Pharmacokinetics and milk secretion of gabapentin and meloxicam co-administered orally in Holstein-Friesian cows

Pradeep R. Malreddy, Johann F. Coetzee, Butch KuKanich, and Ronette Gehring

List of Abbreviations:

Pharmacokinetic Parameters

λ_z: First-order elimination rate constant

$t_{1/2\,\lambda z}$: Terminal (elimination) half-life

T_{max}: Time to maximum plasma concentration

C_{max}: Maximum plasma concentration

C_0: Initial plasma concentration extrapolated to time zero

AUC_{0-t}: Area under curve from time zero to time of last measured concentration

$AUC_{0-\infty}$: Area under curve from time zero to infinity

$AUMC_{0-\infty}$: Area under the first moment curve from time zero to infinity

Cl/F: Plasma clearance corrected for unknown bioavailability

MRT: Mean residence time

Pharmacokinetic Parameters specific for Milk

CL_M/F: Milk Clearance (volume of blood cleared of drug per unit time by passing into the milk) corrected for unknown bioavailability

Percent $_{recovered}$: Cumulative amount of drug eliminated through milk expressed as a percentage of the administered dose

Other Abbreviations

MER: Milk drug excretion rate

MRL: Maximum Residue Limit

M/P: Milk to plasma ratio

SPE: Solid phase extraction

LOQ: Limit of quantitation

GABA: Gamma amino butyric acid

NSAID: Non-steroidal anti-inflammatory drug

SD: Standard deviation

P.O: Per oral

1 **Title:** Pharmacokinetics and milk secretion of gabapentin and meloxicam co-

2 administered orally in Holstein-Friesian cows.

3 **Short Title:** Milk secretion of gabapentin and meloxicam in dairy cattle.

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Abstract

Management of neuropathic pain in dairy cattle could be achieved by combination therapy of gabapentin, a GABA analog and meloxicam, an NSAID. This study was designed to determine specifically the depletion of these drugs into milk. Six animals received meloxicam at 1 mg/kg and gabapentin at 10 mg/kg while another group (n=6) received meloxicam at 1 mg/kg and gabapentin at 20 mg/kg. Plasma and milk drug concentrations were determined over 7 days post-administration by HPLC/MS followed by non-compartmental pharmacokinetic analyses. The mean (± SD) plasma C_{max} and T_{max} for meloxicam (2.89 ± 0.48 µg/ml and 11.33 ± 4.12 hours) were not much different from gabapentin at 10 mg/kg (2.87 ± 0.2 µg/ml and 8 hours). The mean (± SD) milk C_{max} for meloxicam (0.41 ± 0.16 µg/ml) were comparable to gabapentin at 10 mg/kg (were 0.63 ± 0.13 µg/ml and 12 ± 6.69 hours). The mean plasma and milk C_{max} for gabapentin at 20 mg/kg P.O. were almost double the values at 10 mg/kg. The mean (± SD) milk to plasma ratio for meloxicam (0.14 ± 0.04) was lower than for gabapentin (0.23 ± 0.06). The results of this study suggest that milk from treated cows will have low drug residue concentration soon after plasma drug concentrations have fallen below effective levels.

Introduction

Chronic pain associated with lameness is considered one of the most significant welfare concerns in dairy cows (Whay, Main *et al.* 2003). Hyperalgesia has been reported to persist in dairy cattle and lame sheep for at least 28 days after the causal lesion has resolved (Ley, Waterman *et al.* 1996; Whay, Waterman *et al.* 1998). Inflammatory pain associated with lameness responds modestly to treatment with non-steroidal anti-inflammatory drugs (NSAIDs) (Whay, Main *et al.* 2003; Flower, Sedlbauer *et al.* 2008) but neuropathic pain (due to nerve damage or neuronal dysfunction), very limited information for its occurrence in dairy cattle, is considered refractory to the effects of NSAIDs and many opioid analgesics (Woolf and Mannion 1999). Gabapentin (1-(aminomethyl) cyclohexane acetic acid) is a γ-aminobutyric acid (GABA) analogue originally developed for the treatment of spastic disorders and epilepsy (Cheng and Chiou 2006). Subsequent studies have established that gabapentin is also effective for the management of chronic pain of inflammatory or neuropathic origin (Hurley, Chatterjea *et al.* 2002). Although the mechanism of action of gabapentin is poorly understood, it is thought to bind to the α2-δ subunit of voltage gated calcium channels acting pre-synaptically to decrease the release of excitatory neurotransmitters (Taylor 2009).

