and 1.05 ± 0.04 μg mL$^{-1}$. These values were similar to $C_{\text{max}}$/$EC_{50}$ (half maximal effective concentration) values of clinically effective doses in other species ranging between 0.8 and 1.8 μg mL$^{-1}$ according to the intended effect and age (Burgos-Vargas et al. 2004; Montoya et al. 2004; Giraudel et al. 2005a).

Pharmacokinetic study

In the pharmacokinetic study, blood samples of 0.3 mL were taken from the central venous catheter before administration ($t = 0$ hour) and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24 and 28 hours post administration. The blood samples prior to drug administration were taken to check that all meloxicam was completely washed out prior to the next administration in the crossover design. Plasma was separated by centrifugation (9000 × $g$ for 5 minutes and stored at −20°C in cryotubes (cryovials; VWR, PA, USA) until analysis. Animals were clinically evaluated daily during the study. After the experiment, the central venous catheter was removed as described for the pilot animal. After monitoring for discomfort during 7 days, they were placed in group housing and castrated as described for the pilot animal. All animals were reused for educational purposes for as long as they were in good health.

Quantification of meloxicam in plasma

Plasma concentrations of meloxicam were determined using an in-house validated high performance liquid chromatography (HPLC)-UV method based on the method reported by Baert and De Backer (2002). Plasma samples were analyzed on a HPLC system consisting of a model P1000XR pump with vacuum degassing, an AS3000 autosampler and an UV6000LP diode array detector set at 355 nm; all from ThermoFischer Scientific (The Netherlands). Chromatographic separation was performed on a Hypersil GOLD column (dp: 5 μm, 100 × 3 mm i.d.; ThermoFischer Scientific) in combination with a precolumn of the same type. The injection volume was 50 μL. The mobile phase comprised of 0.1% acetic acid in water (A) and acetonitrile (B) and a gradient elution was performed. The flow rate was 0.5 mL minute$^{-1}$. Samples were prepared by pipetting 0.1 mL of plasma into a 15 mL screw-capped tube, followed by the addition of 100 μL methanol, 250 μL water, 25 μL internal standard (IS, piroxicam, 10 μg mL$^{-1}$ in methanol), 150 μL 0.1 M hydrochloric acid solution and 5 mL diethylether. Samples were extracted for 20 minutes on a horizontal rotary apparatus. After centrifugation (2400 × $g$, 5 minutes), the organic layer was transferred to a clean tube and evaporated under nitrogen at a temperature of 40°C. The residue was redissolved in 200 μL of the mobile phase A/B (80/20, v/v), briefly vortexed and 50 μL was injected onto the HPLC-UV system.

Validation of the HPLC-UV method

The method was validated in-house prior to the start of the analysis, according to a protocol described by De Baere et al. (2011) and the following parameters were evaluated: linearity, within- and between-run accuracy and precision, limit of quantification (LOQ), limit of detection (LOD), carry-over and specificity.

Plasma protein binding

The plasma protein binding of meloxicam in guinea pigs was determined. Therefore, fresh blank guinea pig plasma was spiked with meloxicam standard solution at 0.50 and 5.0 μg mL$^{-1}$. One aliquot of each concentration was treated in the same way as the pharmacokinetics trial samples (aliquot 1). Two other aliquots (aliquot 2 and 3) were incubated for 1 hour in a hot water bath of 38°C, and subsequently transferred onto Ultracon centrifugal filters (type Ultrace YM-30; Merck, Belgium) and centrifuged (2980 × $g$, 10 minutes, 41°C). Thereafter, the obtained filtrates of aliquot 2 and 3 were treated and analyzed in the same way as the trial samples. For quantification, corresponding calibration curves for each aliquot were used. The following equation was used to calculate the plasma protein binding:

$$\text{Plasma protein binding} (\%) = \frac{(\text{total plasma concentration} - \text{unbound plasma concentration})}{\text{total plasma concentration}} \times 100$$

Pharmacokinetic analysis

Plasma concentrations were modelled by noncompartmental analysis using Phoenix 7.0 (Certara, NY, USA). Following major pharmacokinetic parameters were calculated: $C_{\text{max}}$, plasma concentration after IV administration at $t = 0$ hours ($C_0$), $t_{\text{max}}$ mean residence time extrapolated to infinity (MRT), area under the plasma concentration–time curve from 0 to time $t$ (corresponding to the last time point with plasma concentrations > LOQ) (AUC $0\rightarrow t$), area under the plasma
concentration—time curve from 0 to infinity (AUC$_{0\to\infty}$) calculated using the linear up—log down trapezoidal method, total body clearance (Cl), volume of distribution (Vd), elimination rate constant (ke) and terminal elimination half-life (T$1/2_{el}$). F was calculated according to the following formula:

$$F = \frac{\text{AUC}_{0\to\infty} \text{PO}}{\text{AUC}_{0\to\infty} \text{IV}}$$  \hspace{1cm} (2)$$

