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DISPOSITIONKINETIC OF MELOXICAM IN BUFFALO CALVES FOLLOWING INTRAVENOUS ADMINISTRATION

Patel H. A*., Mody S. K., Patel H. B. and Modi C. M.

Department of Pharmacology and Toxicology, College of Veterinary Science and Animal Husbandry, Sardarkrushinar Dantiwada Agriculture University, Sardarkrushinagar, North Gujarat, Dantiwada, Pin: 385 506. INDIA

E-mail address: harshadpatel2009@rediff.com

Minimum Inhibitory Concentration (MIC) of Meloxicam was maintained up to 48 hours when Meloxicam is administered intravenously (0.5 mg.kg-1b.wt.) in buffalo calves. In this study of meloxicam in buffalo calves peak concentration achieved at 5 minute of administration and half life remains 41 hours. Thus meloxicam pharmacokinetics data would be effectively used in buffaloes suffering from any inflammatory condition.
Key word : Pharmacokinetic, Meloxicam, Buffalo.

Non steroidal anti inflammatory drugs (NSAIDs) are commonly employed therapeutics in veterinary clinical practices. Diclofenac, phenylbutazone and other similar NSAIDs are currently used for treatment of the inflammation pain and fever. They are non selective cyclooxygenase inhibiters causing variety of adverse drug reactions and toxicity in animal. Meloxicam is a member of the 4-hydroxy 1-2-benzothiazine-3-carboxamide (oxicam) family of non-steroidal anti-inflammatory drugs (Annonymous, 1997). The advantage of this drug over the other traditional NSAIDs is that it has greater in vitro and in vivo inhibitory action against the inducible isoform of cyclo-oxygenase (COX-2), which is implicated in the inflammatory response, than against the constitutive form of this enzyme (COX-1), inhibition of which is associated with gastric, renal and other adverse effects. Meloxicam inhibit COX-2 about 12 times more selectively than COX-1 (Ogino et al., 1997). The Meloxicam Large Scale International Study Safety Assessment (MELISSA) trial reported in 1997 that over 9326 patients tested, it has a significantly lower incidence of gastro-intestinal adverse effects as compared to diclofenac (Hawkey et al., 1998). This was further supported by the Safety and Efficacy Large scale Evaluation of COX-2 Inhibiting Therapies (SELECT) trial, which has showed improvement in GI tolerability of meloxicam compared with other NSAIDs (Dequcker et al., 1998).So their uses are limited. To overcome this limitation the only alternative is meloxicam which is a selective COX-2 inhibiter and has less toxic effects. Meloxicam as NSAIDs in animal have a potential to be the drug of choice as a safer NSAIDs. So keeping in view the present study was under taken to investigate pharmacokinetics of meloxicam in buffalo calves along with its HPLC analysis.

MATERIALS AND METHODS

Six healthy male buffalo calves (Bubalus bubalis) weighing between 120-150 kg were used in present study. The animals were obtained from the Livestock Research Station, Sardarkrushinagar Dantiwada Agricultural University, Sardarkrushinagar and maintained at the Research Station. They were kept under close scientific and managemental observation for two weeks before commencement of the experiment. Animal were not treated earlier by any drugs.

Meloxicam pure powder and 5 % injectable formulation (Melonex) were received from M/s. Intas Pharmaceutical Ltd. Acetonitrile, methanol of lichrosolv grade, sodium acetate powder of analytical grade, glacial acid and perchloric acid (both HPLC grade) were used for analysis. Meloxicam was adminiatered to Jugular vein at dose rate of 0.5 mg.kg-1 body weieht as a 5 % injectable formulation (Melonex). Blood samples (Approximately 5 ml in each) were collected in clean sterilized and heparinised glass test tubes. Blood samples were collected at 0 h and 0.083 (5 min), 0.25 (15 min), 0.5 (30 min), 0.75 (45 min), 1, 2, 4, 6, 8, 12, 24, 36, 48, 72, and 96 h after drug administration. Each blood samples collected was centrifuges at 3000 rpm for 15 min at room temperature to obtain plasma. The plasma samples were stored at -200C until assayed for meloxicam using high performance liquid chromatography (HPLC) procedure.