Gabapentin appears to be absorbed from the gastro-intestinal tract by a saturable amino-acid transporter system (Su *et al.,* 1995). Plasma gabapentin concentrations > 2 µg/mL in humans are associated with a lower frequency of seizures (Sivenius, Kalviainen *et al.* 1991). Similar doses are used to treat epilepsy and neuropathic pain suggesting that these concentrations will also be effective for

analgesia. It has also been reported that gabapentin can interact synergistically with NSAIDs to produce antihyperalgesic effects (Hurley, Chatterjea *et al.* 2002; Picazo, Castaneda-Hernandez *et al.* 2006).

Meloxicam is a NSAID of the enolic acid (oxicam) group that is considered to be non-specific cyclooxygenase inhibitor. However, studies from some laboratories show cyclooxygenase-2 selectively at low concentrations in humans (Lazer, Miao et al. 1997), rats (Ogino, Hatanaka et al. 1997), and dogs (Brideau, Van Staden et al. 2001). The plasma pharmacokinetics of meloxicam co-administered with gabapentin has been previously described in cattle (Coetzee, Mosher *et al.* 2010). Plasma gabapentin concentrations >2 µg/mL were maintained for up to 15 h and meloxicam concentrations >0.2 µg/mL for up to 48 h. The pharmacokinetic profile of oral gabapentin and meloxicam supports clinical evaluation of these compounds for management of neuropathic pain in dairy cattle; however, information regarding the depletion of these compounds in milk is needed to determine when milk from treated animals is safe for human consumption.

Materials and Methods

Animals

Twelve clinically healthy Holstein-Friesian cows, free of mastitis were used in this study as determined by the examination of milk from each animal for gross abnormalities and acceptable level of somatic cell counts, which were in the acceptable range between 13,000 -528,000 cells/mL (The maximum limit allowed is 750,000 per mL according to

the U.S. Food and Drug Administration-2007 Pasteurized Milk Ordinance). The animals were aged between 34 and 62 months and weighed between 543 and 891 Kg at the time of study. All cows were in their first, second or third lactation. Cows were maintained on a diet comprising a total mixed ration comprising, cottonseed, alfalfa hay, sweet bran and corn silage with ad-libitum water at Kansas State University Dairy Farm.

Animal Phase Study Design

The animals were randomly assigned to two treatment groups comprising 6 animals per group. One group was co-administered gabapentin (400 mg and 100 mg capsules, Actavis Elizabeth LLC, Elizabeth, NJ) and meloxicam (15 mg tablets, Unichem Pharmaceuticals, Rochelle Park, NJ) at a dose of 10 mg/kg and 1 mg/kg respectively. The second group received gabapentin and meloxicam at a dose of 20 mg/kg and 1 mg/kg respectively. The drugs were combined in a gelatin capsule and delivered orally with a balling gun into the oropharynx.

Milk and Blood Sample Collection

Twenty milliliters of milk were collected in polycarbonate bottles from each cow just before drug administration and then every 8 hours coinciding with the milking schedules at the dairy farm for 7 days. The samples were collected from the collection vessel once milking of the cow was completed. The milk from these cows was not added to the bulk tank in order to prevent drug residues from entering the human food chain. The volume of milk produced at each milking by each individual cow was also recorded at the time of sample collection. The samples were immediately brought back to the lab and frozen at -80°C until further analysis.

113 At each milk sampling time, 10 ml of blood were collected by venipuncture of the jugular

114 vein and transferred to heparinized vacutainers. A set of blood samples was also

115 collected prior to drug administration to confirm that animals did not have previous

116 exposure to the test compounds. Blood samples were immediately brought back to the

117 lab, centrifuged at 1500 g, the plasma transferred to cryovials, and stored at -80°C until

118 further analysis.