Body extraction ratio (E) was calculated according to the following formula:

$$E = \frac{\text{Cl}}{\text{CO}}$$  \hspace{1cm} (3)$$

Mean absorption time (MAT) was calculated as:

$$\text{MAT} = \frac{\text{MRT}_{\text{PO}}}{\text{MRT}_{\text{IV}}}.$$  \hspace{1cm} (4)$$

Plasma concentration predictions were made towards more frequent oral dosing (twice a day) and an increased dose (3 mg kg$^{-1}$ once and twice a day), with a superposition tool in Phoenix 7.0 (Certara). A prediction was made for each animal and the mean value is reported in the results. The average oral plasma concentration at steady state ($C_{pss}$) was calculated in the various situations and animals using the following formula:

$$C_{pss} = \frac{\text{AUC}_{0\to24h}}{\tau}$$  \hspace{1cm} with $\tau$ = dosing interval (= 24 hours)  \hspace{1cm} (5)$$

Statistical analysis

Descriptive values were reported as mean ± standard deviation. Statistical analysis was performed with a commercially available online software program (R; Free Software Foundation, MA, USA). Kolmogorov–Smirnov tests were performed to check data distribution and paired student $t$-tests were performed to check for differences between IV and oral dosing. Differences were considered significant if $p < 0.05$.

Results

All animals remained in good general condition and showed no adverse clinical effects during the whole trial. Animals had a daily clinical examination by an experienced veterinarian, food and water intake were monitored and normal during the whole duration of the study. Faecal pellet production and urination were normal. No obvious signs of discomfort were recorded, and clinical parameters stayed normal throughout the whole study.

Table 1 Results of the in-house validation for meloxicam in guinea pig plasma, after liquid—liquid extraction in acidic medium using diethylether and reversed phase high-performance liquid chromatography—UV analysis. The method was validated according to a protocol described by De Baere et al. (2011) and the following parameters were evaluated: linearity, within-run and between-run accuracy and precision, limit of quantification, limit of detection, carry-over and specificity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Concentration (ng mL$^{-1}$)</th>
<th>Found concentration (ng mL$^{-1}$)</th>
<th>Precision (RSD %)</th>
<th>Accuracy (%)</th>
<th>$r$</th>
<th>g (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Linearity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.9993</td>
<td>0.00078</td>
</tr>
<tr>
<td>Within-run precision and accuracy</td>
<td>250</td>
<td>231.3 ± 7.8 (n = 6)</td>
<td>3.4</td>
<td>7.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2500</td>
<td>2441.5 ± 220.6 (n = 4)</td>
<td>9.0</td>
<td>−2.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between-run precision and accuracy</td>
<td>250</td>
<td>247.7 ± 9.4 (n = 6)</td>
<td>3.8</td>
<td>−0.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2500</td>
<td>2515.8 ± 52.3 (n = 6)</td>
<td>2.1</td>
<td>0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limit of quantification$^a$</td>
<td>50</td>
<td>54.0 ± 2.6 (n = 4)</td>
<td>4.9</td>
<td>8.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limit of detection$^b$</td>
<td></td>
<td>14.5 ± 5.7 (n = 4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carry-over</td>
<td></td>
<td>No signal at elution zone of MEL in solvent sample</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td></td>
<td>No signal at elution zone of MEL in blank sample</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

$^a$ Limit of quantification: lowest calibrator sample, accuracy and precision within acceptance ranges.

$^b$ Limit of detection: concentration corresponding to a signal-to-noise ratio = 1.1.
The results of the analytical method validation are shown in Table 1. The plasma concentration versus time profile is displayed in Fig. 1. No meloxicam was detected in samples of any animal at the time-point before the administrations.

Values of the main pharmacokinetic parameters are presented in Table 2 for both the IV and the oral treatments in the six guinea pigs.

Overall body extraction ratio was calculated to be 0.0087, as Peeters et al. (1980) reported total cardiac output in guinea pigs to be 248 mL minute⁻¹ kg⁻¹ and total plasma clearance in this study was 0.13 L kg⁻¹ hour⁻¹. This assumes plasma and blood clearance were equal.