HPLC determination of meloxicam was done by using HPLC apparatus of Knauer (Germany) company. In the HPLC assembly, isocratic solvent delivery pump (modal K 501) and UV detector (modal K 2501) were used. Chromatographic separation was performed by using reverse phase C18 column (Zorbax, OD5; 250mm, 4.6 µ) at room temperature. The mobile phase consisted of acetonitrile: buffer ratio of 38: 62. The buffer was 170 mmol of sodium acetate in water with pH adjusted to 3.3 with glacial acetic acid. The flow rate was 1 ml. min-1 at ambient temperature. The effluent was monitored at 355 nm wavelength. The pharmacokinetic parameters were calculated from plasma concentration of meloxicam after its single intravenous administration at dose of 0.5 mg.kg-1 body weight in male buffalo calves with an interactive least-square non-linear regression programme for personal computer and according to the methods described by Baggot (1977), Gibaldi and Perrier (1982) and Notari (1973).

RESULTS AND DISCUSSION

Plasma levels and pharmacokinetics of meloxicam following intravenous administration (0.5 mg.kg-1b.wt.) have been studied in various species viz; dog (Bucsh et al, 1998), cross breed (Dumka, 2002), kankrej cow (Vichare, 2004) and man (Dasandi et al, 2002).

The mean plasma concentration of meloxicam obtained after single intravenous administration at the dose rate of 0.5 mg.kg–1 body weight were determined (Table-1).

Table.1 Plasma concentrations of meloxicam after single dose intravenous administration (0.5 mg.kg-1 body weight) in male buffalo calves.

Time after drug administration (h)	Mean ± S.E. (µg.ml-1)
0.083	2.13±0.01
0.166	2.07±0.01
0.25	1.86 ±0.10
0.5	1.76±0.10
0.75	1.57±0.06
1	1.55±0.08
2	1.53±0.05
4	1.25±0.02
6	1.20±0.02
8	1.11±0.02
12	1.06±0.03
24	0.92±0.01
36	0.69±0.02
48	0.54±0.02
72	ND
96	ND

ND = Not detected

(Concentration of drug in plasma at zero time (Cp0), Absorption half life (t½α), Elimination half life (t½β), Area under curve (AUC), Volume of distribution Vd(ss), Total body clearance (ClB), Area under moment of curve (AUMC), Mean residue time (MRT), Rate constant of transfer of drug from central to tissue compartment (K12),Rate constant of

transfer of drug from tissue to central compartment (K21).

Mean peak plasma meloxicam concentration was 2.13 ± 0.01 μg.ml-1 recorded at 0.083 h (5 min) which rapidly declined to 0.92 ± 0.01 μg.ml-1 at 24 h. Thereafter, the plasma meloxicam concentration in plasma diminished gradually and was not detected after 48 h of drug administration. The detailed pharmacokinetic parameters of meloxicam calculated for male buffalo calves were presented in table 2.

Table 2. Pharmacokinetic parameters of meloxicam after single dose intravenous administration (0.5 mg kg-1 body weight) in male buffaloe calves.

Pharmeco-kinetic parameters	Unit	Mean ± S.E.
Cp0	μg.ml-1	1.53 ± 0.01
t 1/2 α	h	0.68 ± 0.10
t 1/2 β	h	40.48 ± 1.94
AUC	μg.h.ml-1	55.54 ± 5.41
Vd (ss)	L.kg-1	0.21 ± 0.02
Cl (B)	ml.min-1 kg-1	0.17 ± 0.00
AUMC	μg. h2 ml-1	1189.08 ± 25.83
MRT	h	23.51 ± 0.18
K12	h-1	0.18 ± 0.03
K21	h-1	0.98 ± 0.17
K12/K21	h-1	0.18 ± 0.01

Evaluation of the results, and the plasma levels of meloxicam by computer programme indicated that the data could be best fitted to a two-compartment open model and were adequately described by a biexponential equation:

$Cp = Ae^{-\alpha t} + Be^{-\beta t}$

Where, Cp is plasma concentration of meloxicam at time t. A and B are Zero-time plasma drug concentration intercepts of the biphasic disposition curve. α and β are First order rate constants related to distribution and elimination phases, respectively. Whereas 'e' represents the base of natural logarithm.

