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RESEARCH PAPER

Wintertime pharmacokinetics of intravenously and orally administered meloxicam in semi-domesticated reindeer (*Rangifer tarandus tarandus*)

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Abstract

Objective To investigate the pharmacokinetics of orally and intravenously (IV) administered meloxicam in semi-domesticated reindeer (*Rangifer tarandus tarandus*).

Study design A crossover design with an 11 day washout period.

Animals A total of eight young male reindeer, aged 1.5–2.5 years and weighing 74.3 ± 6.3 kg, mean ± standard deviation.

Methods The reindeer were administered meloxicam (0.5 mg kg^{-1} IV or orally). Blood samples were repeatedly collected from the jugular vein for up to 72 hours post administration. Plasma samples were analysed for meloxicam concentrations with ultraperformance liquid chromatography combined with triple quadrupole mass spectrometry. Noncompartmental analysis for determination of pharmacokinetic variables was performed.

Results The pharmacokinetic values, median (range), were determined. Elimination half-life ($t_{½}$) with the IV route (n = 4) was 15.2 (13.2–16.8) hours, the volume of distribution at steady state was 133 (113–151) mL kg^{-1} and clearance was 3.98 (2.63–5.29) mL $hour^{-1}$ kg^{-1}. After oral administration (n = 7), the peak plasma concentration (C_{max}) was detected at 6 hours, $t_{½}$ was 19.3 (16.7–20.5) hours, C_{max} 1.82 (1.17–2.78) µg mL^{-1} and bioavailability (n = 3) 49 (46–73)%. No evident adverse effects were detected after either administration route.

Conclusions and clinical relevance A single dose of meloxicam (0.5 mg kg^{-1} IV or orally) has the potential to maintain the therapeutic concentration determined in other species for up to 3 days in reindeer plasma.

Keywords animal welfare, cervid, meloxicam, NSAID, reindeer, ruminant.

Introduction

Reindeer herding remains a vital livelihood, dating back centuries, and is one of the oldest livelihoods in Fennoscandia. Based on a legislated right (Reindeer Herding Act 848/1990) to graze freely on the landscape covering one-third of Finland, reindeer herding differs remarkably from other forms of animal husbandry, where production animals are mainly kept in shelters and fenced areas. The freely grazing herds are transferred from the wilderness to fenced enclosures twice a year, that is, in the summer for calf marking and in the fall/winter for the round-ups, where the reindeer are counted, earmarked, treated with antiparasitic drugs and separated for slaughter. Those males not required for breeding are castrated, mostly without pain alleviation. A share of the reindeer are kept in separate winter enclosures or unfenced areas for supplemental feeding during the coldest winter months, while the majority of the animals graze freely in the wilderness all year round.

Veterinarians routinely use off-label analgesia on reindeer to treat various inflammatory conditions and injuries. Nevertheless, pain management in reindeer is challenging. Currently, no analgesic drugs have been approved for the European market for this semi-domesticated species. However,

according to cascade rules in Europe, the use of drugs approved for other production animal species is accepted (Directive 2004/28/EC). The dosages in reindeer practice are extrapolated from other ruminant species. The medication of these semi-domesticated, freely grazing animals is confounded by the slowing of metabolism by even more than 50% during the harsh winter months (Mesteig et al. 2000; Pösö 2005; Arnold 2020), affecting drug absorption and metabolism. Furthermore, reindeer are susceptible to handling stress (Rehbinder et al. 1982; Rehbinder 1990; Wiklund 1996; Wiklund et al. 2001; Omsjoe et al. 2009).

Meloxicam is one of the non-steroidal anti-inflammatory drugs (NSAIDs) used for reindeer, for alleviating pain and various inflammatory processes (Laaksonen, 2018). However, no studies have been published concerning the pharmacokinetics of NSAIDs in reindeer. Only a few case reports describe the use of meloxicam in small numbers of animals (Pizzi et al. 2011; Gonzalez-Alonso-Alegre et al. 2013; Monticelli et al. 2017). The pharmacokinetic parameters of meloxicam vary significantly between dosing routes and even between ruminant species (Shukla et al. 2007; Coetzee et al. 2009; Ingvast-Larsson et al. 2011; Kreuder et al. 2012; Stock et al. 2013; Karademir et al. 2016; Woodland et al. 2019; Hempstead et al. 2020). Therefore, extrapolating dosages between species is not a good practice. As the need for medication in reindeer arises mainly during the cold season, influenced by the nature of the reindeer herding practices, our objective was to describe the wintertime pharmacokinetics of intravenously (IV) and orally administered meloxicam in reindeer.

