Wayamba Journal of Animal Science – ISSN: 2012-578X; P322 - P326, 2012
First Submitted May 04, 2012; Number

DISPOSITION STUDY OF MELOXICAM ALONE AND ALONG WITH ENROFLOXACIN IN MALE BUFFALO CALVES AFTER INTRAVENOUS ROUTE

Patel H. A. * and Mody S. K.
Department of Pharmacology and Toxicology, College of Veterinary Science and Animal Husbandry, Sardarkrushinar Dantiwada Agriculture University, Sardarkrushinagar, North Gujarat, Dantiwada, Pin: 385 506. INDIA

Corresponding author: harshadpatel2009@rediff.com

Meloxicam, is a newer member of oxicam family of non-steroidal anti-inflammatory drugs having more selectivity towards cyclooxygenase-2 than cyclooxygenase-1. The meloxicam study was conducted in male buffalo calves to determine plasma disposition and pharmacokinetics of meloxicam (0.5 $mg.kg^{-1}$) after single dose intravenous, alone and in combination with enrofloxacin (2.5 $mg.kg^{-1}$,im). After intravenous administration of meloxicam when given alone, the values of 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. The values of distribution and elimination half–lives, volume of distribution and total body clearance were 0.71 ± 0.07 h, 28.52 ± 1.61 h, 0.48 ± 0.02 $L.kg^{-1}$ and 0.19 ± 0.01$ml.min^{-1}$. kg^{-1},respectively when meloxicam was given along with enrofloxacin.

Key words : Pharmacokinetic, Meloxicam, Enerofloxacin,Buffalo.

Meloxicam, a new potential member of cyclooxygenase-2 (cox-2) inhibiting non-steroidal anti **inflammatory** drug (NSAID), is used extensively in veterinary medicine for pain, fever and inflammatory disorders. Meloxicam is indicated for use in ruminants for the treatment of pneumonia, pleuritis, laminitis, myositis, sprain, mastitis, prolapse of uterus, premature labour etc (Vane and Booting, 1997; Anonymous, 2001a; Samad and Gaikwad, 2000) because of ban on the use of diclofenec sodium in veterinary field practice.

The drug-interactive relationship between Fluroquinolones and particularly NSAID group of drugs are required to be established in animals as both the classes of drugs are very commonly used concomitantly in clinical veterinary practice. Pharmacokinetic interaction of enrofloxacin with Paracetamol in goats (Agrawal *et al*., 2001) and with diclofenac in male sheep (Tripathi *et al*., 2001) and buffalo calves (Kumar *et al*, 2003) were studied. Enrofloxacin pharmacokinetic studies have also been evaluated along with concomitant administration of sulphadiazine and trimethoprim in birds (Varma *et al*., 2001) and with probenecid in goats (Rao *et al*., 2002). But the interaction of meloxicam and enrofloxacin has not been studied in buffaloes. So this study was undertaken to establish the pharmacokinetic interaction between enrofloxacin and meloxicam in buffaloes.

MATERIALS & METHODS

EXPERIMENTAL ANIMALS

The present study was conducted on 6 healthy male buffalo calves (*Bubalus bubalis*) having 6 to7 months age. 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.

DRUGS AND CHEMICALS

0.5 % injectable Meloxicam (Melonex) formulation (5 $mg.ml^{-1}$) and its pure base powder and 10 % enrofloxacin (Quintas) were received from Ms. Intas Pharmaceuticals Ltd., Matoda, Ahmedabad. Deionised water (HPLC grade), acetonitrile, methanol of lichrosolv grade, sodium acetate powder of analytical grade, glacial acetic acid (HPLC grade) and perchloric acid were procured from reputed Indian chemical house.

PLAN OF WORK

The present study was conducted in six animals. Meloxicam 0.5 percent solution was administrated into the jugular vein at a dose rate of 0.5 $mg.kg^{-1}$ body weight. After a washout period of ten days the same animals were given meloxicam 0.5 percent solution at the same rate and route along with enrofloxacin given at the dose rate of 2.5 $mg.kg^{-1}$body weight via the i.m. route. 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 sample collected was centrifuged at 3000 rpm for 15 min at room temperature to obtain plasma. The plasma samples were stored at -20^0C until assayed for meloxicam using high performance liquid chromatography (HPLC) procedure.