119 **Milk Sample Preparation and HPLC/MS analysis**

120 Milk samples were prepared by adding 0.2 mL of the sample or milk standard to 0.1 mL

121 of the internal standard solution containing 1 µg/mL of piroxicam (MP Biomedicals,

122 Solon, OH, USA) and 1 µg/mL of pregabalin (Lyrica, Pfizer, Inc., NY, NY, USA).

123 Trichloracetic acid 0.2 mL 30% in water, was added and then the solution was vortexed

124 for 5 seconds. The samples were centrifuged for 5 minutes at 15, 000 x g and then the

125 analytes were extracted from supernatant using solid phase extraction cartridges (SPE,

126 Varian Bond Elute C18, Varian Inc. Palo Alto, CA). The SPE were conditioned with 1

127 mL methanol followed by 1 mL of water and then 0.35 mL of the sample supernatant

128 was added. The SPE were washed with 1 mL de-ionized water and the analytes eluted

129 with 1 mL methanol. The eluate was evaporated to dryness under an air stream at 40

130 °C and then reconstituted with 0.2 mL 50% methanol and vortexed for 5 seconds. The

131 solution was centrifuged for 5 minutes at 15,000 x g to sediment particulates and 0.020

132 mL was injected onto the HPLC. Milk standards were made by adding meloxicam (LKT

133 Laboratories, St. Paul, MN, USA) and gabapentin (Spectrum Chemicals, Gardena, CA,

134 USA) to untreated milk at 0, 10, 20, 50, 100, 200, 500, 1000, and 2000 ng/mL each. The

135 linear standard curve was accepted if the predicted values were within 15% of the

136 actual values and the correlation coefficient (R) was at least 0.99. The LOQ of the assay

137 for meloxicam and gabapentin in milk was 10 ng/mL and defined as the lowest

138 concentration of the linear standard curve with a predicted value within 15% of the

139 actual value with an R of at least 0.99. The accuracy was 99 ± 6% of the actual

140 concentration and the coefficient of variation was 6% determined on replicates of 4 each

141 at 10, 100, and 2000 ng/mL for gabapentin in milk. The accuracy was 97 ± 3% of the

142 actual concentration and the coefficient of variation was 2% determined on replicates of

143 4 each at 10, 100, and 2000 ng/mL for meloxicam in milk.

144 *Plasma Sample Preparation and HPLC/MS Analysis*

145 Plasma samples were prepared by adding 0.05 mL of plasma or plasma standard to 0.2

146 mL of internal standard solution containing 250 ng/mL of piroxicam and gabapentin in

147 methanol with 0.1% formic acid. The samples were vortexed for 5 seconds and then

148 centrifuged for 10 minutes at 15,000 x g. The supernatant was transferred to an

149 injection vial with the injection volume being 0.020 mL. Plasma standards were made by

150 adding meloxicam and gabapentin to untreated plasma at 0, 25, 50, 100, 200, 500,

151 1000, and 5000 ng/mL each. The linear standard curve was accepted if the predicted

152 values were within 15% of the actual values and the correlation coefficient (R) was at

153 least 0.99. The LOQ of the assay for meloxicam and gabapentin in plasma was 25

154 ng/mL and defined as the lowest concentration of the linear standard curve with a

155 predicted value within 15% of the actual value with an R of at least 0.99. The accuracy

156 was 96 ± 5% of the actual concentration and the coefficient of variation was 5%

157 determined on replicates of 4 each at 10, 100, and 2000 ng/mL for gabapentin in milk.

158 The accuracy was 97 ± 8% of the actual concentration and the coefficient of variation

159 was 7% determined on replicates of 4 each at 50, 500, and 5000 ng/mL for meloxicam

160 in plasma.

161 The plasma concentrations of gabapentin and meloxicam were simultaneously

162 determined using liquid chromatography (Shimadzu Prominence, Shimadzu Scientific

163 Instruments, Columbia, MD, USA) with mass spectrometry (API 2000, Applied

164 Biosystems, Foster City, CA, USA). The mobile phase consisted of acetonitrile (mobile

165 phase A) with 0.1% formic acid (mobile phase B) with a constant flow rate of 0.4

166 mL/min. A mobile phase gradient was used starting at 100% B from 0-1 minutes, a

167 linear gradient to 60% B at 3 minutes which was held until 5 minutes and then a linear

168 gradient to 100% B at 5.5 minutes with a total run time of 8 minutes. A phenyl column

169 (Hypersil Gold, 150x2.1, 5µM, Thermo Scientific, Waltham, MA, USA) maintained at 40

170 °C achieved separation. The qualifying ion for meloxicam was 352.1 and the quantifying

171 ion for meloxicam was 114.9. The qualifying ion for gabapentin was 172.1 and the

172 quantifying ion for gabapentin was 154.1. The qualifying ion for piroxicam (meloxicam

173 internal standard) was 332.1 and the quantifying ion for piroxicam was 95.1. The

174 qualifying ion for pregabalin (gabapentin internal standard) was 160.0 and the

175 quantifying ion for pregabalin was 142.0. The source temperature was 350 °C and the

176 ionization spray energy was 5000 V. The curtain gas, gas 1, and gas 2 flow rates were

177 10, 30, and 75 arbitrary units, respectively.