Materials and methods

Animals and management practices

The study was approved by the Animal Experimental Board (ESAVI/36846/2019) and Finnish Medicines Agency (Vetklnro 04/2019). The study was conducted in February 2020 at the University of Helsinki Reindeer Research site, located in Savukoski, Finland. A total of eight healthy intact male reindeer (six animals born approximately in May–June 2018 and two animals in May–June 2017), aged 1.5–2.5 years and weighing 74.3 ± 6.3 kg, mean ± standard deviation, were obtained from the Kemin-Sompio reindeer herding cooperative for inclusion in this study. The sample size was determined according to previous published research on other ruminant species. The animals were leased from a single reindeer herder, who signed an informed consent. Freely grazing animals were captured from natural pastures in connection with the roundups and acclimatized to their new environment for approximately 1.5–2.0 months (depending on each individual animal caught) before the study. During acclimatization, the reindeer were kept together in a fenced forest enclosure covering approximately 5 hectares (12.36 acres) and fed with commercial feed (Poro 2 Balans; Kinnusen Mylly Ltd, Finland), lichen and dried hay. The animals had sufficient fresh, soft snow to fulfil their water requirements, as described by Soppela et al. (1988).

One week before the experiment, the free movement of the reindeer was restricted with a halter and a 3 m rope, which is a traditional method for taming reindeer for handling. It provided the animals with an approximately 28 m^2 area for moving. Each animal was individually fed within their area, and additional lichen was used as a reward feed. If needed, their location was changed to keep the snow clean and soft for the reindeer to eat and rest. Food was not withheld before the trials. Reindeer were weighed 3 days prior to the first trial with a simple hanging scale and cargo straps, followed by a clinical examination (visual inspection, auscultation of the heart, lungs and rumen).

Inclusion criteria were normal body condition, no signs of infectious diseases in the 2 weeks before the study, and no special remarks in the clinical examination. A reindeer was excluded if clinical signs of disease developed during the study. The animals were released back to the wilderness after the withdrawal period for meloxicam was complete (28 days according to the cascade rules).

Treatments and blood sampling

A partial crossover design with an 11 day washout period was used. A professional reindeer herder, with an assistant, manually restrained each reindeer for handling. The reindeer was restrained in standing position with the neck bent to one side to allow jugular vein puncture. The hair was not shaved, and IV catheters were not used because the weather conditions ranged from 0 °C to almost −30 °C. Hairless skin renders reindeer vulnerable to frostbite, the blood may have frozen in the catheter and furthermore, reindeer tend to dispose of any foreign materials attached to them.

For the first trial, the reindeer herder selected the tamest four reindeer from the group to facilitate IV administration of meloxicam (0.5 mg kg^{-1}; Metacam, 20 mg mL^{-1}, Boehringer Ingelheim Vetmedica GmbH, Germany). A 3 mL syringe with an 18 gauge needle was used. Meloxicam (0.5 mg kg^{-1}; Metacam, 15 mg mL^{-1}, oral suspension for horses; Boehringer Ingelheim Vetmedica GmbH) was introduced into the oral cavity of the remaining four reindeer with a 3 mL syringe.

Blood samples (4 mL) were collected from the jugular vein using 18 gauge needles and 4 mL vacuum ethylenediaminetetraacetic acid tubes at predetermined times after meloxicam administration: 1, 3, 6, 12, 24, 36, 48 and 72 hours for the IV treatment and 3, 6, 12, 24, 36, 48 and 72 hours for the oral treatment, respectively. The reindeer were kept with a halter and tied rope during sample collection but

released into a 5 hectare enclosure for the 11 day washout period and the withdrawal period.

