Pharmacokinetics of meloxicam for medication control in racing greyhounds.

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Abstract

Recent published disciplinary findings from regulators of greyhound racing in Australia, Great Britain and Ireland have shown overall that the most common non-steroidal anti-inflammatory drug (NSAID) adverse analytical finding is for meloxicam. Whilst animals used in sport should be treated as required to ensure animal welfare at the same time any such use of medication should also be controlled to ensure integrity. A pharmacokinetic study on six greyhounds was performed to measure plasma and urine levels of meloxicam to inform medication control advice. Using the standard

methodology for medication control the Irrelevant Plasma Concentration was determined as 5 ng/mL and the Irrelevant Urine Concentration was determined as 0.1 ng/mL for meloxicam. These Irrelevant Plasma and Urine Concentrations allow laboratory Screening Limits, Detection Times and Withdrawal Time advice to be determined and publicised by regulators of greyhound racing. There was identification of meloxicam in plasma prior to its administration in the study, with a potential linkage of this identification to the feeding of 'knackery' meat including from racehorses, and also a finding of an extended terminal phase with a terminal half life of 28 hours, and with this finding the computation that accumulation of meloxicam would occur if such meat containing meloxicam residues was eaten once per day by dogs for a few weeks. Taken together this work supports regulators advising against the feeding of such meat and that this NSAID should not be used in racing greyhounds without a considerably extended Withdrawal Time.

Keywords meloxicam; pharmacokinetics; greyhound; racing.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are important therapeutic agents for animals used in sports. They act to reduce the biosynthesis of prostaglandins (PG) by inhibiting cyclooxygenase (COX) which exists in two isoforms, COX-1 and COX-2. Preferential activity against COX-2 may have fewer adverse effects due to mitigation of concurrent COX-1 inhibition in dogs, with favourable COX1:2 ratios having been reported for meloxicam.[1]

Animals used in sport should be treated as required to ensure their welfare, for example with NSAIDs, but any such medication use should also be controlled to ensure integrity. The accepted approach for medication control of drugs used in animal sports, is the control of analytical sensitivi-

ty based on administration studies, with urine being the sample matrix of choice for medication control.[2] For a particular drug it is especially important to understand the need for an extended administration study that includes urine as well as plasma sampling to allow contemporaneous plasma and urine levels that fully define the terminal phases of drug excretion, with a lower limit of drug detection in the part per billion range (ng/mL) that is appropriate for the different perspectives between therapy and medication control.[3] In addition to the therapeutic use of NSAIDs in dogs, the role of their exposure via feeding meat from animals that contain residues of NSAIDs to greyhounds is an issue that dictates the need for a limit of detection that is also appropriate for control of these residues. Recent published disciplinary findings from regulators of greyhound racing in Australia, Great Britain and Ireland have shown overall that the most common NSAID adverse analytical finding is for meloxicam.

In Australia meloxicam is licensed for use in dogs, cats, cattle, sheep, pigs and horses, in Europe it is licensed for use in horses, dogs, cattle, cats and pigs. There have been a number of studies that examined the levels of meloxicam in the plasma of dogs for relatively short periods,[4,5,6,7,8] with only the most recent study having limits of quantification in an appropriate range of 1 ng/ml. No published studies have been found that measured the levels of meloxicam in the urine of dogs.

The aims of this study were: to characterise the plasma and the urinary pharmacokinetics of meloxicam for the purpose of medication control in racing greyhounds at a dose relevant to its prescription for use by trainers of racing greyhounds; ensure analytical detection extended into the terminal phase and at a higher sensitivity than previous studies; derive Irrelevant Plasma and Urine Concentrations; produce regulatory advice for greyhound racing nationally and internationally in respect of both medication and meat residue control limits; and so enable science-based advice to veterinarians prescribing for racing greyhounds.

Materials and methods

Animal care and use

Six greyhounds in good health were selected from the SCEC research colony for inclusion in each study. They were fed a commercial dry dog food (Dogpro PLUS Working Dog, Hypro Petcare Pty. Ltd.) twice daily with an additional portion of fresh knackery meat (Luddenham Pet Meat, Luddenham, NSW), and had access to water at all times. Drug administration preceded the morning feed, excluding the final oral dose, which was given with a small amount of food. The studies were conducted in accordance to the principles of the VICH GCP guidelines.[9] Ethics approval was obtained from the Secretary's Animal Care and Ethics Committee of the NSW Department of Primary Industries (Approval reference TRIM #15/1406(158)). At least seven days elapsed between the last sample collection point in each study and the commencement of another study if the same animal was to be used in consecutive studies.

