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Pharmacokinetics of meloxicam in mature swine after intravenous and oral administration

Abstract

The purpose of this study was to compare the pharmacokinetics of meloxicam in mature swine after intravenous (IV) and oral (PO) administration. Six mature sows (mean bodyweight \pm standard deviation = 217.3 \pm 65.68 kg) were administered an IV or PO dose of meloxicam at a target dose of 0.5 mg/kg in a cross-over design. Plasma samples collected up to 48 hours post-administration were analyzed by high pressure liquid chromatography and mass spectrometry (HPLC-MS) followed by non-compartmental pharmacokinetic analysis. Mean peak plasma concentration (C_{MAX}) after PO administration was 1070 ng/ml (645-1749 ng/ml). T_{MAX} was recorded at 2.40 hour (0.50-12.00 hours) after PO administration. Half-life (T_{1/2} λ_z) for IV and PO administration was 6.15 hours (4.39-7.79 hours) and 6.83 hours (5.18-9.63 hours) respectively. The bioavailability (F) for PO administration was 87% (39-351%). The results of the present study suggest that meloxicam is well absorbed after oral administration.

Keywords

Swine, meloxicam, pharmacokinetics, NSAIDs, oral bioavailability, pig

Disciplines

Agriculture | Animal Sciences | Meat Science | Pharmacy and Pharmaceutical Sciences

Comments

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2 Running title: Pharmacokinetics of meloxicam in mature swine

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18

19 **Abbreviations**

20 AUC_{extrap}, Percent of the AUC extrapolated; AUC_{INF}, Area under the curve extrapolated to
21 infinity; Cl, Plasma clearance; Cl/F, Cl per fraction of the dose absorbed; C₀, Concentration
22 extrapolated to time 0 using log-linear regression of the first two time points; C_{MAX}, Maximum
23 plasma concentration; T_{MAX}, Time to C_{MAX}; T_{1/2 λ_Z}, Terminal half-life; λ_Z, Terminal rate
24 constant; MRT, Mean residence time extrapolated to infinity; V_{ss}, Volume of distribution at
25 steady state; V_Z, Volume of distribution, area method; V_Z/F, V_Z per fraction of the dose
26 absorbed; MAT, Mean absorption time; F, Fraction of the dose absorbed; COX, Cyclo-
27 oxygenase; HPLC-MS, High pressure liquid chromatography and mass spectrometry detection;
28 PK, Pharmacokinetic; NSAIDS, Non-steroidal anti-inflammatory drugs; IV, Intravenous; IM,
29 Intramuscular; PO, Per os (by mouth)

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38 **Abstract**

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40 after intravenous (IV) and oral (PO) administration. Six mature sows (mean bodyweight \pm standard
41 deviation = 217.3 \pm 65.68 kg) were administered an IV or PO dose of meloxicam at a target dose
42 of 0.5 mg/kg in a cross-over design. Plasma samples collected up to 48 hours post-administration
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46 hour (0.50-12.00 hours) after PO administration. Half-life ($T_{1/2\lambda_z}$) for IV and PO administration
47 was 6.15 hours (4.39-7.79 hours) and 6.83 hours (5.18-9.63 hours) respectively. The
48 bioavailability (F) for PO administration was 87% (39-351%). The results of the present study
49 suggest that meloxicam is well absorbed after oral administration.

50 **Keywords**

51 Swine, meloxicam, pharmacokinetics, NSAIDs, oral bioavailability, pig

52 **Introduction**

53 Over the past decade there has been increased awareness from the public on issues related
54 to farm animal welfare. More specifically, concern over procedures that inflict pain upon pigs (i.e.
55 castration, tail docking) and lack of pain relief available during these procedures has been
56 highlighted as major concerns from the public (Guatteo et al., 2012; Coetzee, 2013a; Millman,
57 2013). Non-steroidal anti-inflammatory drugs (NSAIDs) including ketoprofen, carprofen, flunixin
58 meglumine and meloxicam are common analgesics used to manage animal pain and are labeled

59 for pain control for livestock in Canada and some European Union countries (Coetzee, 2013b).
60 However there are currently no drugs approved for use in swine and specifically labelled to provide
61 pain relief in the United States (FDA 2010).