After the washout period, the animals were captured again the day before the second trial. They were moved from the 5 hectare enclosure to a small corral to be caught by hand and then tied with a rope. A baseline blood sample was taken at the time of the clinical examination, for measurement of meloxicam plasma concentration, to ensure the adequacy of the washout period. An injured pelvic limb was observed in one reindeer which was excluded from the second trial. The second trial was performed according to the crossover design, animals first in the IV treatment now assigned to the oral treatment, and *vice versa*.

Blood samples were stored on snow, and the plasma was separated by centrifugation for 10 minutes at 1509 ***g*** immediately after blood was collected from all eight reindeer. Afterwards, the plasma was stored at −20 °C until analysed.

Meloxicam concentration in plasma

A quantitative analysis of meloxicam was performed with ultraperformance liquid chromatography combined with triple quadrupole mass spectrometry (Waters Acquity UPLC + Waters Xevo TQ-S triple quadrupole MS, Waters Corp., MA, USA) with a reversed-phase column (Waters Acquity HSS T3, 1.8 µm, 2.1 × 30 mm; Waters Corp.). Plasma samples were prepared for analysis by treating them with a precipitation agent: acetonitrile containing 1% formic acid and 50 ng mL^{-1} tenoxicam as an internal standard (50 µL sample + 150 µL precipitation solution). Samples were mixed for 3 minutes and centrifuged for 20 minutes at 2182 ***g***. The obtained supernatant was diluted with an equal volume of 150 mM phosphate-buffered saline, and the sample was submitted to analysis.

The chromatography consisted of a gradient elution of 0.1% formic acid (eluent A) and acetonitrile (eluent B) at a flow rate of 0.500 mL $minute^{-1}$ with a gradient of 5−5−80−98−98−5% eluent B at 0−0.3−1.25−1.3−1.8−2.5 minutes. Injection volume was 4 µL and the temperature of the column oven was 40 °C. The analysis was performed with positive ionization. Meloxicam was quantitatively analysed with multiple reaction monitoring mass spectrometry (MRM) transitions of 352 > 115 and 352 > 184, with respective collision energies of 19 eV and 15 eV and a retention time of 1.29 minutes. Tenoxicam was quantitatively analysed with an MRM transition of 338 > 121, with a collision energy of 22 eV and a retention time of 1.02 minutes. MassLynx 4.2 software (Waters Corp.) was used to process the obtained data.

Calibration standards and quality control (QC) samples were prepared by spiking pooled blank reindeer plasma to concentrations ranging from 0.2 ng mL^{-1} to 10,000 ng mL^{-1} for the standards and at 2.5, 25 and 250 ng mL^{-1} for the QC samples. Standards and QCs were treated similarly to actual samples. The lower limit of quantification (LLoQ) was 0.5 ng mL^{-1} with the coefficient of determination (R^2) > 0.997, accuracies ranging from 82.8% to 113.7%, and the coefficient of variation (CV%) ranging from 0.5% to 9.6% above the LLoQ. Accuracy and CV at the LLoQ were 82.8% and 13.4%, respectively.

Noncompartmental analysis

Noncompartmental analysis was used to calculate the following pharmacokinetic parameters from the concentration−time−dose data (WinNonlin 5.2; Certara, NJ, USA; Linear Trapezoidal LinearLog Interpolation, uniform weighting): area under curve (AUC), maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), mean residence time (MRT), clearance (CL), and volume of distribution at the steady state (V_{ss}), last two variables for the IV route only. Elimination half-life was calculated with the formula: $t_{½} = \ln 2 \times MRT$ (In2 = the natural logarithm of 2).

Results

Plasma concentration is expected to peak immediately after IV injection; however, t_{max} was measured later than the first collected blood sample in three reindeer in the IV treatment. This difference probably resulted from incomplete IV administration, and the data were excluded from analysis (Table 1). Because one reindeer had already been excluded before the second trial, complete series of blood samples were analysed from four animals in the IV treatment. Data were missing (laboratory error) at 6 hours post administration in one reindeer in the oral treatment, and all data from this animal were excluded from analysis (Table 1).

Measured meloxicam concentrations in reindeer plasma over time after a single dosage of 0.5 mg kg^{-1} administered IV or orally are presented in Figure 1. Pharmacokinetic parameters are presented in Table 2. The t_{max} of orally administered meloxicam was 6 hours and plasma mean half-life was 19.3 (16.7−20.5) hours (Table 2). No evident adverse effects were detected after either treatment. Bioavailability (F) calculated for the three reindeer with complete data for both treatments was 49 (46−73)%, median (range).