Drug administrations and sample collections

Meloxicam (Ilium Meloxicam® Injection 5 mg/mL, Troy Laboratories Australia Pty. Ltd.) was administered intravenously on one occasion to six different greyhounds at the label dose of 0.2 mg/kg. Three female and three male animals were studied, with a mean bodyweight of 33.1 kg and mean age of 3.8 years. Blood and urine were collected before drug administration. Blood samples were collected after 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 60, 72, 96, 120 and 144 hours post dose. Urine samples were collected after 2, 4, 6, 8, 10, 12, 24, 36, 48, 60, 72, 96, 120, 144, 168 and 192 hours.

The blood samples were heparinised and plasma obtained by centrifugation. All samples were then stored and transported at -20°C until analysis.

Sample chemical analysis and quantification

Urine and plasma samples were extracted using solid phase extraction (SPE). For urine: samples (1 mL) were diluted with phosphate buffer (0.5 M, pH 6.3, 1 mL). After centrifugation, samples were extracted using Bond Elut Nexus SPE cartridges (3 mL, 60 mg). SPE cartridges were conditioned with methanol (1 mL) and water (1 mL) prior to loading samples and then washed with 0.5 mL hexane. Samples were eluted with methanol:ethyl acetate (10:90, 2mL) and then evaporated to dryness under nitrogen at ambient temperature, followed by reconstitution in methanol:water (10:90, 100 µL). For plasma: samples (200 µL) were treated with a mixture of trichloroacetic acid:trizam base:sodium azide (47:51:2, 100 µL) and after 5 minutes with methanol (100 µL). Samples were diluted with phosphate buffer (1 M, pH 6.3, 3.5 mL) and centrifuged prior to SPE with Varian Focus cartridges (3 mL, 20 mg). SPE cartridges were conditioned with methanol (1 mL) and water (1 mL) prior to loading samples and then washed with 1 mL hexane. Samples were eluted with methanol:acetonitrile (60:40, 1mL) and then evaporated to dryness under nitrogen at ambient temperature, followed by reconstitution in methanol:water (10:90, 100 µL).

Samples were analysed by liquid chromatography mass spectrometry using a Waters Xevo TQ-S triple quadruple mass spectrometer (Waters Corp., Manchester, UK) coupled to an Acquity I-Class (Waters Corp., Manchester, UK) liquid chromatograph. The mass spectrometer was operated in multiple reaction monitoring (MRM) mode with positive polarity. Electrospray ionisation was carried out with a capillary voltage of 3.2 kV, a source temperature of 150ºC, a desolvation gas temperature of 500. Meloxicam was monitored using the precursor ion m/z 352.1 and daughter ions m/z

115.1 (for quantification) and m/z 141.0 (for identification) and 5'OH-meloxicam using the precursor ion m/z 368.1 and daughter ions m/z 131.1 (for quantification) and m/z 157.0 (for identification). The internal standard, piroxicam, was monitored using the transition m/z 332.1 > 95.1.

Chromatographic separation was achieved using an Acquity BEH C18 column (2.1 mm x 100 mm, 1.7 µm particle size) (Waters Corp., Manchester, UK). The mobile phase consisted of 0.1 % formic acid in methanol (A) and of 0.1 % formic acid in water (B). The initial composition was 10% A, which was held for 0.5 minutes and then ramped to reach 99.9% A at 6 minutes. This was held for 1 minute before being returned to 10% A and equilibrated for 1 minute.