High performance liquid chromatography (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 C_{18} column (Zorbax, OD_5; 250mm, 4.6 µ) at room temperature. The mobile phase consisted of acetonitrile : buffer (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 intravenous administration alone and along with enrofloxacin(2.5 $mg.kg^{-1}$, intramuscularly) 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

Following intravenous administration the pharmacokinetics of meloxicam was described by two compartment open model. Based on plasma meloxicam levels achieved following 0.5 $mg.kg^{-1}$ intravenous administration alone and along with enrofloxacin, various pharmacokinetic parameters were shown in Table 1.

The present study was planned to determine the plasma disposition kinetic of meloxicam at the dose rate of 0.5 $mg.kg^{-1}$ *via* intravenous route alone and in combination with enrofloxacin at a dose rate of 2.5 $mg.kg^{-1}$ *via* intramuscular route, respectively. Anonymous (2001b) studied the pharmacokinetic of meloxicam in cattle after single intravenous administration (0.5 $mg.kg^{-1}$ body weight). Baert and Backer, (2003) investigated the pharmacokinetics of meloxicam in pigs, chikens, ostrides, ducks and turkeys with single intravenous administration (0.5$mg.kg^{-1}$body weight). Where as Lees *et al*., (1991) used a little high intravenous dose of meloxicam (0.6 $mg.kg^{-1}$body weight) in horse. After intravenous administration of meloxicam given alone (0.5 $mg.kg^{-1}$ body weight) and in combination with enrofloxacin (2.5 $mg.kg^{-1}$ body weight, I.M.), the drug was detected for up to 48 h. Busch *et al*., (1998) have detected meloxicam concentration for more than 72 h in dog following single dose intravenous administration (0.2 $mg.kg^{-1}$ body weight). Dumka (2002) has also reported the meloxicam concentration detected up to 72 h in cross breed cattle. In Kankrej cow calves it was detected for up to 72 h after administration of meloxicam given intramuscularly and intravenously (Vichare, 2004).

Table 1. Comparative pharmacokinetics of meloxicam in male buffalo calves alone and along with enrofloxacin (2.5 mg.kg^{-1}, intramuscularly) following its intravenous dose of 0.5 mg.kg^{-1} body weight .

Pharmacokinetic parameter	Unit	Drug administered (Mean ± S.E.) (n=6)	
		Meloxicam	Meloxicam and Enrofloxacin
Zero time intercept of distribution phase(A)	μg.ml^{-1}	0.26 ± 0.01	0.25 ± 0.01
Zero time intercept of elimination phase (B)	μg.ml^{-1}	1.28 ± 0.02	1.26 ± 0.02
Distribution rate constant(α)	h^{-1}	1.17 ± 0.21	1.04 ± 0.15
Elimination rate constant(β)	h^{-1}	0.017 ± 0.01	0.025 ± 0.01*
Concentration of drug in plasma at zero time($Cp^0_{)}$	μg.ml^{-1}	1.53 ± 0.01	1.51 ± 0.02
Absorption half life ($t_{½α)}$	h	0.68 ± 0.10	0.71 ± 0.07
Elimination half life ($t_{½β)}$	h	40.48 ± 1.94	28.52 ± 1.61 *
Area under curve (AUC)	μg.h.ml^{-1}	55.54 ± 5.41	43.27 ± 0.71
Area under moment of curve (AUMC)	μg.h^2.ml^{-1}	1189.08 ± 25.83	897.76 ± 15.13 **
Elimination rate constant of drug from central compartment ($K_{el)}$	h^{-1}	0.03 ± 0.01	0.03 ± 0.00
Rate constant of transfer of drug from tissue to central compartment ($K_{21)}$	h^{-1}	0.98 ± 0.17	0.87 ± 0.12
Rate constant of transfer of drug from central to tissue compartment ($K_{12)}$	h^{-1}	0.18 ± 0.03	0.16 ± 0.02
K_{12}/K_{21}	Ratio	0.19 ± 0.01	0.18 ± 0.01
Volume of distribution $V_{d(area)}$	L.kg^{-1}	0.58 ± 0.03	0.48 ± 0.02
Volume of distribution $V_{d(ss)}$	L.kg^{-1}	0.21 ± 0.02	0.23 ± 0.01
Volume of drug in central compartment (Vc)	L.kg^{-1}	0.32 ± 0.01	0.32 ± 0.01
Volume of drug in peripheral compartment (Vp)	L.kg^{-1}	0.05 ± 0.00	0.06 ± 0.00
Total body clearance ($Cl_{B)}$	ml.min^{-1}. kg^{-1}	0.17 ± 0.00	0.19 ± 0.01 **
Fraction of drug in central compartment (Fc)	–	0.62 ± 0.06	0.76 ± 0.04
Tissue to plasma ratio (T/P)	Ratio	0.66 ± 0.13	0.32 ± 0.07
Mean residue time (MRT)	h	23.51 ± 0.18	21.07 ± 0.13 **
Maximum drug concentration ($C_{max)}$	μg.ml^{-1}	2.13 ± 0.01	1.96 ± 0.02
T_{max}	h	0.083 ± 0.00	0.083 ± 0.00

* Pharmacokinetic values of concomitant administration of both meloxicam and enrofloxacin significantly varied at $p < 0.05$ when compared to the same achieved after single dose administration of meloxicam, alone.

