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COMPARATIVE PHARMACOKINETICS OF MELOXICAM IN THE CAMELS AND HEIFERS

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ABSTRACT

The aim of this study was to compare the pharmacokinetics of the non steroidal anti-inflammatory drug meloxicam in heifers and camels following intravenous administration at a dose of 0.5 mg/kg body weight. Jugular blood samples were collected serially for 48 hours and the plasma concentrations of meloxicam were determined by reverse phase high performance liquid chromatography. The plasma concentrations versus time curve were adequately described by a two-compartment open model. The plasma concentrations of meloxicam were significantly higher in camels than in heifers along all the sampling period and the drug was detected for 36 hours and 48 hours in both species, respectively. There was no significant difference in the distribution half life and steady state volume of distribution between heifers and camels. The elimination half life ($t_{1/2}\beta$) and mean residence time (MRT) were significantly longer in camels (12.8 h; 17.6 h) than in heifers (7.9 h; 10.3 h). Value of total body clearance (CL_B) was significantly lower in camels (0.013 l h^{-1} kg^{-1}) than in heifers (0.029 l h^{-1} kg^{-1}). The area under the curve ($AUC_{0-\infty}$) were significantly higher in camels (36.6 µg h mL^{-1}) than in heifers (17.6 µg h mL^{-1}). The results indicate that elimination kinetics of meloxicam differ significantly between heifers and camels and the elimination of the drug tend to be faster in heifers compared to camels.

Key words: Bioavailability, camels, heifers, HPLC, meloxicam, NSAID, pharmacokinetics

Nonsteroidal anti-inflammatory drugs suppress one or more components of the inflammatory response and are often indicated as an adjunct to antimicrobial therapy in veterinary practice. In ruminants, the use of NSAIDs is associated with the treatment of pain, mastitis, pneumonia and inflammatory conditions (Pugh,1991; Ziv, 1992; Deleforge *et al,* 1994). Meloxicam is a cyclooxygenase-2 (COX-2) preferential non-steroidal anti-inflammatory drug (NSAID) of the oxicam class belonging to the group of enolic acids (Turner *et al,* 2006). Meloxicam retains high anti-nociceptive potency (Engelhardt *et al,* 1996) with minimal side-effects such as those associated with non-selective inhibitors of COX-1. It is extensively used to provide both acute and chronic pain relief in a variety of animal species (Turner *et al,* 2006). It is approved by the European union for use in cattle, pig and horse to alleviate inflammatory conditions (locomotors disorders, mastitis, metritis and agalactia syndrome) and as adjunctive therapy of acute respiratory disease and diarrhoea. The recommended dose of meloxicam by the manufacturer in cattle is 0.5 mg/kg body weight following I.V. or subcutaneous routes. Favourable kinetic properties of meloxicam like good absorption, longer elimination half-life and optimum bioavailability make it an ideal and suitable NSAID for use in animals (Busch *et al,* 1998). Despite the therapeutic potential of meloxicam in large ruminants, to the best of our knowledge no published data is available on the pharmacokinetics of meloxicam in camels and heifers. It is well documented that marked differences in the disposition kinetics of NSAIDs in general exist between species and pharmacokinetic data cannot be extrapolated from one to another species (Welsh *et al,* 1993; Cunningham and Lees, 1994). The purpose of the present study was to compare the pharmacokinetics of meloxicam in heifers and camels following intravenous administration in order to encourage the safe use of this NSAID in clinical studies for evaluation of its pharmacodynamic profile in both species.

Materials and Methods

Animals

Ten healthy Holstein heifers and 10 healthy young female camels (*Camelus dromedarius*) were used in this experiment. Heifers were acquired from a private dairy farm and were 11-14 months old and weighed between 190-300 kg. Camels were purchased from a commercial sale barn and were 10-13 months old and weighed between 250-370 kg.