The MAT was calculated based on the results of MRTIV and MRTPO. MRTIV was 3.36 ± 1.49 hours (range 1.0–4.1 hours) and MRTPO equaled 7.16 ± 1.87 hours (range 5.6–10.5 hours), which resulted in a MAT of 3.81 ± 1.68 hours.

Statistical analysis showed significant differences in AUC, Vd, Cl (not corrected for bioavailability) and MRT between IV and oral dosing (Table 2). A plasma protein binding of 98.4 ± 0.36% could be determined.

Based on these pharmacokinetic parameters, the plasma concentration–time profiles were predicted in four different dosing scenarios. Calculated mean plasma concentrations at steady state (Cpss) for the once daily oral dosing were on average 0.28 µg mL⁻¹ for the 1.5 mg kg⁻¹ dose and 0.54 µg mL⁻¹ for the 3 mg kg⁻¹ dose. When dosed every 12 hours, mean Cpss were 0.54 and 1.07 µg mL⁻¹ for 1.5 and 3 mg kg⁻¹, respectively.

**Discussion**

This study reports the pharmacokinetics and oral bioavailability of meloxicam in guinea pigs. There were some limitations to this study. We used only six animals, which limited the power of the study; however, the crossover design excluded some interindividual variations between the two routes of administration. The washout period was adequate because blood samples withdrawn prior to the next administration confirmed meloxicam was no longer detected. Additionally, the washout period (48 hours) was more than 10 × t1/2 (e.g. t1/2 = 3.69 ± 0.71 hours for IV administration and 3.51 ± 1.11 hours for oral administration) (Toutain and Bousquet-Mélon 2004).

In this study, the first blood collection for IV administration was 30 minutes after meloxicam administration, which was late compared to other studies. This may have influenced the computation of AUC0–∞. However, the difference between AUC0–t and AUC0–∞ was on average only 3% (for IV administration) and 8% (for oral administration). The difference between the measured AUC (e.g. AUC0–t) and the computed AUC0–∞ should not exceed 20%. Our results indicate that the sampling points were well chosen and the estimation of AUC0–∞ was valid (Toutain and Bousquet-Mélon 2004). Another consideration was the wide interindividual variations in pharmacokinetic parameters. This might have been due to the influence of experimental factors. Stress for example might have delayed gastrointestinal motility (and absorption rate), although no clinically obvious ileus was recorded in any animal. Only one animal showed a markedly delayed tmax (8 hours) after oral administration compared to the other animals (2–4 hours); the AUC was however comparable to the other animals.

In the present study, peak plasma concentrations after oral dosing were higher (0.92 ± 0.30 µg mL⁻¹) compared to rabbits that received the same dose as in our study (0.30 ± 0.09 µg

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**Table 2** Pharmacokinetic parameters of meloxicam administered to six male guinea pigs as a single dose of 1.5 mg kg⁻¹ orally or intravenously (IV) in a crossover design

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>IV</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0–∞ (hours µg L⁻¹)</td>
<td>13.76 ± 4.76*</td>
<td>6.44 ± 0.60*</td>
</tr>
<tr>
<td>AUC0–t (hours µg L⁻¹)</td>
<td>13.38 ± 4.83*</td>
<td>5.94 ± 0.76*</td>
</tr>
<tr>
<td>Cmax (µg mL⁻¹) (IV or Cmax (µg mL⁻¹) (oral)</td>
<td>0.98 ± 0.09</td>
<td>0.92 ± 0.30</td>
</tr>
<tr>
<td>MRT (hours)</td>
<td>3.3 ± 1.4*</td>
<td>7.2 ± 1.9*</td>
</tr>
<tr>
<td>tmax (hours)</td>
<td>3.7 ± 1.7</td>
<td>7.2 ± 1.9*</td>
</tr>
<tr>
<td>Vd (IV) (L kg⁻¹)</td>
<td>0.72 ± 0.36</td>
<td>0.76 ± 0.39</td>
</tr>
<tr>
<td>Cl (IV) (L hour⁻¹ kg⁻¹)</td>
<td>0.13 ± 0.04</td>
<td>0.12 ± 0.04</td>
</tr>
<tr>
<td>T1/2a (hours)</td>
<td>3.69 ± 0.71</td>
<td>3.51 ± 1.11</td>
</tr>
<tr>
<td>kcl (hour⁻¹)</td>
<td>0.20 ± 0.03</td>
<td>0.23 ± 0.07</td>
</tr>
<tr>
<td>F</td>
<td>0.54 ± 0.14</td>
<td>0.58 ± 0.12</td>
</tr>
</tbody>
</table>

AUC0–∞, area under the plasma concentration–time curve from 0 to infinity; AUC0–t, area under the plasma concentration curve from 0 to t; Cmax, maximal plasma concentration; Cl, total body clearance; F, bioavailability; kcl, elimination rate constant; MRT, mean residence time; tmax, time to maximal plasma concentration; T1/2a, terminal half-life; Vd, volume of distribution.