178 ***Non-compartmental analysis of plasma and milk time-concentration data***

179 Non-compartmental pharmacokinetic analyses were performed using Excel (Microsoft,

180 WA) add-in program, PK solver (Zhang, Huo *et al.* 2010) The various parameters

181   estimated included area under the plasma time-concentration curve from time zero to

182   infinity ($AUC_{0-\infty}$), area under the first moment curve from time zero to infinity (AUMC),

183   first-order elimination rate constant (λ_z), terminal half-life ($T_{1/2\ \lambda z}$), mean residence time

184   (MRT), maximum plasma concentration (C_{max}), and time to maximum plasma

185   concentration (T_{max}).

186   ***Milk excretion analysis***

187   The milk collection times, concentration and production data were fit to an excretion

188   model using Phoenix® WinNonlin^{TM} (Pharsight Corporation, Mountain View, CA) to

189   calculate the milk drug excretion rate (MER) over the period using Equation 1.

190    $$MER = \Delta A / \Delta t \ = \ \frac{[C] \times Volume}{(Ending\ time - Starting\ time)}$$

191   Equation 1

192   Where MER is the Milk drug Excretion Rate between subsequent milk collections and

193   represents the amount of drug (ΔA) eliminated in the milk per unit time (Δt), [C] is the

194   milk drug concentration, Ending time is the time of milk collection, and Starting time is

195   the time of collection of the previous milk sample. Other parameters calculated by

196   Phoenix analysis of milk excretion data included: Percent $_{recovered}$ (cumulative amount of

197   drug eliminated expressed as percentage of administered dose), λz (first order rate

198   constant associated with the terminal portion of the curve), $T_{1/2\ \lambda z}$ (terminal half-life),

199   area under the time- milk concentration curve from time zero to infinity ($AUC_{0-\infty}$),

200   maximum plasma concentration (C_{max}), and time to maximum plasma concentration

201   (T_{max}).

Milk clearance calculation

To determine whether the rate of milk excretion was linearly related to plasma drug

concentration, the milk excretion rate (ΔA/Δt) was plotted against the plasma drug

concentration at the mid-point between the two sampling times ($C_{mid,}$ calculated by

averaging the plasma drug concentrations that were measured at the current and

preceding sampling times). In addition, the slope of the regression line drawn through

the points of this graph represents the drugs' milk clearance (CL_M/F) (Tucker GT, 1981)

and was calculated using Equation 2.

$$CL_M = \frac{\Delta A/\Delta t}{C_{mid}}$$
Equation 2

Results

Figure 1 is a plot of the means (± standard error) of both plasma and milk concentration-

time profile for gabapentin administered orally at two dose rates of 10 mg/kg and 20

mg/kg. Table 1 is a summary of the non-compartmental pharmacokinetic analysis for

gabapentin at 10 mg/Kg and Table 2 is a summary of the non-compartmental

pharmacokinetic analysis for gabapentin at 20 mg/Kg dose rates in both milk and

plasma. The mean (± SD) plasma C_{max} and T_{max} for gabapentin administered at 10

mg/kg P.O. were 2.87 ± 0.2 µg/ml and 8.0 ± 0.0 hours respectively while for higher dose

(20 mg/kg) the mean (± SD) plasma C_{max} and T_{max} were 5.42 ± 0.69 µg/ml and 9.33 ±

3.27 hours respectively. On the other hand, the mean (± SD) milk C_{max} and T_{max} for

gabapentin administered at 10 mg/kg P.O. were 0.63 ± 0.13 µg/ml and 12 ± 6.69 hours

223 respectively while for higher dose (20 mg/kg) the mean (± SD) milk C_{max} and T_{max} were

224 1.19 ± 0.14 µg/ml and 12 ± 4.4 hours respectively.