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Housing and husbandry

The camels were kept in shaded and ventilated barns and heifers were housed in pens with concrete floors in a naturally ventilated building. All animals were acclimatised for 3 months before commencement of the experiment and fed Lucerne (alfa alfa) and concentrate ration, good quality hay and water were offered *ad lib*. Animals were observed daily for general health conditions. No concurrent medications were administered to the animals during the course of the study.

Animal dosing and sample collection

All animals were catheterised in the jugular vein the morning of dosing meloxicam (Metacam, 20 mg/ml, Boehringer Ingelheim, Vetmedica, Gmbh, Germany). The drug was administered as an (intravenous) I.V. bolus via the indwelling jugular catheter at a dose of 0.5 mg/kg body weight. Following dosing, blood samples were collected periodically via a needle, and heparin treated syringe. Blood samples were collected at 5, 10, 15, 30 minutes and 1, 2, 4, 6, 8, 10, 12, 24, 36 and 48 hours after administration of meloxicam. Plasma was separated by centrifugation at 3000 g for 15 min and stored at -80°C until analysed.

Meloxicam assay

Drug concentration in plasma was determined using reverse phase high performance liquid chromatography (HPLC) according to the method previously described by Bae *et al* (2007). The HPLC system consisted of a Model 616 solvent delivery pump (Waters, Milford, MA,USA), a Waters Model 600 S controller, a Model 717 plus autosampler equipped with a temperature – controlled rack (Waters), a variable wave length UV detector (Shimadzu, UV12).

The mobile phase consisted of acetonitrile-20mM potassium hydrogen phosphate (40:60, v/v, pH 3.5). Separation was achieved with a reverse phase C18 column (Discovery, Supelco, 5 µm, 4.6× 150 mm). The UV detection wavelength was 355 nm and the flow rate was 1.2 ml/min.

The plasma samples or calibration standards to be assayed (300 µl) were placed in centrifuge tube and spiked with 75 µl of internal standard (piroxicam 5 µg ml^{-1} in 0.05 M phosphate buffer). Diethyl ether (0.5 ml) was added, samples were vortexed, the aqueous layer was removed by aspiration, and the organic layer was evaporated to dryness. The residue was reconstituted using HPLC mobile phase (150 µl) and transferred to autosampler vial for injection.

For preparation of the calibration curves, drug free plasma obtained from camels and heifers were spiked with 0.02, 0.04, 0.08, 0.25, 0.5, 1.0, 2.0 and 4.0 µg ml^{-1} meloxicam. The standard curves of meloxicam in plasma of camels and heifers were linear between 0.04 and 4 µg ml^{-1}. The correlation coefficients (r) of standard curves were > 0.99 for plasma of both species. The lower detection and quantitation limits (LOQ) were 0.02 µg ml^{-1} and 0.04 µg ml^{-1}, respectively.

The precision and accuracy of the method were evaluated by repetitive analysis of the plasma samples (n=12) spiked with 0.04, 0.08, 0.2, 0.5 and 4 µg ml^{-1} meloxicam. The percentage of recovery was calculated by comparison of the peak height of blank samples spiked with known standard concentrations of the drug and treated as test samples, with the peak height of the same standard prepared in the mobile phase (n=6).

The intra-assay precision and accuracy were < 4.4 % and > 94 %, respectively. The interassay precision and accuracy were < 3.9 % and > 95 %, respectively. Recovery percentage of meloxicam from plasma of camels and heifers were > 94%.

Pharmacokinetic analysis

Following intravenous administration, the plasma concentration time data of the drug in camels and heifers were fitted to a two compartment open model system (Baggot, 1978) according to the following biexponential equation: $C_t = Ae^{-\alpha t} + Be^{-\beta t}$ where C_t is the plasma concentration of meloxicam; t is time after intravenous administration; A and α are the intercept and slope, respectively of the distribution phase; B and β are the intercept and slope of the elimination phase. Pharmacokinetic variables were obtained by use of a computer program (WinNonlin, Pharsight Corporation, Mountain View, CA, USA). The distribution and elimination half lives ($t_{1/2\alpha}$ and $t_{1/2\beta}$), the volume of distribution at steady state (V_{dss}) and the total body clearance (Cl_B) were computed according to standard equations (Gibaldi and Perrier, 1982).