Discussion

No studies evaluating the pharmacokinetics of NSAIDs in reindeer (*Rangifer tarandus tarandus*) were found in the literature, even though analgesia should be employed for ethical and animal welfare reasons. The results of the present study indicate that approximately half of the orally administered meloxicam reached systemic circulation. In addition to good bioavailability, meloxicam had a long $t_{½}$ in both IV and oral treatments, suggesting that the oral route is a feasible option when medicating reindeer with meloxicam.

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Table 1 Meloxicam (0.5 mg kg^{-1}) was administered intravenously (IV treatment) and orally (oral treatment) to eight reindeer in a crossover study. Data included in the analysis (✓), data excluded (✗), with cause of exclusion, and bioavailablity (F) are indicated for each animal.

Reindeer identification	Oral treatment	IV treatment	F reported
1	✓	✗ (t_{max} delay)	✗
2	✓	✓	✓
4	✓	✗ (injured)	✗
22	✓	✗ (t_{max} delay)	✗
37	✓	✗ (t_{max} delay)	✗
41	✓	✓	✓
47	✓	✓	✓
49	✗ (laboratory error)	✓	✗

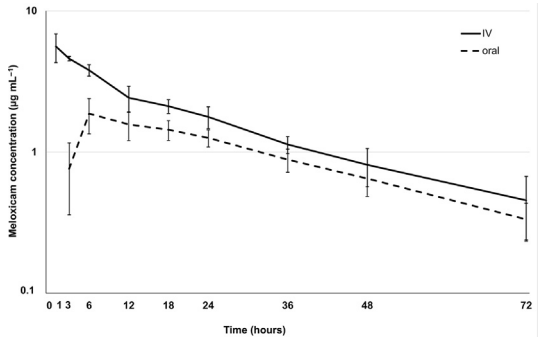

Figure 1 Mean ± standard deviation plasma meloxicam concentrations (in a half-logarithmic scale) in semi-domesticated reindeer after administration of single doses (0.5 mg kg^{-1}) of oral ($n = 7$) and intravenous ($n = 4$) meloxicam.

Table 2 Median (range) values for pharmacokinetic parameters of meloxicam after administration of a single dose (0.5 mg kg^{-1}) to semi-domesticated reindeer through intravenous (IV) ($n = 4$) and oral ($n = 7$) routes.

Parameters	Oral treatment	IV treatment
$t_{½}$ (hours)	19.3 (16.7–20.5)	15.2 (13.7–16.8)
t_{max} (hours)	6 (6–6)	na
C_{max} (µg mL^{-1})	1.82 (1.17–2.78)	na
AUC_{last} (hour* µg mL^{-1})	62.4 (51.5–88.6)	130.7 (102.9–876.0)
MRT_{last} (hours)	27.8 (24.1–29.6)	22.0 (19.8–24.3)
CL (mL^{-1} $hour^{-1}$ kg^{-1})	na	3.98 (2.63–5.29)
V_{ss} (mL kg^{-1})	na	133 (113–151)

AUC_{last}, area under the concentration-time curve from dosing (time 0) to the time of the last measured concentration; CL, clearance; C_{max}, maximum plasma concentration; MRT_{last}, mean residence time; na, not determined; $t_{½}$, elimination half-life, t_{max}, time to maximum plasma concentration, V_{ss}, volume of distribution at steady state.

The present study supports previous results that meloxicam absorption is delayed in ruminants after oral dosing (Lees et al. 2004). In the reindeer in the present study, plasma meloxicam concentrations reached peak concentrations 6 hours after oral administration, which would be an undesirable delay for treatment of acute pain. However, blood samples were not collected for drug analysis between 3 and 6 hours or between 6 and 12 hours post medication so that the time to reach peak concentration and the duration of peak concentration are unknown. The intervals between blood collections were long to minimize the number of samples and avoid excessive sampling stress.