62 Meloxicam is a member of the oxicam class with anti-inflammatory, analgesic and antipyretic
63 properties (Friton et al., 2003; Hirsch et al., 2003). Meloxicam is highly protein bound (95-99%),
64 demonstrates good systemic absorption (Busch et al., 1998) and may be a good candidate for pain
65 mitigation in swine. To identify the optimal dose regimen for pain management, the
66 pharmacokinetics of a drug must be determined. Pharmacokinetic (PK) parameters for meloxicam
67 have been evaluated in several species including cattle (Coetzee et al., 2009; Mosher et al., 2012;
68 Malreddy et al., 2013), small ruminants (Shukla et al., 2007; Ingvast-Larsson et al., 2010; Wasfi
69 et al., 2012; Krueder et al., 2012; Stock et al., 2013), horses (Toutain et al., 2004; Sinclair et al.,
70 2006), exotics (Divers et al., 2010) and companion animals (Lees et al., 2013; Lehr et al., 2010).
71 There have been two peer-reviewed articles published on Meloxicam PK in swine (Fosse et al.,
72 2008; 2010). However, these studies evaluated meloxicam PK properties in pre-pubertal swine age
73 14-23 days and neither study evaluated oral bioavailability (F) of meloxicam. The purpose of this
74 study was to compare the pharmacokinetic parameters of IV and oral meloxicam PK in mature
75 swine and to determine the oral bioavailability.

76 **Methods**

77 This study was approved by the Institutional Animal Care and Use Committee at Iowa
78 State University.

79

80 *Animals and housing*

81 Six healthy multiparous commercial cross-bred Newsham cull sows (mean bodyweight \pm
82 standard deviation = 217.3 ± 65.68 kg) were used for this study. Sows were housed in individual
83 pens with a concrete floor with and rubber mat (2.4 m length x 2 cm height x 1.4 m width). Sows
84 were provided *ad libitum* access to water via one nipple drinker (Trojan Specialty Products Model
85 65, Dodge City, KS) and hand-fed a custom mixed diet free of antibiotics or medications composed
86 of corn, soybean meal and soy hulls, designed to meet or exceed nutrient requirements for sows.
87 Approximately 1.8 kg of feed was fed at 0800 and 0.45 kg of feed was fed at 1600 hours onto a
88 raised concrete step (55 cm length x 55 cm in width x 24 cm). Matrix (Altrenogest formulation;
89 Intervet/Schering-Plough, Millsboro, DE- Dose: 6.8 ml-15 mg) was added to one kg of feed daily
90 to prevent estrus cycle initiation.

91 Twenty-four hours before study commencement, sows were moved to individual gestation
92 stalls (2.1 m length x 0.6 m width) with nonslip rubber flooring. Sows had access to the same type
93 of nipple drinker previously described for the pen, and remained in their stalls for a total of 72
94 hours while on trial (on trial defined as sows receiving drug and having blood collected). Sows on
95 trial, regardless of administration route, received the same ration and were fed on the same
96 schedule as follows: **Day 1:** 0.9 kg at 5:00 (three and half hours prior to oral drug administration),
97 1.4 kg at 12:30 and .45 kg at 17:00; **Day 2:** 2.3 kg at 8:30 and 0.45 kg at 17:00. Lights were on a
98 12:12 light dark cycle (light hours [0600 and 1800]). Feed schedule was different on trial days due
99 to trial schedule and blood collection time-points. Attitude, appetite, and blood collection sites of
100 sows were monitored twice daily during each study period. Sows were assessed for immediate
101 adverse reactions to drug administration including demonstrating signs of sedation, seizures,
102 vomiting, diarrhea or respiratory compromise. Post-mortem necropsies were not conducted and
103 clinical signs of melena were not evaluated.