The area under the plasma concentration time curve ($AUC_{0-\infty}$) and the area under the first moment curve ($AUMC_{0-\infty}$) were calculated by the trapezoidal rule for all measured data with extrapolation to infinity using C_{last}/β where Clast is the plasma concentration at 36 and 48 hours in heifers and camels, respectively. The mean residence time (MRT) was calculated as MRT= $AUMC_{0-\infty}/AUC_{0-\infty}$.

Statistical Analysis

The statistical analysis was performed using the SPSS® 6.1.3 software package (SAS, Cary, NC, USA). Results were expressed as mean ± S.D. Analysis of variance was performed by one-way analysis of variance (ANOVA) procedures. Significant differences between results reported in camels and heifers were determined by the method of least significant difference (LSD). Difference with a P-value <0.05 was considered to be significant.

Results

Following intravenous administration of meloxicam (0.5 mg kg^{-1}) in camels and heifers, the plasma concentration versus time data comply the two compartment open model and exhibited a biphasic decline. Plasma concentrations following I.V. administration of the drug were significantly higher ($P < 0.001$) in camels than that in heifers (Fig 1). Table 1 shows the pharmacokinetic parameters of meloxicam following I.V. administration in camels and heifers. As compared with heifers, the values of elimination half life ($t_{1/2\beta}$), area under the curve (AUC) and mean residence time (MRT) were significantly ($P < 0.001$) higher whereas the elimination rate constant (β) and total body clearance (Cl_B) were significantly ($P < 0.001$) lower following I.V. administration of meloxicam in camels.

Discussion

Meloxicam [4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2- benzothiazine-3-carboxamide-1,1-dioxide] is a novel NSAID of the acidic enolcarboxamide class. Many recent studies for the clinical efficacy of meloxicam as analgesic and anti-inflammatory therapy (Constable, 2009; Heinrich *et al,* 2009; Stewart *et al,* 2009; Coetzee *et al,* 2010; Heinrich *et al,* 2010; Todd *et al,* 2010) have approved the successful use of the drug to ameliorate the pain and inflammatory conditions in the dose of 0.5 mg/kg BW. So this dose was used in this experiment as a result of lack of pharmacodynamic studies of meloxicam in cattle.

In the current study, no adverse effects were observed following I.V. administration of meloxicam in camels and heifers. The plasma concentration time profile following a single I.V. dose of meloxicam in all animals of both species was best fitted with a 2- compartment open model. This is comparable with plasma concentration time profile following a single I.V. dose of meloxicam in other animal species including horse (Toutain *et al,* 2004) sheep and goats (Shukla *et al,* 2007) and pigs (Fosse *et al,* 2008). Significantly higher meloxicam plasma concentrations were measured in camels along the whole sampling period after the drug administration. Meloxicam was rapidly distributed in camels and heifers following I.V. administration with distribution half lives of 0.41 h and 0.47 h, respectively. These values are close to those reported by Shukla *et al* (2007) in sheep (0.42 h) and goats (0.37 h) and by Lees *et al* (1991) in horses (0.4 h).

In the present study, significantly shorter elimination half life of 8.1 h was observed in heifers when compared to camels (12.41 h). Terminal half lives of 6.73 h, 10.85 h have been reported in sheep and goats, respectively following a dose of 0.5 mg kg^{-1}