The mean values of K12 and K21 was found as 0.18 ± 0.03 h-1 and 0.98 ± 0.17 h-1 following intravenous meloxicam administration. The ratio of K12/K21 was found as 0.18 ± 0.01 h-1 after intravenous meloxicam administered. The high rate of K12/K21 indicates good accumulation of meloxicam in body tissues and peripheral compartment.

The values of Vd(ss) was found to be 0.21 ± 0.02 L.kg-1 following intravenous administration of meloxicam in buffalo calves higher than in crossbreed cattle 0.09 ± 0.001 L.kg-1 as reported by Dumka (2003). The lower values of Vd(ss) laboratory animals Like rat (0.467 L.kg-1), and mice (0.257 L.kg-1) reported by Busch et al., (1998).

The values of ClB of meloxicam following intravenous administration at dose rate of 0.5 mg.kg-1 was to be 0.17 ± 0.00 ml.min-1.kg-1. On the contrary, high ClB values of meloxicam was found as 2.4 ± 0.03 ml.min-1.kg-1 in crossbreed cow (Dumka, 2002). Whereas low values of ClB as 0.01 ml.min-1.kg-1 was found in intravenous administration of meloxicam (0.2 mg.kg-1) in dogs (Busch et al, 1998). The clearance of meloxicam from buffalo calves body may be due to low protein binding, high lipid solubility, and excretion as unchanged form or minimal tubular reabsorption

The values of elimination half lives (t½β) (40.48 ± 1.94 h) is longer than corresponding value reported (14.33 ± 0.10 h) in male kankrej cow. (Vichare, 2004). In chickens, pigeons, duck, turkey and ostriches short elimination half lives were reported respectively as 3.21, 2.4, 0.72, 0.99 and 0.5 h following intravenous administration of meloxicam (0.5 mg.kg-1) as compared to present study. (Baert and Backer, 2003)

The MRT values (23.51 ± 0.18 h) of sheep is lower than corresponding reported in (36.76 ± 1.01 h) male Kankrej calves (Vichare, 2004). In male rat the values of MRT following intravenous administration at a dose rate of 1 mg.kg-1was 18 h whereas in female rat it was found 52.8 h (Busch et al, 1998).

AUC is the parameter that suggested the integral of the plasma drug concentration

(Cp) after it is administered. AUC obtained in present study for meloxicam was found as 55.54 ± 5.41 μg.h.ml-1 following intravenous administration. Galbraith and Mckellar (1991) observed the AUC of another oxicam derivatives piroxicam by intravenous route in dogs to be 45.4 ± 3.3 μg.h.ml-1. The variation of AUC in different species may be due to species variation, differences in doses and age of animals.

SUMMARY

The values of important phramcokinetic parameters viz.; values of the distribution and elimination half–lives, volume of distribution and total body clearance were 0.68 ± 0.10 h, 40.48 ± 1.94 h, 0.58 ± 0.03 L.kg-1 and 0.17 ± 0.00 ml.min-1.kg-1, respectively.

Cp0, Plasma drug concentration at t=0; t 1/2α, distribution half life; t ½ β, elimination half life; AUMC, area under the first moment of plasma concentration time curve; MRT, mean resident time; Cl(B), total body clearance of drug; Vd(ss), volume of distribution of drug at steady-state; K12 and K21 , Rate constants of drug transfer from central compartment to peripheral compartment and vice versa, respectively.

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