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Comparative plasma pharmacokinetics of meloxicam in sheep and goats following intravenous administration

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Abstract

Meloxicam, a novel cyclooxygenase-2 selective nonsteroidal anti-inflammatory drug (NSAID), has been used extensively in humans and recently in some domestic animal species. Although it is an attractive NSAID for use in small ruminants, meloxicam pharmacokinetics have not been investigated in sheep and goats and this information is essential for rational therapeutic use of the drug in these species. In this investigation, comparative pharmacokinetic properties of meloxicam were studied in sheep and goats after a single intravenous dose of 0.5 mg kg^{-1} body mass. Blood samples were collected via jugular venepuncture into heparinised tubes at predetermined times after drug administration. Plasma concentrations of meloxicam were determined by reversed-phase high performance liquid chromatography. The plasma concentrations of meloxicam were detectable in sheep and goats up to 72 and 48 h, respectively. The plasma concentration versus time data of meloxicam in both sheep and goats were adequately described by a two-compartment open model. The values obtained for sheep and goats for distribution half-life, volume of distribution at steady state and volume of the central compartment were almost similar in sheep and goats. The elimination half-life ($t_{1/2\beta}$), area under the plasma concentration–time curve (AUC), mean residence time (MRT) and total systemic clearance (Cl_B) in sheep were significantly different from those of goats. The mean±S.E. values of $t_{1/2\beta}$, MRT, AUC and Cl_B in sheep were 10.85±1.21 h, 15.13±1.67 h, 31.88±2.97 μg h mL^{-1} and 0.016±0.002 L h^{-1} kg^{-1}, respectively whereas the respective values in goats were 6.73±0.58 h, 9.37±0.83 h, 19.23±2.23 μg h mL^{-1} and 0.03±0.01 L h^{-1} kg^{-1}. The results indicate that elimination kinetics of meloxicam differ significantly between sheep and goats and the elimination of the drug tends to be faster in goats compared to sheep.

Keywords: Goats; HPLC; Intravenous; Meloxicam; NSAIDs; Pharmacokinetics; Plasma concentrations; Sheep

1. Introduction

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 belongs to enolic acid class of NSAIDs having anti-inflammatory, analgesic and antipyretic activity. It preferentially inhibits cyclooxygenase-2, which is induced by inflammatory stimuli in pathophysiological conditions. Meloxicam is extensively metabolized in the liver into three inactive polar metabolites namely 5′-carboxy metabolite (acid metabolite), 5′-hydroxymethyl metabolite (alcohol metabolite) and the metabolite formed by the cleavage of the side chain (Schmid et al., 1995). It has a high intrinsic activity combined with a low ulcerogenic potential and its therapeutic index is relatively higher than that of other NSAIDs including piroxicam, diclofenac, and indomethacin (Engelhardt et al., 1996).

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). The pharmacokinetic behaviour of meloxicam has been investigated in horses, dogs, minipigs, rats, chickens, ostriches, rabbits and humans (Lees et al., 1991; Busch et al., 1998; Ziegler, 2001; Baert and De Backer, 2002; Baert et al., 2002; Montoya et al., 2004; Toutain et al., 2004;

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Turner et al., 2006). Despite the therapeutic potential of meloxicam in small ruminants, to the best of our knowledge no information is available on the pharmacokinetics of meloxicam in either sheep or goats. It is well documented that marked differences in the disposition kinetics of NSAIDs in general exist between species and pharmacokinetic data cannot be transposed from one to another species (Mckellar et al., 1989; Welsh et al., 1993; Cunningham and Lees, 1994; Lees et al., 1998). Recently, it has also been reported that disposition of meloxicam varies even among different avian species (Baert and De Backer, 2003). Interspecies variations in the disposition kinetics of meloxicam limit the extrapolation of data from other species to sheep and goats and its pharmacokinetic properties need to be investigated in the target species to enable its rational clinical use. In this study, we evaluated the pharmacokinetic profiles of meloxicam in sheep and goats.

2. Materials and methods

2.1. Experimental animals

Six healthy 1–2 year-old crossbred female sheep with an average mass of 30 kg and five healthy 1–2 year-old nondescript female goats weighing approximately 20 kg were procured from Livestock Production Research Unit, IVRI, Izatnagar. Animals were examined for any apparent clinical signs before the commencement of the study. All the animals were dewormed and acclimatized to the new environment. They were housed in an animal shed with concrete floor and were maintained on concentrate, green fodder and dry grass. Water was provided *ad libitum*.