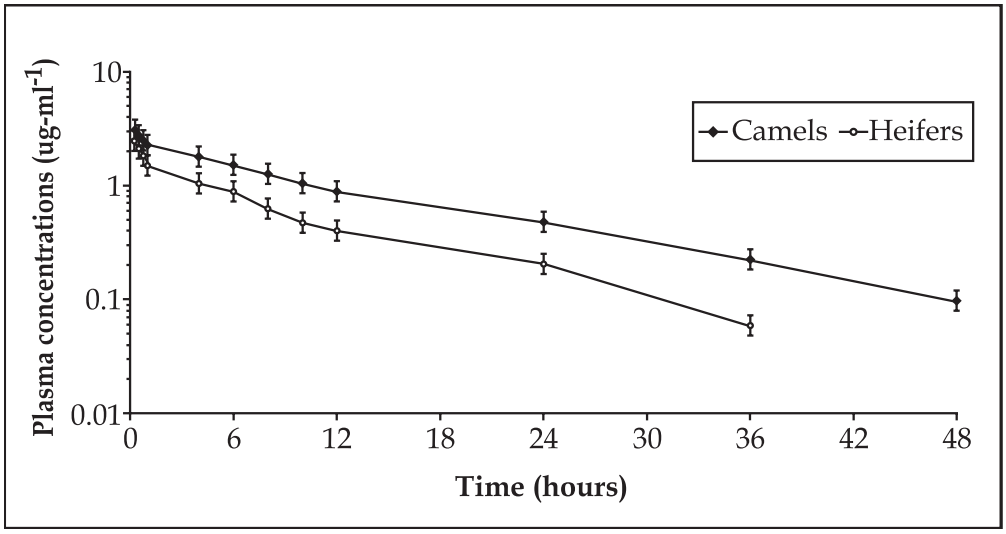

Fig 1. Semi-logarithmic graph depicting the time-concentrations course of meloxicam in camels and heifers following intravenous administration of 0.5 mg Kg^{-1} weight (n=10).

Table 1. Pharmacokinetic parameters of meloxicam in camels and heifers after intravenous administration at a dose of 0.5 mg/kg body weight.

Parameters	Units	Camels (n=10)			Heifers (n=10)			Level of significance
		Range	Mean± SD	Median	Range	Mean±SD	Median	
α	h^{-1}	1.13-2.14	1.55± 0.31	1.6	1.02-2.7	1.56±0.49	1.44	NS
β	h^{-1}	0.048-0.07	0.057±0.007	0.054	0.057-0.12	0.09±0.02	0.09	P<0.001
$t_{1/2\alpha}$	h	0.32-0.60	0.46±0.09	0.43	0.25-0.67	0.47±0.13	0.482	NS
$t_{1/2\beta}$	h	9.83-14.3	12.41±1.5	12.81	5.7-12.1	8.1±1.98	7.64	P<0.001
V_{dss}	L kg^{-1}	0.18-0.44	0.26±0.084	0.24	0.24-0.44	0.32±0.06	0.31	NS
CL_B	L h^{-1} kg^{-1}	0.01-0.025	0.015±0.005	0.015	0.023-0.04	0.03±0.004	0.03	P<0.001
MRT	h	13.6-20.52	17.5±2.23	17.8	7.2-15.74	10.5±2.5	10.1	P<0.001
$AUC_{0-\infty}$	μg h mL^{-1}	21-57.5	37.1±11.87	35.9	14.6-22.7	17.6±2.6	17.51	P<0.001
$AUMC_{0-\infty}$	μg h^2 mL^{-1}	368-1181	663±278	601	114.7-299	187.8±62.6	181.7	P<0.001

α,β, hybrid rate constants representing the slopes of distribution and elimination phases; $t_{½\alpha}$, distribution half-life; $t_{1/2\beta}$, elimination half-life (i.v.); V_{dss}, volume of distribution at steady state; Cl_B, total body clearance; MRT, mean residence time; $AUC_{0-\infty}$, area under curve from zero time to infinity; $AUMC_{0-\infty}$, area under the moment curve from zero time to infinity; NS, not significant.