Although the 49% bioavailability is based on three animals only with complete data from both treatments, this suggests that the oral dosage used in the study (0.5 mg kg^{-1}) may need to be doubled in reindeer. The oral dosage was chosen with caution because the main side effect of meloxicam is ulcerogenic activity in the gastrointestinal tract (EMEA 1999) and because reindeer may develop gastric ulcers resulting from stress of handling and herding (Rehbinder 1990). Nonetheless, studies in cattle show that meloxicam at 0.5–1.5 mg kg^{-1} for 5 days has minimal side effects (EMEA 1999); therefore, increasing the dosage in reindeer could be considered. This idea is also supported by Türck et al. (1996) who showed that the meloxicam pharmacokinetics in humans is dose-linear. However, when compared with goats treated with the same dosage as that used in the present study (Ingvast-Larsson et al. 2011), the C_{max} in reindeer was clearly higher. Furthermore, oral C_{max} in reindeer was at the same concentration as reported after an oral dosage of 1.0 mg kg^{-1} in sheep (Stock et al. 2013), calves (Glynn et al. 2013), and llama (Kreuder et al. 2012). Thus, without toxicity and efficacy studies, the optimal oral dosage in reindeer remains speculative.

The C_{max} after oral administration was reached considerably faster in reindeer than in other ruminant species, such as bovine calves (Coetzee et al. 2009; Melendez et al. 2019), goats (Ingvast-Larsson et al. 2011), llamas (Kreuder et al. 2012) and sheep (Stock et al. 2013). Rumen flora are effective in metabolizing and inactivating contaminants, and binding to digesta delays absorption (Lees 2018). Seasonal changes occur in reindeer metabolism; during the winter, freely grazing reindeer adapt to the Arctic climate and scarce nutrition, lower their metabolism even more than 50% and the rumen and microbial flora enter a resting state (Mesteig et al. 2000; Arnold 2020). However, if additionally fed during the winter months, reindeer continue ruminating (Åhman & White 2018). Consequently, the drug absorption and metabolism may be considerably different when an animal is captured from natural grazing lands in winter, in contrast to an animal fed for weeks or months in an enclosure or during summer. According

to the manufacturer, the oral suspension used in the present study reaches t_{max} at 4.5 hours in dogs and at 2−3 hours in horses. The results of the present study on C_{max} and t_{max} indicate that from a pharmacokinetics perspective reindeer in wintertime could be considered a monogastric animal rather than a ruminant.

In the present study, plasma meloxicam concentrations measured after both IV and oral administration were within the therapeutic concentration of meloxicam as determined in other species. However, reported therapeutic concentrations of meloxicam vary considerably from 0.13−0.2 μg mL^{-1} in horses (Toutain & Cester 2004), 0.82 μg mL^{-1} in dogs (Montoya et al. 2004) and 0.57−0.93 μg mL^{-1} in humans (Türck et al. 1996). The therapeutic concentration in reindeer is yet unknown. The present study also demonstrates that $t_{½}$ is longer and CL slower in reindeer than in sheep or goats (Shukla et al. 2007; Ingvast-Larsson et al., 2011; Stock et al. 2013). Thus, after the concentration determined therapeutic in a dog (Montoya et al. 2004) or a human (Türck et al. 1996) was reached in reindeer, it was maintained for at least 24 hours after oral administration and for 36 hours after IV administration. When compared with a horse (Toutain & Cester 2004), our data suggest that a single IV or oral dose of meloxicam (0.5 mg kg^{-1}) may potentially maintain therapeutic concentration in reindeer for approximately 2−3 days.

Regarding AUC, it was more justifiable to report AUC to the time of last measured concentration (AUC_{last}) than AUC extrapolated to infinite time (AUC_{inf}) here. Extrapolating the latter may not be sufficiently accurate because blood sampling was finished at the time (72 hours) when a marked concentration of meloxicam was still detected in the plasma samples. Respectively, MRT_{last} was reported instead of MRT_{inf}, as MRT is greatly influenced by the terminal phase measurements, and its estimate may therefore be unreliable in this study design.