Calibration and quality control samples were used in the range of 0.05-80 ng/mL and 0.5-150 ng/mL for meloxicam and 5'OH-meloxicam, respectively, in urine and 0.05-100 ng/mL and 0.1-100 ng/mL for meloxicam and 5'OH-meloxicam, respectively, in plasma. The methods were shown to be linear with correlation coefficients greater than 0.99 for meloxicam and 0.98 for 5'OH-meloxicam. A lower limit of quantification (LLOQ) was 0.05 ng/mL for meloxicam in urine and plasma and 0.5 and 0.1 ng/mL for 5'OH-meloxicam in urine and plasma, respectively. The methods were shown to be accurate and reproducible with acceptable inter-batch variability of precision and accuracy. The accuracy of the urine method was demonstrated to be -5.0% at LLOQ for meloxicam, and the precision 5.6% at LLOQ for meloxicam, respectively. The accuracy of the plasma method was demonstrated to be 4.4% at LLOQ for meloxicam, and the precision 7.6% at LLOQ for meloxicam.

Pharmacokinetic analysis

Phoenix WinNonlin 7.0 (Pharsight Corporation, Cary, NC) was used for; a non-compartmental analysis of the plasma data for meloxicam and firocoxib; a 2-compartmental pharmacokinetic analysis for the 0-24 hours plasma data for carprofen; a non-compartmental analysis for the last oral dose of carprofen from 120-192 hours - in order to determine average steady-state plasma concentrations and terminal half-life. Phoenix WinNonlin 7.0 (Pharsight Corporation, Cary, NC) was used to compute the area under the urine carprofen concentration-time curve, a measure of carprofen exposure in the urine, which was compared to the time weighted average urine pH for each dog using a non-compartmental approach.

Results

Following intravenous administration meloxicam concentrations in plasma declined to a small extent over the first 4 hours, before progressing into an extended terminal phase, where the measurements in this study extended beyond the timescales used in previous studies (Figure 1). One dog had an unusually long plasma terminal half-life compared to the other dogs. It was noted that plasma samples taken before intravenous drug administration contained significant levels of meloxicam; range 0.9-22.8 ng/mL, mean 6.94 ng/mL, median 1.63 ng/mL. Pharmacokinetic data were corrected by subtracting pre-dose concentrations from the original data giving PK parameters (Table 1(a)). There was no significant difference in the pharmacokinetic parameters between the original and corrected meloxicam pharmacokinetic data, (Table 1 (b)). There were no quantifiable levels of meloxicam in the pre-dose urine samples. Urine meloxicam concentrations peak within 12 hours before declining in a single phase, with a longer terminal phase similar to the plasma terminal phase (Figure 2). 10/52 of the plasma, and 19/52 of the urine, samples were not available for analysis due to partial or full loss of material during transport from the Australian administration study site to the UK laboratory for analysis. No 5'OH-meloxicam was detected prior to intravenous ad-

ministration and levels post dose were much lower than for parent meloxicam, becoming unquantifiable before the last samples were taken.

Discussion

The finding of meloxicam in plasma prior to intravenous administration, as further discussed below may be attributed to meloxicam being present in meat being fed to the dogs. It was considered justified to correct the pharmacokinetic data by subtracting pre-dose concentrations from the original data (Table 1(a)) as there was no significant difference in the pharmacokinetic parameters between the original and corrected data, and the half-life was similar to those previously published,[4,5,6] although there was a two-fold difference in clearance.[4,5] Even in this study, where plasma and urine sampling continued for 144 and 192 hours, it was clear that a longer sampling period should have been used to accommodate the extended terminal phase of excretion. A similarly extended elimination profile for plasma and urine of 25 and 27 days respectively was found in an administration study for medication control in racing camels.[10] 5'OH-meloxicam was not found to be useful as a marker for meloxicam. There is some variability in the meloxicam urine concentrations between dogs and this may be due to the influence of urine pH on the ionisation state of meloxicam within urine. Changes on the ionisation state of a weak acid drug such as meloxicam may lead to different reabsorption rates from urine back into blood. However no urine pH data exists for the urine pharmacokinetic samples.