225 Figure 2 is a plot of the means (± standard error) of both plasma and milk concentration-

226 time profile for meloxicam administered orally at a dose of 1 mg/kg. Table 3 is a

227 summary of various pharmacokinetic parameters in both milk and plasma following non-

228 compartmental analysis for meloxicam. The mean (± SD) plasma C_{max} and T_{max} for

229 meloxicam (1 mg/kg) were 2.89 ± 0.48 µg/ml and 11.33 ± 4.12 hours respectively while

230 the mean (± SD) milk C_{max} and T_{max} were 0.41 ± 0.16 µg/ml and 9.33 ± 3.11 hours

231 respectively.

232 Figures 1-3 shows the calculation of Cl_M/F for meloxicam and gabapentin by calculating

233 the average slopes of the regression lines drawn through the milk excretion rate versus

234 plasma drug concentration plots. The mean ± SD milk clearance for meloxicam was

235 166.52 ± 82.15 mL/h while for gabapentin at 10 mg/kg and 20 mg/kg were 300.48 ±

236 57.4 and 259.57 ± 102.82 mL/h respectively. Since CL_M/F was not significantly different

237 between the two gabapentin dose rates, these were combined in Figure 3 to simplify the

238 graph.

239   Milk concentrations depleted below measurable concentrations within 80 hours

240 for meloxicam and 48 and 64 hours for the low and high dose of gabapentin,

241 respectively. Milk to plasma (M/P) ratio was calculated as a measure of the ratio of

242 AUC_{0-t} (milk) over AUC_{0-t} (plasma) to determine the extent of concentration of the given

243 drugs in milk. The mean ± SD M/P ratio for meloxicam was 0.14 ± 0.04 while

244 gabapentin (for combined dose rates) was 0.23 ± 0.06 (Tables 1, 2 and 3). The

245 percentage of meloxicam excreted in milk when given at 1 mg/kg P.O was 1.61 ± 0.76

246 % while 0.18 ± 0.02 % and 0.17 ± 0.05 % of gabapentin excreted into the milk when

247 given at 10 and 20 mg/kg respectively. The average milk production rate was 980 ± 290

248 mL/hour.

249

250 **Discussion**

251 Lactation did not appear to alter the plasma pharmacokinetics of either meloxicam or

252 gabapentin. The pharmacokinetic parameters from this study are comparable to those

253 previously reported for ruminant beef calves (Coetzee, Mosher *et al*. 2010). Meloxicam

254 and gabapentin crossed from the plasma into the milk following oral administration at

255 clinically relevant doses. For both drugs, milk concentrations depleted to concentrations

256 that were below the level of detection of the analytical technique within approximately 3

257 days. Milk concentrations that are safe for human consumption have not been

258 established for either of these drugs in the United States, but a maximum residue limit

259 (MRL) has been established in Europe for meloxicam. The level of quantitation of the

260 analytical technique in milk for meloxicam (10 ng/ml) used in this study is lower than the

261 maximum MRL set by the European Agency for the Evaluation of Medicinal Products

262 (15 ng/ml) (www.ema.europa.eu).

263   CL_M/F was low (~0.2-0.3 L/h) for both meloxicam and gabapentin when compared to

264 total body clearance (CL/F ~ 10 L/h for meloxicam and ~ 150 L/h for gabapentin) and

265 mammary tissue blood flow in the lactating cow (~120 L/h). This suggests that the

266 mammary gland is inefficient in extracting these drugs from the plasma. Less than 1 and

267   2% of the administered dose was excreted from the animals' bodies through the milk for

268   gabapentin and meloxicam, respectively.

269   Two different doses of gabapentin were administered to the animals to determine

270   whether saturable transport across either the gastrointestinal or mammary epithelial

271   barriers at 10 and 20 mg/kg PO would result in non-linear pharmacokinetics. Doubling

272   the dose resulted in a dose-proportional increase in milk and plasma concentrations,

273   whilst the milk clearance remained constant. This suggests that, if the movement of

274   gabapentin across either of these epithelia is facilitated by a transporter, the system

275   was not saturated under the circumstances of this study (doses up to 20 mg/kg PO).

276   The percentage of the administered gabapentin dose that was excreted through

277   the milk was approximately a tenth lower than for meloxicam. This is despite gabapentin

278   having a higher milk clearance and milk to plasma ratio. The most likely reason for this

279   difference is a lower oral bioavailability for gabapentin. Further studies comparing oral

280   absorption to intravenous pharmacokinetics for this drug would be needed to confirm

281   this hypothesis.