The specific aim in the present study was to inspect the wintertime pharmacokinetics of meloxicam in reindeer, as the nature of the livelihood creates a larger demand for medication mainly during the winter period when the freely grazing animals are gathered from the wilderness. Reindeer are adapted to the Arctic climate with their thick, dense winter hair, which made venous access difficult in the freezing field setting, with animals insufficiently accustomed to human handling. Harsh winter weather conditions and captive wild animals caused extra challenges in the present study, resulting in some results being lost. Furthermore, the level of plasma protein binding of meloxicam is unknown in reindeer. Protein binding is an important factor in the variance of effective plasma concentrations of NSAIDs (Galbraith & McKellar 1996). NSAIDs bind strongly to plasma proteins and, therefore, the volume of distribution is usually moderate (Türck et al. 1996; Busch et al. 1998), but inflammation facilitates the leakage of plasma proteins with bound NSAID into tissue damage exudate (Lees et al. 2004) assisting NSAIDs to the injury sites. According to EMEA (1999), meloxicam is at least 96.5% bound to plasma proteins in cattle. However, NSAID binding to plasma proteins varies greatly among species and cannot be extrapolated from one species to another (Galbraith & McKellar 1996). Therefore, missing knowledge of protein binding is an important confounding factor when approximating the therapeutic plasma concentration in reindeer.

Conclusions

The present study indicates that meloxicam administered by IV or oral route is a promising option for reindeer in field conditions. However, the therapeutic concentration in reindeer remains unknown. Further experimental research on efficacy of meloxicam is required, evaluating adequacy of analgesia after various dosing routes and to explore protein-binding, tolerance and toxicity.

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Authors' contributions

HN: study design, data acquisition, analyses and interpretation, manuscript preparation, funding acquisition. SL: study design, data acquisition and interpretation, manuscript preparation. MR: study design, data analyses and interpretation, manuscript preparation. LH: study design, data acquisition and interpretation, manuscript preparation, funding acquisition.

Conflict of interest statement

The authors declare no conflict of interest.

References

Åhman B, White RG (2018) Rangifer diet and nutritional needs. In: Reindeer and Caribou: Health and Disease. Tryland M, Kutz SJ (eds). CRC Press, Taylor & Francis Group, USA. pp. 107−134.

Arnold W (2020) Review: Seasonal differences in the physiology of wild northern ruminants. Animal 14 (S1), S124−S132.

Busch U, Schmid J, Heinzel G et al. (1998) Pharmacokinetics of meloxicam in animals and the relevance to humans. Drug Metab Dispos 26, 576–584.

Coetzee JF, KuKanich B, Mosher R, Allen PS (2009) Pharmacokinetics of intravenous and oral meloxicam in ruminant calves. Vet Ther 10, E1–E8.

EMEA (1999) The European Agency for the evaluation of medicinal products - Committee for Veterinary medicinal products: meloxicam summary report. Last accessed 8 March 2022. https://www.ema.europa.eu/en/documents/mrl-report/meloxicam-summary-report-2-committee-veterinary-medicinal-products_en.pdf.

Galbraith EA, McKellar QA (1996) Protein binding and in vitro serum thromboxane B_2 inhibition by flunixin meglumine and meclofenamic acid in dog, goat and horse blood. Res Vet Sci 61, 78–81.

Glynn HD, Coetzee JF, Edwards-Callaway LN et al. (2013) The pharmacokinetics and effects of meloxicam, gabapentin, and flunixin in postweaning dairy calves following dehorning with local anesthesia. J Vet Pharmacol Ther 36, 550–561.

Gonzalez-Alonso-Alegre EM, Rodriguez-Alvaro A, Martinez-Nevado E et al. (2013) Conjunctival squamous cell carcinoma in a reindeer (*Rangifer tarandus tarandus*). Vet Ophthalmol 16 (Suppl 1), 113–116.

Hempstead MN, Waas JR, Stewart M et al. (2020) Can isoflurane and meloxicam mitigate pain associated with cautery disbudding of 3-week-old goat kids? Animals 10, 878.

Ingvast-Larsson C, Högberg M, Mengistu U et al. (2011) Pharmacokinetics of meloxicam in adult goats and its analgesic effect in disbudded kids. J Vet Pharmacol Ther 34, 64–69.

Karademir U, Erdogan H, Boyacioglu M et al. (2016) Pharmacokinetics of meloxicam in adult goats: a comparative study of subcutaneous, oral and intravenous administration. N Z Vet J 64, 165–168.