European Union (EU) maximum residue limits (MRL) for meloxicam in cattle are 20 µg/kg for muscle and 65 µg/kg for liver/kidney; cattle muscle at 8 hours post dose can give meloxicam levels of 500 µg/kg.[11] Assuming that a greyhound fed meat eats up to 600 g of meat per day at a level of

500 µg/kg then that would be equivalent of delivering 300 µg of meloxicam. If the meat was eaten once per day for a few weeks, then accumulation of meloxicam would occur due to the long half-life. A 30 hour half-life would lead to ~ 3 fold accumulation and therefore the effective dose of meloxicam would be 900 µg or approximately 30 µg/kg Greyhound. This administration study delivered 0.2 mg/kg (= 200 µg/kg) meloxicam, around 6 times higher than 30 µg/kg from ingestion of meat. Therefore, the expected plasma levels due to cattle muscle at 500 µg/kg meloxicam 24 hours after the last feed could be up to approximately 150 ng/mL and the expected urine levels could be 1.5 ng/mL. Both these levels of 150 and 1.5 ng/mL for plasma and urine respectively would be above their corresponding LLOQs. This is consistent with the background levels seen in plasma (1-22 ng/mL) and urine within this administration study as well as observations seen from pre/post-race Greyhound urine samples (LGC personal communication). Therefore, the background levels observed in this study may be due to meloxicam residues within the meat fed to the dogs. The source of the meat fed, a 'knackery', would indicate that residues were possible, and as well as meat from farm animals this supplier appears to have received meat from racehorse carcasses.[12] Whilst accumulation of meloxicam has not been reported with repeated dosing at therapeutic concentration,[5] because of the extended terminal phase, with a 30 hour half-life, accumulation may occur if meat containing meloxicam residues is fed. This would be exacerbated if the greyhound was also treated with meloxicam. Whilst the levels then found in urine may not be clinically significant, they may well have significance for medication control in racing greyhounds.

Overall, and despite the presence of meloxicam in plasma samples before drug administration, the need to extrapolate the levels to define the terminal phase, the lack of information on urinary pH, and the loss of some samples, this part of the study yielded enough useful data, especially in providing for urine levels for the first time, to inform medication control in racing greyhounds.

Using the standard methodology for medication control,[3] the Irrelevant Plasma Concentration (IPC) was determined as 5 ng/mL for meloxicam and the Irrelevant Urine Concentration (IUC) was determined as 0.1 ng/mL for meloxicam (Table 2). Extrapolation for the terminal phase was used for meloxicam computations.

The actual Screening Limit (SL), being the reporting levels used by the analytic laboratories, and Detection Time (DT), being the time after drug administration when the SL is not exceeded, as determined and publicised by regulators will not necessarily be absolutely based on these Irrelevant Concentrations.[13] Regulatory Risk Management is not a scientific exercise but it should be scientifically sound, and the SL may be (slightly) higher or lower than the IPC/IUC to take into account other relevant factors other than residual drug efficacy as the common goal to achieve harmonisation.[14] In the plasma of dogs the half maximal inhibitory concentration (IC_{50}) for meloxicam ranged from 210-546 ng/mL depending on the methodology used,[15] in contrast with the calculated IPC of 5.0 ng/mL.

The DT, as issued by the regulator is a regulatory decision based on experimental data, whereas a Withdrawal Time (WT) is a recommendation and, as such, is a matter for professional judgement of the treating veterinarian. The WT should be longer than the DT because the WT should take into account the impact of all sources of animal variability (age, sex, breed, training, racing, etc.) and those of the medicinal product actually administered.[16]

For meloxicam the computed Effective Plasma Concentration (EPC) of 1775 ng/mL is higher than these estimated IC_{50} values due to the methodology used which estimates the EPC based on an average concentration for multiple dosing with the drug every 24 hours to steady-state.[3] Given that meloxicam has a long terminal half-life the EPC estimated is elevated relative to a single dose due

to accumulation. The DT is defined by the worst case rather than the average and with one dog having elevated terminal phase, (Figure 1/Figure 2), the DT for meloxicam is further extended. The related WT for meloxicam will therefore be even greater.[16] This extended terminal phase of meloxicam has led to greyhound regulators to advise that it should not be used in racing greyhounds without an extended WT and that suitable alternatives include carprofen and firocoxib.[18]

Given that dogs are fed meat, and if this contains drug residues, a regulatory SL for medication control of meloxicam, derived from the IPC and IUC, can also serve as a Recommended Limit of Detection for drug residues when feeding animal byproducts.[24] These administration studies enabled the IPCs and IUCs to be determined after the exposure of greyhounds to clinical doses of meloxicam. This information will allow greyhound regulators to provide regulatory advice for greyhound racing in respect of both a SL for medication control and a Recommended Limit of Detection for drug residues if meat containing such residues is fed, and for veterinarians to advise a WT.