282   In summary, milk gabapentin and meloxicam concentrations were directly related

283   to plasma concentrations. There was no apparent delay in the appearance of these

284   drugs in the milk, and their rate of depletion from the milk was similar to that from

285   plasma. Neither of the drugs appears to have been sequestered in the mammary tissue

286   or milk. The results of this study suggest that milk from treated cows will have low drug

287   residue concentration soon after plasma drug concentrations have fallen below effective

288 levels. This study further supports the feasibility of using these drugs for the control of

289 pain in food-producing animals, but efficacy studies are needed.

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377 **Figures**

378 <Figure 1>
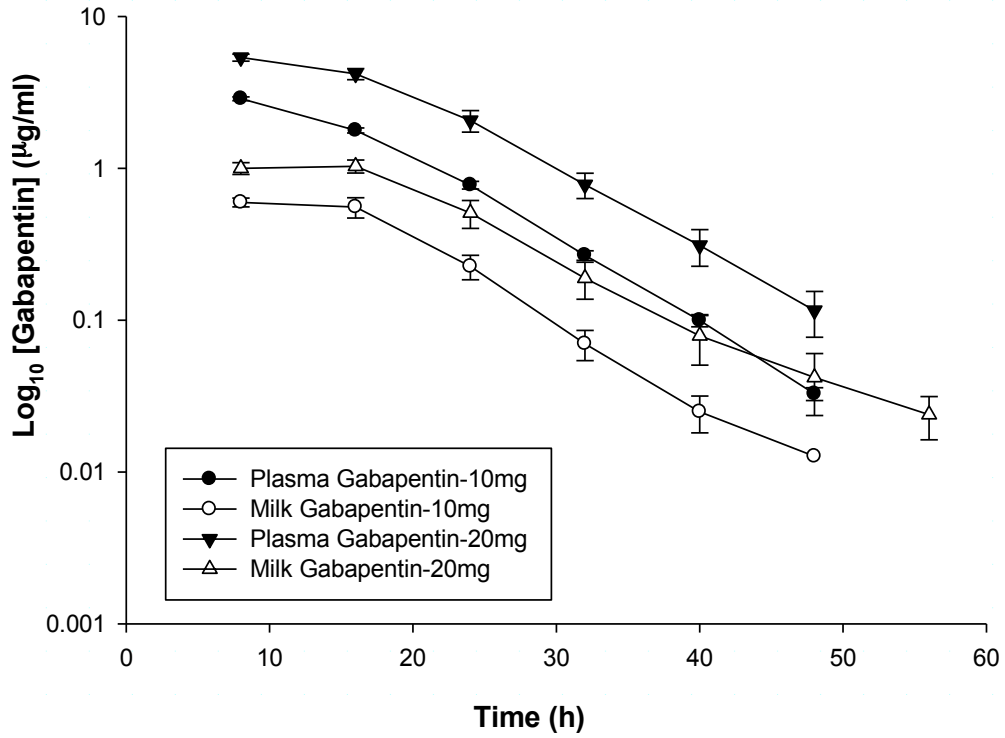
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380 Figure 1. Mean plasma and milk concentrations of Gabapentin following 10 and 20

381 mg/kg PO administration.

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<Figure 2>
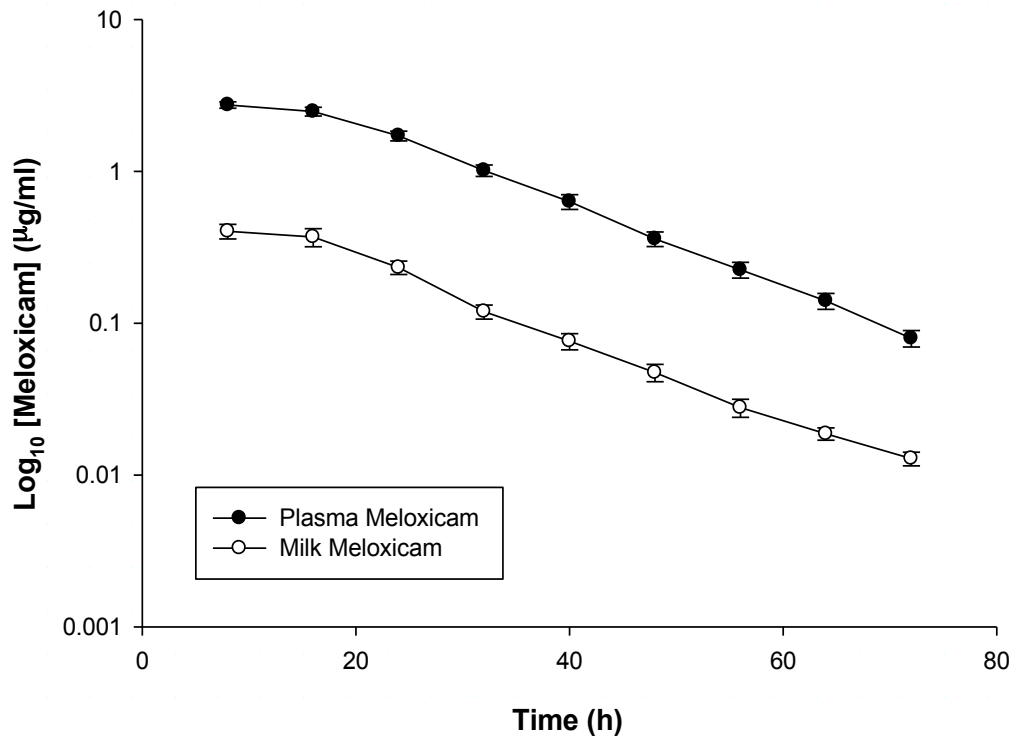
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392   Figure 2. Mean plasma and milk concentrations of Meloxicam following 1 mg/kg PO