104 *Study design*

105 A cross-over design study (Navidi, 2008) was conducted over two rounds such that all
106 sows received each administrative route. Sows were blocked by body weight and treatments were
107 randomly assigned to sows within a block (three sows per block) with three sows allocated to each
108 administration route for the first round. A 10-day washout period was chosen as it was greater than
109 89 times the half-life reported in swine (Fosse et al., 2008; $T_{1/2b}$: 2.7 hours). Sows were weighed
110 20 hours prior to study initiation and these weights were used to calculate drug dosages.

111 In the first round, three sows were administered an intravenous injection of meloxicam
112 (**IV-M**) at 0.5 mg/kg (Loxicam 5 mg/ml; Norbrook Pharmaceuticals Worldwide, Station Works,
113 Newry, Ireland # 1155103) as a single bolus injection into an indwelling auricular vein catheter
114 using techniques described by Pairis-Garcia and colleagues (2014). Three sows received
115 meloxicam per os (**PO-M**) at 0.5 mg/kg (Meloxicam 15 mg/tablet; Zydus Pharmaceuticals USA
116 Inc, Pennington, New Jersey #MM5058). Tablets were mixed with approximately 24 g of sugar
117 cookie dough (sows had been previously trained using cookie dough as a positive reinforcement),
118 divided into three, 8 gram round balls, and administered in a clean feeding bowl. In the second
119 round, this process was repeated so that all sows received both meloxicam routes. For oral
120 administration, the dose was rounded to the nearest whole tablet. For intravenous administration,
121 the dose was rounded to the nearest half milliliter. The experimental unit was the individual sow
122 ($n = 6/\text{treatment}$).

123 *Blood collection*

124 All blood samples (9.0 mL/sample) were collected via the jugular vein using a 25.4 mm 16
125 gauge hypodermic needle (Air-Tite Products, Virginia Beach, VA, USA) and 12 ml luer lock
126 syringe (TycoHealth Care, Mansfield, MA, USA). During blood collection, sows were manually

127 restrained using a pig snare. Blood was collected from sows receiving IV-M at 0.05, 0.1, 0.17,
128 0.33, 0.5, 1, 2, 4, 8, 12, 16, 24, 36 and 48 hours after drug administration. Blood was collected
129 from sows receiving PO-M at 0.25, 0.5, 1, 2, 4, 8, 12, 16, 24, 36, and 48 hours after PO
130 administration. A baseline sample was collected 20 hours prior to drug administration for both
131 routes. Samples were immediately transferred to a sodium heparin 10 ml blood collection tube
132 (BD Vacutainer, Franklin Lakes, NJ, USA) and remained on ice for no longer than 150 minutes
133 prior to centrifugation for 10 minutes at 1,500 g. Collected plasma was placed in cryovials and
134 frozen at -70 °C until analysis.

135 *HPLC/MS analysis of meloxicam concentrations*

136 Plasma meloxicam concentrations were determined using high-pressure liquid chromatography
137 (Surveyor MS Pump and Autosampler, Thermo Scientific, San Jose, CA, USA) with mass
138 spectrometry (TSQ Quantum Discovery MAX, Thermo Scientific, San Jose, CA, USA). Plasma
139 samples, spikes (0.20 ml) and the internal standard (piroxicam; 10 µL 40ng/ml) were treated with
140 20 µL of 30% perchloric acid. Samples were vortexed for 5 seconds and centrifuged for 20
141 minutes at 2,500 x g to precipitate the sediment. The supernatant (~80 µL) was pipetted into a
142 glass insert containing 120 µL of 1.9% ammonium hydroxide in 25% aqueous acetonitrile and
143 fitted to an injection vial. The injection volume equaled 12.5 µL. Two mobile phases utilized
144 were as follows: A. 0.1% formic acid in water B. 0.1% formic acid in an acetonitrile at a flow
145 rate of 0.250 mL/min. The mobile phase began at 15% B with a linear gradient to 95% B at 7
146 minutes, which was maintained for 1.5 minutes, followed by a re-equilibration to 15% B.
147 Separation was achieved with a solid-core c18 column (KinetexXB -C18, 100 mm×2.1 mm, 2.6
148 µm particles, Phenomenex, Torrance, CA, USA) maintained at 40°C. Piroxicam eluted at 4.85
149 minutes and meloxicam at 5.95 minutes. Four SRM transitions were monitored for meloxicam