Conflict of interest statement

Greyhound Racing Victoria funded this study, the administration study was performed at Eurofins SCEC, the chemical analysis was performed at LGC, and the pharmacokinetic analysis was performed at the University of Nottingham. Tim Morris is Independent Scientific Adviser to the Greyhound Board of Great Britain and receives fees for this activity, holds an unpaid appointment the University of Nottingham and has received fees from Greyhound Racing Victoria. Steven Karamatic is Chief Veterinarian at Greyhound Racing Victoria and receives payment for this activity. Marjaana Viljanto is an employee of LGC. Stuart Paine is an employee of the University of Nottingham and has received fees for advice from Greyhound Racing Victoria. Sally Colgan was an employee of Eurofins SCEC.

Author contribution statement

Tim Morris wrote and coordinated the interpretation and reporting of this study, Stuart Paine performed pharmacokinetic analysis and interpretation. Marjaana Viljanto developed methodology and provided chemical analysis for meloxicam. Sally Colgan was the principal investigator for the in-vivo study. Steven Karamatic designed the study and contributed to regulatory interpretation. All authors contributed to and reviewed the manuscript and are accountable for its contents

References

1. Edwards SE. Nonsteroidal Anti-inflammatory Drugs. In: MSD Veterinary Manual 2016. https://www.msdvetmanual.com/pharmacology/anti-inflammatory-agents/nonsteroidal-anti-inflammatory-drugs Accessed April 2019
2. Morris T. Forensic Aspects of Horseracing. In: Jamieson A, Moenssens AA.editors. Wiley Encyclopaedia of Forensic Science.John Wiley & Sons 2009.
3. Toutain PL, & Lassourd V. Pharmacokinetic/pharmacodynamic approach to assess irrelevant plasma or urine drug concentrations in postcompetition samples for drug control in the horse. *Equine Vet J* 2002;34:242-249.
4. Busch U, Schmid J, Heinzel, G, Schmaus H, Baierl J, Huber C, & Roth,W. Pharmacokinetics of meloxicam in animals and the relevance to humans. *Drug Metab Dispos* 1998;26:576-584.
5. Poulsen BN & Hörstermann D. Pharmacodynamic and pharmacokinetic aspects of the non-inflammatory non-steroidal agent meloxicam in dogs. *Dtsch Tierarztl Wochenschr* 1999;106:94-100.

6. Montoya L, Ambros L, Kreil V, Bonafine R, Albarellos G, Hallu R. & Soraci, A. A pharmacokinetic comparison of meloxicam and ketoprofen following oral administration to healthy dogs. *Vet Res Commun* 2004;28:415-428.

7. Mahmood KT, & Ashraf M. Absolute bioavailability of oral meloxicam in healthy dogs. *J Anim Plant Sci* 2010;20:193-196.

8. Lees P, Cheng Z, Keefe TJ, Weich E, Bryd J, Cedergren R, & Cozzi E. Bioequivalence in dogs of a meloxicam formulation administered as a transmucosal oral mist with an orally administered pioneer suspension product. *J Vet Pharmacol Ther* 2013;36: 78-84.

9. International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal (VICH) Good Clinical Practice Guideline 2000 https://www.vichsec.org/en/guidelines/pharmaceuticals/pharma-efficacy/good-clinical-practice.html Accessed June 2019

10. Subhahar MB, Praseen OK, Kadry AM, Rasik PT, Albert PH. Pharmacokinetics and urinary elimination profile of meloxicam after intravenous administration to camels. In: Proceedings of the International Conference of Racing Analysts and Veterinarians, Dubai 2018.

11. European Agency for the Evaluation of Medicinal Products. Committee For Veterinary Medicinal Products Meloxicam Summary Report 1999 https://www.ema.europa.eu/en/documents/mrl-report/meloxicam-summary-report-2-committee-veterinary-medicinal-products_en.pdf Accessed April 2019.