Kreuder AJ, Coetzee JF, Wulf LW et al. (2012) Bioavailability and pharmacokinetics of oral meloxicam in llamas. BMC Vet Res 8, 85.

Laaksonen S (2018) Assessment and treatment of reindeer diseases. In: Reindeer and Caribou: Health and Disease. Tryland M, Kutz SJ (eds). CRC Press, Taylor & Francis Group, USA. pp. 383–444.

Lees P (2018) Analgesic, anti-inflammatory, antipyretic drugs. In: Veterinary Pharmacology and Therapeutics (10th edn). Riviere JE, Papich MG (eds). Wiley Blackwell, USA. pp. 467–500.

Lees P, Landoni MF, Giraudel J, Toutain PL (2004) Pharmacodynamics and pharmacokinetics of nonsteroidal anti-inflammatory drugs in species of veterinary interest. J Vet Pharmacol Ther 27, 479–490.

Melendez DM, Marti S, Pajor EA et al. (2019) Pharmacokinetics of oral and subcutaneous meloxicam: Effect on indicators of pain and inflammation after knife castration in weaned beef calves. PLoS One 14, e0217518.

Mesteig K, Tyler NJC, Blix AS (2000) Seasonal changes in heart rate and food intake in reindeer (*Rangifer tarandus tarandus*). Acta Physiol Scand 170, 145–151.

Monticelli P, McSloy A, Morath U, Adami C (2017) Challenging anaesthetic management of captive reindeer (Rangifer tarandus): Report of 4 cases. Schweiz Arch Tierheilkd 159, 657–662.

Montoya L, Ambros L, Kreil V et al. (2004) A pharmacokinetic comparison of meloxicam and ketoprofen following oral administration to healthy dogs. Vet Res Commun 28, 415–428.

Omsjoe EH, Stien A, Irvine J et al. (2009) Evaluating capture stress and its effects on reproductive success in Svalbard reindeer. Can J Zool 87, 73–85.

Pizzi R, Girling S, Bell A et al. (2011) Laparoscopic-assisted cryptorchidectomy in an adult reindeer (Rangifer tarandus). Vet Med Int 2011, 131368.

Pösö RA (2005) Seasonal changes in reindeer physiology. Rangifer 25, 31–38.

Rehbinder C (1990) Management stress in reindeer. Rangifer 10 (Special Issue No 3), 267–288.

Rehbinder C, Edqvist LE, Lundstrom K, Villafane F (1982) A field study of management stress in reindeer (*Rangifer tarandus* L.). Rangifer 2, 2–21.

Shukla M, Singh G, Sindhura BG et al. (2007) Comparative plasma pharmacokinetics of meloxicam in sheep and goats following intravenous administration. Comp Biochem Physiol C Toxicol Pharmacol 145, 528–532.

Soppela P, Nieminen M, Saarela S (1988) Water requirements of captive reindeer hinds with artificial feeding. Rangifer 8 (Special Issue No 2), 74–75.

Stock ML, Coetzee JF, KuKanich B, Smith BI (2013) Pharmacokinetics of intravenously and orally administered meloxicam in sheep. Am J Vet Res 74, 779–783.

Toutain P, Cester CC (2004) Pharmacokinetic-pharmacodynamic relationships and dose response to meloxicam in horses with induced arthritis in the right carpal joint. Am J Vet Res 65, 1533–1541.

Türck D, Roth W, Busch U (1996) A review of the clinical pharmacokinetics of meloxicam. Br J Rheumatol 35 (Suppl 1), 13–16.

Wiklund E (1996) Pre-slaughter handling of reindeer (*Rangifer tarandus tarandus*): effects on meat quality. PhD thesis. Swedish University of Agricultural Sciences. p. 102.

Wiklund E, Rehbinder C, Malmfors G et al. (2001) Ultimate pH values and bacteriological condition of meat and stress metabolites in blood of transported reindeer bulls. Rangifer 21, 3–12.

Woodland AN, Van der Saag D, Kimble B et al. (2019) Plasma pharmacokinetic profile and efficacy of meloxicam administered subcutaneously and intramuscularly to sheep. PLoS One 14, e0215842.

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