150 and three SRM transitions were used with the internal standard, piroxicam. The quantifying ions
151 for meloxicam were 72.99, 88.01, 114.99, and 140.98 m/z and 77.97, 94.98, and 120.98 m/z for
152 piroxicam. Sequences consisting of plasma blanks, calibration spikes, QC samples, and swine
153 plasma samples were batch processed with a processing method developed in the Xcalibur
154 software (Thermo Scientific, San Jose, CA, USA). The processing method automatically
155 identified and integrated each peak in each sample and calculated the calibration curve based on
156 a weighted (1/X) linear fit. Plasma concentrations of meloxicam in unknown samples were
157 calculated by the Xcalibur software based on the calibration curve. Results were then viewed in
158 the Quan Browser portion of the Xcalibur software. The standard curve in swine plasma was
159 linear from 0.005 to 10.0 $\mu\text{g/mL}$. The coefficient of determination (R squared) exceeded 0.995
160 and all measured values were within 15% of the actual values with most of the values less than
161 5% difference from the actual values. The accuracy of the assay for meloxicam in swine plasma
162 was $99 \pm 3\%$ of the actual concentration while the coefficient of variation was 5% determined on
163 4 sets of replicates for each of the following concentrations: 0.015, 0.15, and 1.5 $\mu\text{g/mL}$. The
164 limit of quantitation (LOQ) for this assay was determined to be 0.005 $\mu\text{g/mL}$, while the limit of
165 detection (LOD) was 10-fold lower than that at 0.0005 $\mu\text{g/mL}$.

166 *Pharmacokinetic analysis*

167 Pharmacokinetic analyses for plasma meloxicam concentrations over time were performed
168 with computer software (WinNonlin 5.2, Pharsight Corporation, Mountain View, CA, USA) and
169 analyzed using non-compartmental methods (Gibaldi and Perrier, 1982). The parameters included
170 the area under the curve from time 0 to infinity (AUC_{INF}) using the linear trapezoidal rule, percent
171 of the AUC extrapolated to infinity ($\text{AUC}_{\text{EXTRAP}}$), plasma clearance (Cl), first-order rate constant

172 (λ_z), terminal half-life ($T_{1/2}$ λ_z), apparent volume of distribution at steady state (V_{ss}), apparent
173 volume of distribution of the area (V_z), mean residence time extrapolated to infinity (MRT), and
174 mean absorption time (MAT). The maximum plasma concentration (C_{MAX}) and the time to
175 maximum plasma concentration (T_{MAX}) were observed for PO administration. The concentration
176 at time 0 (C_0) was calculated by log-linear regression using the first two time points after IV
177 administration. The AUC_{EXTRAP} was the percent of the AUC extrapolated to infinity. The range of
178 the λ_z was determined by visual inspection of the plasma profile and determined by linear
179 regression of time and natural log (ln) of the plasma concentration. The V_z was determined using
180 the following equation:

$$181 \quad V_z = \frac{Dose}{\lambda_z * AUC_{INF}}$$

182 The V_{ss} was determined with the following equation:

$$183 \quad V_{ss} = MRT * Cl$$

184

185 The F was estimated with the following equation:

$$186 \quad F = \frac{\frac{AUC (PO - M)}{Dose (PO - M)}}{\frac{AUC (IV - M)}{Dose (IV - M)}}$$

187

188 The MAT with the following equation:

189
$$MAT = MRT (PO - M) - MRT (IV - M)$$

190 Given that pharmacokinetic parameters data follow a log-normal distribution, geometric statistics
191 are more appropriate summary descriptors and have been presented in this study.