12. ABC (2019) Mass slaughter and abuse of racehorses undermines industry's commitment to animal welfare. https://www.abc.net.au/news/2019-10-18/slaughter-abuse-of-racehorses-undermines-industry-animal-welfare/11603834 Accessed January 2019

13. Morris T. Irish Greyhound Board Anti Doping and Medication Review 2015 https://www.agriculture.gov.ie/media/migration/legislation/horsegeryhoundlegislation/IrishGreyhoundBoard-AntiDopingMedicationReview130217.pdf Accessed April 2019.

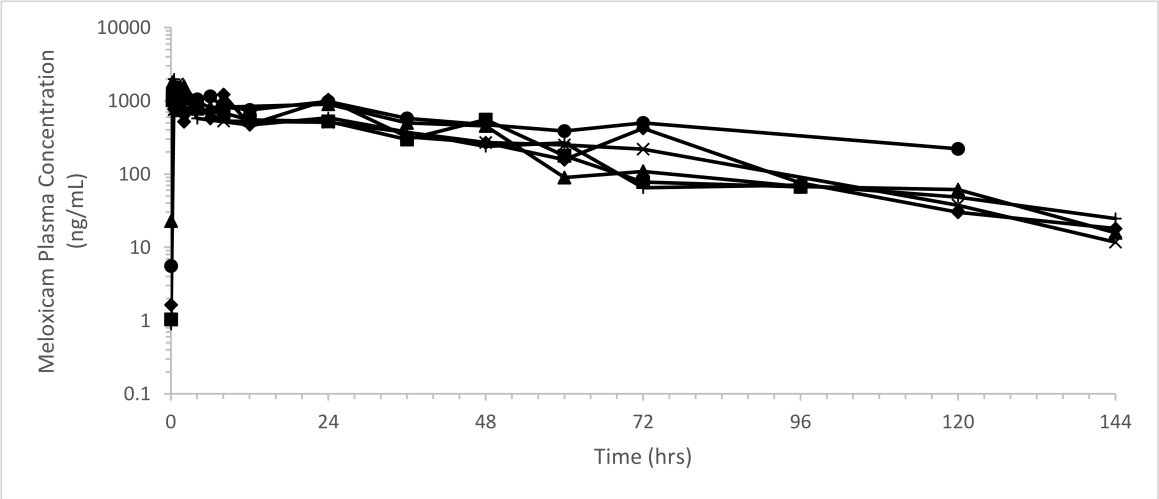
14. Toutain PL. Veterinary medicines and competition animals: The question of medication versus doping control. In: Cunningham F, Elliott J, & Lees P, editors. *Handbook of Experimental Pharmacology. Comparative and Veterinary Pharmacology*. Springer, Berlin, 2010:315–339.

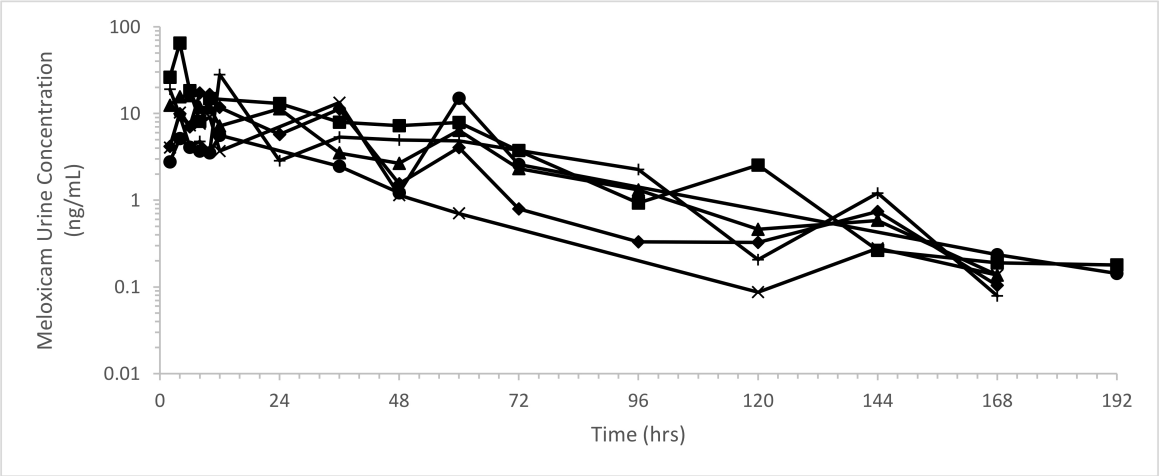
15. Jeunesse EC, Bargues IA, Toutain CE, Lacroix MZ, Letellier IM, Giraudel JM, Toutain PL. Paw inflammation model in dogs for preclinical pharmacokinetic/pharmacodynamic investigations of nonsteroidal anti-inflammatory drugs. *J Vet Pharmacol Ther*. 2011;338:548-58.