** Pharmacokinetic values of concomitant administration of both meloxicam and enrofloxacin significantly varied at $p < 0.01$ when compared to the same achieved after single dose administration of meloxicam, alone.

The high values of distribution rate constant α as 1.17 ± 0.21 and 1.04 ± 0.15 $h^{-1}$and comparatively low values of β as 0.017 ± 0.01 and 0.025 ± 0.01 h^{-1} found, respectively for administration of meloxicam (iv) alone and with enrofloxacin are indicative of rapid distribution and slow elimination of meloxicam when given intravenously. It seems that distribution is retarded and elimination is enhanced when given in combination with enrofloxacin. Lees *et al*., 1991 reported the values of α (distribution rate constant) and β (elimination constant) as 2.78 ± 0.60 h^{-1} and 0.25 ± 0.10 h^{-1}, respectively following intravenous administration of meloxicam given at the dose rate of 0.6 $mg.kg^{-1}$ body weight in horses. Vichare (2004) has found the values of α (distribution rate constant) as 3.70 ± 0.34 h^{-1} and the β values as 0.014 ± 0.01 h^{-1} following single dose intravenous administration of meloxicam (0.5 $mg.kg^{-1}$ body weight), respectively in male Kankrej cow calves.

Following iv administration of meloxicam alone the distribution half life ($t_{½\,\alpha}$) achieved as 0.68 ± 0.10 h was lower than 0.71 ± 0.07 h achieved following intravenous administration of meloxicam given along with intramuscular enrofloxacin (2.5 $mg.kg^{-1}$) administration. The difference in values of $t_{½\alpha}$ are non-significant in intravenous study.

The values of elimination half lives ($t_{½\beta}$) were found, respectively 40.48 ± 1.94 and 28.52 ± 1.61 following intravenous administration of meloxicam alone and along with intramuscular administration of enrofloxacin. The $t_{½\beta}$ values of meloxicam with intravenous study was reported significantly differed. This indicates that meloxicam is eliminated slowly following intravenous administrations of meloxicam when given alone as compared to when given with enrofloxacin. In the crossbreed cow calves and lactating cows comparative low values of $t_{½\beta}$ were found as 26 h and 17.5 h (Anonymous, 2001[b]). Comparatively the values of $t_{½\beta}$ were 14.33 ± 0.10 h and 46.95 ± 1.28 h found following single dose intramuscular and intravenous administrations of meloxicam (0.5 $mg.kg^{-1}$) in male Kankrej cow calves (Vichare, 2004).

The total body clearance (Cl_B) gives sum of clearance of drug by each organ. The values of Cl_B of meloxicam following intravenous administration at dose rate of 0.5 $mg.kg^{-1}$ were 0.17 ± 0.00 $ml.min^{-1}.kg^{-1}$ and 0.19 ± 0.01 $ml.min^{-1}.kg^{-1}$, respectively found in meloxicam administration alone and with enrofloxacin. It suggest that rate of clearance of drug from body is higher in combination of intramuscular enrofloxacin group. The changes of Cl_B were significantly higher. On the contrary, high Cl_B values of meloxicam were found in crossbreed cow as 2.4 ± 0.03 $ml.min^{-1}.kg^{-1}$ (Dumka, 2002) whereas low values of Cl_B as 0.01, 0.009 and 0.008 $ml.min^{-1}.kg^{-1}$ were found in intravenous, oral and subcutaneous routes of meloxicam administration (0.2 $mg.kg^{-1}$) in dogs (Busch *et al*, 1998).

The calculated MRT values were 23.51 ± 0.18 h and 21.07 ± 0.13 h in intravenous administration of meloxicam alone and with enrofloxacin. Comparative lower MRT values of meloxicam were reported by Baert and Backer (2003) in pigeon (3.89 ± 1.49 h), duck (0.77 ± 0.20 h), turkey (1.47 ± 0.27 h), ostrich (0.41 ± 0.25 h) and chicken (4.41 ± 0.84 h). In male rat the values of MRT following intravenous administration at a dose rate of 1 $mg.kg^{-1}$was 18 h whereas in female rat it was found 52.8 h (Busch *et al*, 1998).