192

193 **Results**

194 No adverse effects (sedation, seizures, vomiting, diarrhea, or respiratory compromise) from the
195 sow were observed following IV or PO meloxicam administration and drug levels were below the
196 limit of detection on baseline days. Two samples were excluded for IV administration at the 24
197 hour time point due to unclear labeling with unclear sow identification. Two samples were
198 excluded for IV administration and PO administration at the 48 hour time point as samples were
199 below LOQ. A 13.9% variation within samples was detected as compared to the internal standard
200 response across all samples.

201 Figure 1 and 2 presents the individual plasma profiles for IV-M and PO-M administered at 0.5
202 mg/kg (actual mean dose: IV: 0.50 mg/kg; range: 0.49-0.50 mg/kg; PO: 0.49 mg/kg; range 0.47-
203 0.51 mg/kg).

204 Table 1 summarizes the calculated PK for IV-M and Table 2 summarizes the calculated PK for
205 PO-M.

206 **Discussion**

207 In this study, we compared the PK parameters of IV and PO meloxicam in mature swine
208 and determined the oral bioavailability. Although meloxicam PK properties were previously
209 evaluated at 0.4 mg/kg in swine (Fosse et al., 2008; 2010), the authors completed this work using

210 younger, immature pigs (14-23 days of age) and did not evaluate PO-M administration. Hence,
211 the present study is novel because we determined these parameters, including oral, in mature pigs
212 using a different route of administration and dose. .

213 The MRT of 4.26 hour and Cmax at 5705 ng/ml were numerically greater than results
214 reported by Fosse and colleagues, 2008 (MRT: 3.5 ± 0.3 h; Cmax: 3277 ± 250 ng/ml) although
215 Vss was similar at 0.16 l/kg (Fosse et al 2008; Vss: 0.19 ± 0.02 l/kg) and the Cl was slower at
216 0.63 ml/min/kg (Fosse et al 2008; Cl: 1.01 mL/kg/min). Half-life was also different when
217 compared to previous results from Fosse and colleagues (2010; $T_{1/2} \lambda z$ 2.6h), Norbrook
218 Laboratories (2014; $T_{1/2} \lambda z$ 2.5h) and laboratory pigs ($T_{1/2} \lambda z$ 2.48h; European Agency for the
219 Evaluation of Medicinal Products (EMA), 1999), although similar to results for mice and mini-
220 pigs (EMA, 1999; $T_{1/2} \lambda z$ 4-6h). Although the cause of these differences is unknown, several
221 factors may have contributed to the numerical differences. Since these were separate studies,
222 direct comparison should always be cautious as differences in study design such as routes of
223 administration, fed or fasted animals, sample collection times, analytical method (including limit
224 of quantification, sensitivity, and specificity), drug formulations, environmental factors and
225 pharmacokinetic analyses differences could all contribute to some of the perceived differences.
226 Differences in pharmacokinetic parameters from our study compared to previously published
227 results may also be due to differences in age, genetics, weight or additional unknown differences
228 between study populations. Although it is often assumed that young animals always have slower
229 drug metabolism / elimination than adults, this is not the case. In Beagle dogs for example,
230 puppies aged 5-20 weeks have shorter half-lives and more rapid clearance of caffeine than adult
231 dogs (Tanaka et al., 1998). Similarly the half-life is shorter in puppies aged 3-30 weeks and the
232 clearance is more rapid of trimethadione (a nonspecific metabolism substrate) than adult dogs

233 (Tanaka et al., 1998). Mosher and colleagues (2012) demonstrated differences in half-life when
234 comparing pre-ruminant calves and ruminant calves administered meloxicam by gavage (pre-
235 ruminant calves dosed via gavage: $T_{1/2} \lambda z$ 40.0h; ruminant calves dosed via gavage: $T_{1/2} \lambda z$
236 29.9h). In addition, breed or strain differences may also contribute due to genetic differences
237 (polymorphisms) in metabolism, but to the authors' knowledge, genetic polymorphisms or
238 extensive studies of the effects of age on drug metabolism in pigs have not been reported.