2.2. Drug treatment and sample collection

Injectable formulation of meloxicam (Melonex®) supplied by M/s Intas Pharmaceuticals, Ahmedabad, India was used. Pure technical standard meloxicam was a generous gift from M/s Zydus Cadila, Ahmedabad, India which was employed as reference external standard in HPLC assay. The drug was administered intravenously into jugular vein of each animal (sheep/goat) at a single dose of 0.5 mg kg^{-1} body mass. Blood samples (2–3 mL) were collected into heparinised tubes by jugular venepuncture prior to and at 0.033, 0.083, 0.167, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 48, and 72 h after meloxicam administration. Plasma was separated after centrifugation of blood samples at 1000 ×*g* for 20 min and stored at −20 °C until analysis for meloxicam.

2.3. Assay of meloxicam in plasma

2.3.1. Sample extraction

Meloxicam was extracted from plasma samples by adding 0.5 mL of acetonitrile to 0.5 mL of plasma in 1:1 ratio. This was subjected to vortex mixing at high speed for 1 min, and then centrifuged for 10 min at 9000 ×*g*. The clear supernatant thus obtained was transferred to clean tube. To 0.5 mL of supernatant, 0.5 mL of HPLC grade water was added and mixed well. The aliquot was filtered through 0.22 μm nylon filter and 20 μl of the aliquot was injected into HPLC system for the analysis.

2.3.2. High performance liquid chromatography

Meloxicam concentrations in plasma samples of sheep and goats were determined by using an HPLC method as described by Baert and De Backer (2003). Separation was achieved by using a reversed phase C_{18} column with guard column [Phenomenex, particle size 5 μm; 4.6 mm×250 mm] as stationary phase. The mobile phase consisted of a mixture of 65% water:acetic acid (99:1, v/v) and 35% acetonitrile. The flow rate of the mobile phase was adjusted to 0.8 mL min^{-1}. Oven temperature was set at 35 °C. Meloxicam was detected at 355 nm wave length (PDA detector). The method was validated prior to the analysis of samples. Stock solution of meloxicam at 1 mg mL^{-1} concentration was prepared in acetonitrile:acetic acid (1:1, v/v) and stored at 4 °C. The working standard solutions of meloxicam prepared daily were used to spike blank plasma samples of sheep/goat. Plasma standards at 4, 2, 1, 0.5, 0.25, 0.12, 0.06, 0.03 and 0.015 μg mL^{-1} for meloxicam (external standard) were prepared and extracted as described for the experimental samples. Meloxicam was quantified from its respective peak area and the concentrations in plasma samples were determined by means of calibration curves obtained on analysis of blank plasma samples spiked with meloxicam. The retention time for meloxicam was 6.7 min. The limits of detection and quantification in plasma for meloxicam were 0.02 and 0.06 μg mL^{-1}, respectively. The respective limits of detection and quantification were determined as 3 and 10 times the signal to noise ratio at the time of elution of the meloxicam. Mean recovery of meloxicam in sheep/goat plasma was in the range of 89–93%. The method was found to be linear and reproducible in the concentration range of 0.06 to 4 μg mL^{-1} with typical $r^2=0.999$. The intra- and inter-day assay coefficients of variation were <12%. No endogenous interferences were detected in the chromatograms of blank plasma samples of either sheep or goat at the retention time of meloxicam.

2.4. Pharmacokinetic analysis

Plasma drug concentration–time data of meloxicam for each animal (sheep/goat) were best described by a two-compartment open model and analysis was performed using a non-linear iterative curve-fitting computer programme PHARMKIT ((Version 2.10, Johnston and Woolard, 1988, supplied by the Department of Pharmacology, JIPMER, Pondichery, India as quoted by Sanyal, 1997). It provided estimates of A and B and slopes α and β of the distribution and elimination phases, respectively. The following biexponential equation was fitted to the plasma concentrations of meloxicam as a function of time after intravenous administration in each sheep and goat.

$$C_p = Ae^{-at} + Be^{-Bt}$$

where C_p is the plasma drug concentration at time t, A and B are zero time plasma drug concentration intercepts for the α and β phases and α and β are the hybrid rate constants related to the