393   administration.

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403   \<Figure 3\>

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Figure 3. Average slopes of the regression lines drawn through the milk excretion rate

versus plasma drug concentration plots for meloxicam and gabapentin, representing the

milk clearance of these two drugs.

TABLE 3 Meloxicam Milk and Plasma non-compartmental Pharmacokinetic Parameters following PO Administration at 1mg/kg

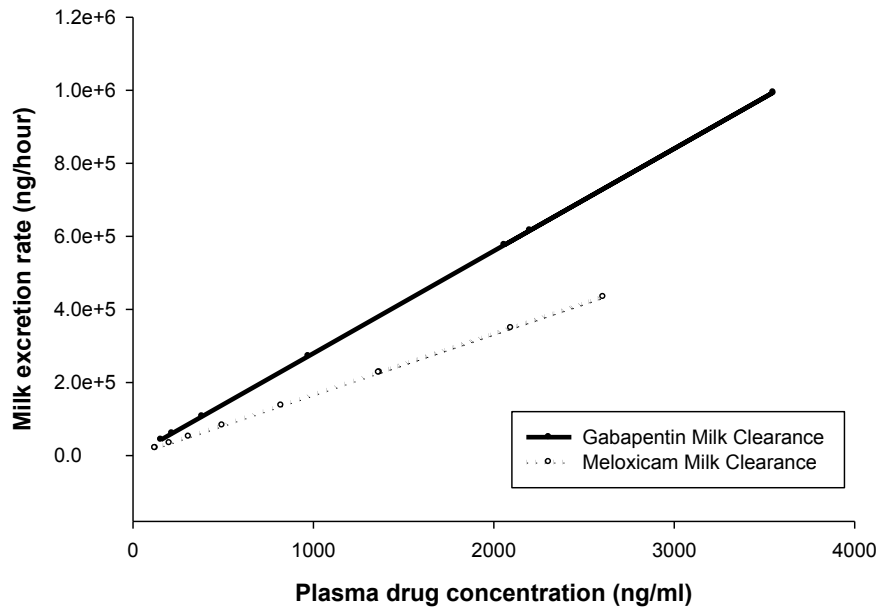| Parameters	Units	Meloxicam 1 mg/kg (targeted dose)									
		Milk					Plasma				
		Mean	STDEV	Min	Median	Max	Mean	STDEV	Min	Median	Max
λ_Z	1/h	0.07	0.01	0.06	0.07	0.08	0.06	0.02	0.01	0.06	0.08
$t_{1/2}$	h	10.38	1.20	8.25	10.62	12.41	14.58	11.32	8.58	11.69	50.29
T_{max}	h	9.33	3.11	8.00	8.00	16.00	11.33	4.12	8.00	8.00	16.00
C_{max}	µg/ml	0.41	0.16	0.25	0.36	0.76	2.89	0.48	2.18	2.97	3.64
C_0	µg/ml	0.46	0.16	0.27	0.42	0.72	3.43	1.60	2.11	2.71	7.79
AUC_{0-t}	µg/ml*h	12.15	4.36	5.84	11.05	21.25	89.45	16.93	65.16	86.65	119.52
$AUC_{0-\infty}$	µg/ml*h	12.34	4.39	5.96	11.22	21.50	89.99	16.91	65.53	87.07	119.99
$AUMC_{0-\infty}$	µg/ml*h^2						1768.71	477.06	1016.02	1733.20	2690.31
MRT	h						19.46	2.54	14.18	19.60	22.42
CL/F	mL/h						9944.72	1961.75	6071.01	9710.86	14092.62
CL_M/F	mL/h	166.52	82.15	64.10	163.10	374.20					
Percent recovered	%	1.61	0.76	0.97	1.44	3.69					
AUC_{0-t} (Milk)/AUC_{0-t} (Plasma)		0.14	0.04	0.08	0.13	0.21					