*Significant difference between IV and oral parameters (p < 0.05).
mL$^{-1}$) (Turner et al. 2006). Others reported similar peak plasma concentrations (between 0.7 and 1.07 mg mL$^{-1}$) in rabbits after receiving 1.0 mg mL$^{-1}$ orally (Fredholm et al. 2013; Delk et al. 2014). Furthermore, the $C_{\text{max}}$ in our study was comparable with $C_{\text{max}}$ values of therapeutic doses established in horses and cats, namely between 1 and 2.5 mg mL$^{-1}$ (Toutain et al. 2004; Giraudel et al. 2005a; Raidal et al. 2013). $t_{\text{max}}$ was variable between individuals (range 2–8 hours), and MRT after IV and oral administration was shorter in goats and rabbits (Toutain and Bousquet-Mérou 2004; Fredholm et al. 2013; De Vito et al. 2018). The MRT after IV administration was shorter (3.3 hours) than after oral administration (7.2 hours), which resulted in a MAT of 3.8 hours, which is in agreement with our mean $t_{\text{max}}$ of 3.7 hours. MAT can be considered fairly rapid and is comparable to the MAT found for horses fasted overnight by Toutain et al. (2004).

Volume of distribution for IV administration is large (0.72 ± 0.36 L kg$^{-1}$) compared to the $V_d$ of horses (0.27 L kg$^{-1}$), donkeys (0.09 L kg$^{-1}$), swine (0.16 L kg$^{-1}$) and goats (0.26 L kg$^{-1}$) (Sinclair et al. 2006; Pairis-Garcia et al. 2015; De Vito et al. 2018). Plasma protein binding was 98.4%, which is comparable to other species ranging between 96% and 98% (EPAR 2010).

Clearance following IV administration was higher in guinea pigs (0.13 L hour$^{-1}$ kg$^{-1}$) compared to other species [values between 0.001 (birds) to 0.081 (horses) L hour$^{-1}$ kg$^{-1}$], but comparable to that of donkeys (0.19 L hour$^{-1}$ kg$^{-1}$) and goats (0.26 L kg$^{-1}$) (Baert and De Backer 2002; Toutain and Cester 2004; Sinclair et al. 2006; Stock et al. 2013). Meloxicam is reported to be a drug with low extraction ratios in all species. In mice, for example Chen et al. (2016) reported an extraction ratio of 0.029. In our study, we calculated a low overall body extraction ratio of 0.0087. Both moderate clearance and volume of distribution in guinea pigs led to a rather moderate terminal elimination half-life after oral administration (3.51 ± 1.11 hours). Similar half-lives were reported in piglets and horses (2.5–2.7 hours) (Lees et al. 1991; Fosse et al. 2008). Most species, however, have longer elimination half-life values compared to guinea pigs. In rabbits, the elimination half-life after oral administration is between 6 and 9 hours. No data in guinea pigs have been published yet, but it is important to note that juvenile animals were used in the current study. In horses and humans, it was demonstrated that clearance of meloxicam was more rapid in juvenile individuals (Burgos-Vargas et al. 2004; Raidal et al. 2013). Another consideration is the fact that all animals were male. Sex-specific differences in plasma concentrations of meloxicam have been noted in rats and dogs. Female rats demonstrated a slower elimination. Meloxicam is cleared by biotransformation in the liver through cytochrome P450 2C isoenzymes. CYP450 2C11 isoenzyme is absent in female rats, which might explain the slower elimination (Busch et al. 1998).