CONCLUSIONS

In conclusion, the results of the present study indicate that meloxicam can be safely and effectively administered either alone or in combination with enrofloxacin in male buffalo calves by intravenous route.

REFERNECES

1. Agrawal, A. K., Kumari, S., Jayachandran, C. and Singh, M. K. (2001). Pharmacokinetics interaction of enrofloxacin and Paracetamol in goats. Proceeding of 2nd annual conference of Indian society of veterinary pharmacology and toxicology held at dept. of pharmacology veterinary college, GAU, Sardarkrushinagar, Gujarat. pp–122.

2. Anonymous(2001 a). Boehringer–Ingelheim pharmaceuticals Inc. Prescribing information for meloxicam.
3. Anonymous (2001 b). Metacam 20 mg/ml solution for injection for cattle (c.f.http://www.emea.eu.int).
4. Baert, K. and Backer, P. De. (2003). Comparative pharmacokinetics of three non steroidal anti inflammatory drugs in five bird species. *Comparative Biochemistry and Physiology*. Part C. **134 :** 25–33.
5. Baggot, J. D. (1977). Principles of drug disposition in domestic animals. The basis of' veterinary clinical pharmacology, 1st Ed., W.B, Saunders Co., Philadelphia, USA., pp. 144-189.
6. Busch, U., Schmid, J., Heinzel, G., Schmaus, H., Baierl, J., Huber, C. and Roth, W. (1998). Pharmacokinetics of meloxicam in animals and the relevance to humans. *Drug Metab. Dispos*. **26** (6) **:** 576–584.
7. Dumka, V. K. (2002). Interaction kinetics of levofloxacin and meloxicam in cross bred cow calves. Ph. D. Thesis submitted to Punjab Agricultural University, Ludhiana.
8. Gibaldi, M. and Perrier, D. (1982). Pharmacokinetics. 2nd Ed. Marcel-Dekker Inc. New York.
9. Kumar, N., Singh, S. D. and Jayachandran, C. (2003). Pharmacokinetics of enrofloxacin and its active metabolite ciprofloxacin and its interaction with diclofenac after intravenous administration in buffalo calves. *The Veterinary Journal*. **165** : 302 – 306.
10. Lees, P., Sedgwick, A. D., Higgins, A. J., Pugh, K. E. and Busch, U. (1991). Pharmacodynamics and pharmacokinetics of meloxicam in the horse. *British Veterinary Journal*. **147** : 97-108.
11. Notari, R. E. (1973). Pharmacokinetics and molecular modification: Implication in drug, design and evaluation. *J. Pharm. Sci*. **62 :** 865-881.
12. Rao, G. S., Ramesh, S., Ahmad, A. H., Tripathi, H. C., Sharma, L. D. and Malik, J. K. (2002). Pharmacokinetics of enrofloxacin and its metabolite ciprofloxacin in goats given enrofloxacin alone and in combination with probenecid. *The Veterinary Journal*. **163** : 85–93.
13. Samad, A. and Gaikwad, G. V. (2000). Meloxicam as an anti–inflammatory agent in veterinary practice. *Intas Polivet.* **1** (1) **:** 35–38.
14. Tripathi, A., Tripathi, R. M., Mody, S. K. and Makkar, M. S. (2001). Pharmacokinetics of enrofloxacin and its interaction with diclofenac sodium after intramuscular administration in male sheep. Proceeding of 2nd annual conference of Indian society of veterinary pharmacology and toxicology held at dept. of pharmacology veterinary college, GAU, Sardarkrushinagar, Gujarat. pp – 131.
15. Vane, J. R. and Botting, R. M. (1997). Mechanism of action of aspirin–like drugs. *Semin Arthritis Rheum*. **26** (6) **:** 2–10.
16. Varma, R., Ahmad, A. H. and Sharma, L. D. (2001). Dispositionkinetics of enrofloxacin and its interaction with sulphadiazine plus trimethoprim combination in laying poultry birds. Proceeding of 2nd annual conference of Indian society of veterinary pharmacology and toxicology held at dept. of pharmacology veterinary college, GAU, Sardarkrushinagar, Gujarat. pp – 134.
17. Vichare, A. S. (2004). Studies on comparative pharmacokinetics of meloxicam in male cow calves. M.V.Sc thesis submitted to Gujarat Agriculture University, Saradarkrushinagar.