(Shukla *et al,* 2007) and of 8.56 h in horses following a dose of 0.6 mg kg^{-1} (Sinclair *et al,* 2006). Total body clearance (Cl_B) of meloxicam in the present study was significantly faster in heifers (0.03 l h^{-1} kg^{-1}) than in camels (0.015 l h^{-1} kg^{-1}). This is further reflected in the significant longer mean residence time in camels (17.5 h) as compared to heifers (10.5 h). There was no significant difference between heifers and camels in the steady state volume of distribution (V_{dss}). This suggests that the difference in half life and clearance between heifers and camels were not due to difference in body distribution of meloxicam in the 2 animal classes. The range of Vdss reported in heifers and camels were comparable to those reported by Shukla *et al* (2007) in other ruminant animals, sheep (0.24 lkg^{-1}) and goats (0.25 lkg^{-1}). This is in contrast with previous literature reports in which a lower values for Vdss was reported in some species including horses (0.15 lkg^{-1}), chickens (0.058 lkg^{-1}), pigeons (0.14 lkg^{-1}), ducks (0.065 lkg^{-1}) and turkey (0.079 lkg^{-1}) after I.V. administration (Lees *et al,* 1991; Baert and Debacker, 2003). The significantly lower value of AUC of meloxicam obtained in heifers (17.6 μg h mL^{-1}) is consistent with the 2 fold faster systemic clearance of the drug in this species as compared to camels.

Marked species variations with regard to elimination kinetics of non steroidal anti-inflammatory drugs (NSAID) have been demonstrated between camels and heifers, heifers have been shown to eliminate flunixin (Anderson *et al,* 1990) and ketoprofen (De Graves *et al,* 1996) at a significantly faster rate than camels (Oukessou, 1994; Oukessou *et al,* 1995). These differences between camels and heifers in flunixin and ketoprofen elimination could be attributed to differences in their metabolism and / or renal excretion (Ali *et al,* 1996).

The daily urine volume of camels is very small (1.0 l) and the glomerular filtration rate of camels is lower than that of other animals (Wilson, 1984). These factors taken all together would allow the slower elimination of the drug through urine, albeit the alkaline nature of camel urine (pH, 9.5) comparable to cattle urine (pH, 7.5-8) which is theoretically expected to enhance the clearance of acidic drugs. However, a great species variation was previously reported for renal elimination of meloxicam and its metabolites. Urinary recovery of unchanged meloxicam and its metabolites accounted for 43% and 21% of the given dose in human and cats, respectively (Schmid *et al,* 1995a,b; Grude *et al,* 2010). In horse, meloxicam excreted in urine in high concentration comparable to its plasma concentrations (Toutain *et al,* 2004). Additionally, it has been shown that, meloxicam is cleared almost exclusively metabolically in rats and pigs, therefore, biotransformation governs the elimination of parent compound in those species (Woolf and Radulovic, 1989; Busch *et al,* 1998).

Several studies have shown that the basal activities of several drug metabolising enzymes of phase I and phase II are lower in camels (Ali, 1988; Ali and El Sheikh, 1992; El Sheikh *et al,* 1991; Damanhouri and Tayeb, 1993) and certain drug metabolising enzymes (or isoenzymes thereof) may be deficient or lacking (Ali and El Sheikh, 1992; Raza and Montague, 1993; Wasfi *et al,* 1998; Damanhouri, 2002). However, the results of the present work could not sufficiently

explain the mechanism for such difference in total body clearance reported for meloxicam in camels and heifers.

The results of the present study showed that plasma meloxicam concentrations in camels and heifers were maintained above the effective plasma concentration of 0.2 μg ml^{-1} (Toutain and Cester, 2004) in horse for up to 36 and 24 hours, respectively after a dose of 0.5 mg kg^{-1}. These findings suggest that the tested dose is tolerable by camels and heifers and could be useful for studying the pharmacodynamic and dose response to this drug in clinical studies for evaluating the potential uses in camels and heifers.

In conclusion, findings of the present study showed significant differences in meloxicam plasma concentrations and clearance rate of the drug following I.V. administration in camels and heifers. These findings strongly support the idea of establishing dose regimens in camels following controlled pharmacokinetic studies rather than extrapolating dose from other species like cattle or horse.

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