Absolute oral bioavailability was 54% (range 25–77%), which is low compared to other herbivorous species such as horses (98%), goats (79%), llamas (76%) and sheep (72%) (Toutain et al. 2004; Ingvast-Larsson et al. 2011; Kreuder et al. 2012; Stock et al. 2013). Several experimental factors can influence the bioavailability, for example, the feeding protocol or pharmaceutical formulation. Animals in this study were not fasted prior to gavage. As it was the goal to mimic clinical settings, animals were fed ad libitum meadow hay, pelleted food and had permanent access to water. For several NSAIDs, absorption is delayed when given orally due to binding to hay and/or ingesta. In horses, bioavailability of meloxicam was not significantly influenced by the availability of food; however, the absorption was significantly slower in the presence of food (Toutain et al. 2004). The low oral bioavailability might limit the use of the oral formulation of meloxicam in guinea pigs and other routes of administration might be more appropriate, but this was not the scope of this study. In this study, plasma concentration–time profiles were also predicted using a different dose (1.5 and 3 mg kg$^{-1}$) and dosing interval (once or twice a day). In rats, the effective dose to treat postoperative pain is determined at 1–2 mg kg$^{-1}$ BW (Bourque et al. 2010) and in rabbits an oral dose of 1.5 mg kg$^{-1}$ BW was shown to be safe if given for 5 consecutive days (Turner et al. 2006). Therefore, a dose of 1.5 mg kg$^{-1}$ was presumed to be safe in guinea pigs and this dose was hypothesized to be necessary to reach therapeutic concentrations in guinea pigs.

Unfortunately, no EC$_{50}$ values or clinical efficacy data have been published in guinea pigs. Reported EC$_{50}$ values for meloxicam in other species are: 0.78–1.3 μg mL$^{-1}$ in cat and 0.13–0.73 μg mL$^{-1}$ in the horse, depending on the desired effect (Toutain and Cester 2004; Giraudel et al. 2005a). Based on these data, a dose of 1.5 mg kg$^{-1}$ twice a day could be advised in guinea pigs (C$_{\text{pa}}$ 0.54 μg mL$^{-1}$ and $C_{\text{max}}$ 0.84 μg mL$^{-1}$) (Fig. 2). Another method to estimate effective doses is to calculate mean effective concentration (MEC) values based on the advised dose (or dose used in a study) and the clearance in that same study. Compared to the MEC values calculated by other authors (horses 0.735 μg mL$^{-1}$, dogs 0.833 μg mL$^{-1}$ and cats 0.347 μg mL$^{-1}$), this dosing schedule (1.5 mg kg$^{-1}$ twice a day administered orally) would be insufficient based on the dog and horse data (Montoya et al. 2004; Toutain et al. 2004; Lehr et al. 2010).

If one calculates the time above this MEC value, the difference is even more clear. In comparison to cats, this dose would be sufficient as the time above the MEC would be on average between 17.5 and 18 hours, compared to between 5 and 6 hours for the horse MEC.

If one would consider dosing 3 mg kg$^{-1}$ orally once a day to guinea pigs the same $C_{\text{pa}}$ was reached, however caution is warranted because $C_{\text{max}}$ would reach 1.42 μg mL$^{-1}$ and in
horses this concentration would cause COX-1 inhibition related toxicity (Beretta et al. 2005).

Furthermore, predictions should always be interpreted with caution as showed in cats. Lehr et al. (2010) concluded, based on simulations, that a dose of 0.05 mg kg\(^{-1}\) once daily would not be enough to reach the EC\(_{50}\) values described by Giraudel et al. 2005a. However, in cats that same dose has clinical proven efficacy (EPAR 2010; EPAR 2018). This clearly shows the need for efficacy studies besides safety and pharmacokinetic data or simulations.

In rabbits, a dosing of 1 mg kg\(^{-1}\) for 29 days was proven to be safe but no data are available concerning possible accumulation and safety in guinea pigs. However, in view of the short half-life no accumulation is expected with a once daily regimen. Further research on the safety of multiple dosing of meloxicam, that is, on guinea pig gastrointestinal mucosa and renal and hepatic function, is necessary. Furthermore, no real pain scoring system is established in guinea pigs and pain scoring might be very difficult compared to other species due to the stoic nature of this species (Ellen et al. 2016; Gleeson et al. 2016).

**Conclusion**

Despite the high dose of meloxicam used in this study, we showed moderate absorption and elimination in guinea pigs. Together with the prediction data, it should be considered that dosing schedules might be very different in guinea pigs compared to other species. More research on repeated dosing, pharmacodynamics, accumulation and safety is needed to develop appropriate dosing schedules in guinea pigs.

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**Authors’ contributions**

IM: design, acquisition of data (animal experiment), data interpretation, preparation of manuscript. MD: pharmacokinetic analysis, preparation of manuscript. SDB: quantification of meloxicam in plasma. SC: design, data interpretation, preparation of manuscript. KH: design, acquisition of data (animal experiment), data interpretation, preparation of manuscript. All authors have read and approved the final version of the manuscript.

**Conflict of interest**

The authors declare no conflict of interest.

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