16. Toutain PL. How to extrapolate a withdrawal time from an EHSLC published detection time: A Monte Carlo simulation appraisal. *Eq Vet J* 2010;42:248-54.

17. Gower S. Meloxicam in racing greyhounds. *Vet Rec* 2018;182:518.

18. Morris T, Paine S, Zahra P, Li E, Colgan S, Karamatic S. (P(2020) Pharmacokinetics of carprofen and firocoxib for medication control in racing greyhounds *Submitted for publication*


Meloxicam Plasma Concentration (ng/mL)
10000
1000
100
10
1
0.1
0
24
48
72
96
120
144
Time (hrs)


Meloxicam Urine Concentration (ng/mL)
100
10
1
0.1
0.01
0
24
48
72
96
120
144
168
192
Time (hrs)

Tables

Pharmacokinetics of meloxicam for medication control in racing greyhounds.

Table 1(a): Corrected plasma pharmacokinetic parameters for meloxicam following a single intravenous dose of 0.2 mg/kg to 6 greyhounds fitted to a non-compartmental pharmacokinetic model. Terminal HL is the half-life of the terminal phase; MRT is the mean residence time (average time spent in animal) of meloxicam; Vss is the steady-state volume of distribution; CL is the plasma clearance for meloxicam.

Animal	Weight (Kg)	Terminal HL (hrs)	MRT (hrs)	Vss (L/Kg)	CL (mL/min/kg)
Dog 1	35.2	22.2	38.0	0.20	0.09
Dog 2	30.7	27.1	37.2	0.21	0.09
Dog 3	39.4	23.5	38.5	0.17	0.07
Dog 4	33.8	20.2	30.3	0.14	0.08
Dog 5	31.4	21.8	35.5	0.20	0.09
Dog 6	28.0	55.4	77.1	0.19	0.04
Mean	**33.1**	**28.4**	**42.8**	**0.19**	**0.08**
Median	**32.6**	**24.2**	**38.0**	**0.19**	**0.08**

Table 1(b) Uncorrected plasma pharmacokinetic parameters for meloxicam following a single intravenous dose of 0.2 mg/kg to 6 greyhounds fitted to a non-compartmental pharmacokinetic model. Terminal HL is the half-life of the terminal phase; MRT is the mean residence time (average time spent in animal) of meloxicam; Vss is the steady-state volume of distribution; CL is the plasma clearance for meloxicam.

Animal	Weight (Kg)	Terminal HL (hrs)	MRT (hrs)	Vss (L/Kg)	CL (mL/min/kg)
Dog 1	35.2	22.2	38.0	0.20	0.09
Dog 2	30.7	27.4	38.6	0.22	0.10
Dog 3	39.4	24.2	39.0	0.17	0.07
Dog 4	33.8	24.7	33.1	0.14	0.07
Dog 5	31.4	21.9	35.8	0.20	0.09
Dog 6	28.0	56.2	78.4	0.19	0.04
Mean	**33.1**	**29.4**	**43.8**	**0.19**	**0.08**
Median	**32.6**	**24.4**	**38.3**	**0.20**	**0.08**

Table 2 Computed EPC, IPC, IUC and corresponding Detection Times for meloxicam. *Extrapolated Detection Time

Mean Plasma Clearance	0.08 mL/min/kg
Dosing Interval	24 hours
EPC	1775 ng/mL
IPC	3.6 ng/mL
IPC on Ordinal Scale	5 ng/mL
Plasma Detection Time*	420 hours
Rss	0.02
IUC	0.07 ng/mL
IUC on Ordinal Scale	0.1 ng/mL
Urine Detection Time*	211 hours