TABLE 1 Gabapentin Milk and Plasma non-compartmental Pharmacokinetic Parameters following PO Administration at 10 mg/kg

Parameters	Units	Gabapentin 10 mg/kg (targeted dose)									
		Milk					Plasma				
		Mean	STDEV	Min	Max	Median	Mean	STDEV	Min	Max	Median
λ_Z	1/h	0.15	0.02	0.14	0.19	0.15	0.13	0.014	0.11	0.15	0.13
$t_{1/2}$	h	4.54	0.53	3.60	4.99	4.71	5.50	0.63	4.74	6.56	5.43
T_{max}	h	12.00	6.69	8.00	24.00	8.00	8.00	0.00	8.00	8.00	8.00
C_{max}	µg/ml	0.63	0.13	0.47	0.78	0.64	2.87	0.20	2.61	3.22	2.87
C_0	µg/ml	0.71	0.08	0.61	0.81	0.72	4.71	0.81	3.36	5.54	4.91
AUC_{0-t}	µg/ml*h	15.48	5.40	9.90	25.12	15.16	65.35	3.86	61.91	72.62	63.98
$AUC_{0-\infty}$	µg/ml*h	15.60	5.40	10.01	25.22	15.26	65.59	3.84	62.29	72.85	64.21
$AUMC_{0-\infty}$	µg/ml*h^2						683.14	54.60	621.66	765.53	668.82
MRT	h						10.44	0.99	9.72	12.29	9.99
CL/F	mL/h						156101.41	26098.84	124358.23	183650.18	158103.92
CL_M/F	mL/h	300.48	57.40	225.10	358.00	308.70					
Percent $_{recovered}$	%	0.18	0.02	0.16	0.23	0.18					
AUC_{0-t} (Milk)/AUC_{0-t} (Plasma)		0.24	0.09	0.15	0.41	0.24					

TABLE 2 Gabapentin Milk and Plasma non-compartmental Pharmacokinetic Parameters following PO Administration at 20 mg/kg

Parameters	Units	Gabapentin 20 mg/kg (targeted dose)									
		Milk					Plasma				
		Mean	STDEV	Min	Median	Max	Mean	STDEV	Min	Median	Max
λ_Z	1/h	0.14	0.02	0.11	0.17	0.13	0.13	0.01	0.12	0.15	0.14
$t_{1/2}$	h	5.20	0.77	4.08	6.10	5.20	5.26	0.57	4.79	6.03	4.99
T_{max}	h	12.00	4.40	8.00	16.00	12.00	9.33	3.27	8.00	16.00	8.00
C_{max}	µg/ml	1.19	0.14	1.01	1.35	1.23	5.42	0.69	4.07	6.04	5.57
C_0	µg/ml	1.22	0.46	0.69	1.86	1.25	7.31	2.45	4.21	10.51	7.24
AUC_{0-t}	µg/ml*h	27.56	3.12	22.29	31.36	27.28	132.00	18.25	101.08	149.73	134.42
$AUC_{0-\infty}$	µg/ml*h	27.71	3.13	22.36	31.50	27.46	132.31	18.33	101.24	150.10	134.69
$AUMC_{0-\infty}$	µg/ml*h^2						1650.27	456.98	1195.46	2273.30	1624.75
MRT	h						12.38	2.37	9.38	15.15	13.10
CL/F	mL/h						150371.87	39531.60	104942.90	145184.25	210949.66
CL_M	mL/h	259.57	102.82	152.50	424.10	249.65					
Percent recovered	%	0.17	0.05	0.11	0.25	0.16					
AUC_{0-t} (Milk)/AUC_{0-t} (Plasma)		0.21	0.03	0.18	0.27	0.21					