239 Previous studies have demonstrated excellent bioavailability for meloxicam ranging
240 between 72-100% F when administered to horses and ruminants (Calves: Coetzee et al., 2009;
241 Goats: Ingvast-Larsson et al., 2010; Horses: Toutain et al., 2004; Sheep: Stock et al., 2013;
242 Camels: Wasfi et al., 2012; Llamas: Krueder et al., 2012). Our study demonstrated oral F at 87%
243 (range 39-350%). The lower range in F coincides with previous studies conducted in sheep
244 (Stock et al, 2013; 40%) and llamas (Kreuder et al, 2012; 48%). As there are no other studies
245 assessing bioavailability in sows, it is unclear if variability in F should be expected in sows, or
246 other factors such as feeding regimen or drug formulation influenced this outcome.

247 When assessing the upper range of F at 350% a possible explanation for the elevated F
248 from this particular sow may be due to slow absorption. As the drug was administered orally we
249 can rule out slow absorption due to administration complications such as hemorrhage, injection
250 into fascial plane or seroma formation. However, drug absorption by oral administration can be
251 influenced by local damage at the site of absorption (gastrointestinal tract), decreased blood flow
252 and variation in stomach contents (Maddison et al, 2008). Gastric ulcers, intestinal torsions,
253 volvulus and proliferative enteropathy are common problems seen in swine (Thomson and
254 Friendship, 2012). Compromised gastric mucosa due to disease may result in decreased blood

255 flow to the affected site, prolonged retention of feed and decrease in total surface area resulting
256 in potentially slower drug absorption (Page and Maddison, 2008). As sows enrolled on trial were
257 purchased from a group of commercial cull sows, chronic gastrointestinal disease or compromise
258 may be possible. Necropsies of sows were not performed therefore gastrointestinal tract status is
259 unknown and may have played a role in variations seen with oral meloxicam F. Therefore, it may
260 be more appropriate to use the median F at 69% or estimated F without this sow (67%) as a
261 better indicator of true F.

262 **Conclusions**

263 The pharmacokinetic profile of oral meloxicam described in this study including the high relative
264 bioavailability support clinical evaluation of this compound for management of pain in sows.
265 Meloxicam may be both cost effective and require little additional training for administration on
266 farm.

267 **Competing interests**

268 The authors state that there are no competing interests related to the present study. Dr. Coetzee has
269 been a consultant for Intervet-Schering Plough Animal Health, Boehringer-Ingelheim Vetmedica
270 and Norbrook Laboratories Ltd. Dr. KuKanich has been a consultant for Bayer Animal Health,
271 Central Life Sciences, Pfizer Animal Health, and Procyon Pharmaceuticals. Dr. Millman has been
272 a consultant for or has received funding from Boehringer-Ingelheim Vetmedica, Bayer Animal
273 Health and Pfizer Animal Health. Dr. Johnson and Dr. Stalder has been a consultant for or have
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275 Animal Health. Dr. Karriker has been a consultant for or has received funding from Boehringer
276 Ingelheim Vetmedica and Bayer Animal Health.

277 **Authors' contributions**

278 JFC and LAK conceived the study, participated in the design and coordination and assisted with
279 the drafting the manuscript. MPG participated in data compilation, sample processing, design and
280 coordination and drafted the manuscript. AKJ provided funding participated in the design and
281 coordination, and aided in interpretation of the data and drafting the manuscript. KJS and STM
282 participated in the study design, coordination and drafting the manuscript. BK performed the
283 pharmacokinetic analysis and assisted with the data interpretation. LWW performed the plasma
284 drug analysis on all samples. All authors read and approved the final manuscript.

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291

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