DISPOSITION KINETICS OF DICLOFENAC IN FEMALE GOATS.

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ABSTRACT:

The pharmacokinetic of diclofenac was studied in five clinically healthy female goats (*Capra hircus*) following i.v. administration (2 mg. kg-1 body weight). Blood and urine samples were collected at different time intervals and were analysed using HPLC. The plasma concentration–time data following i.v. administration of diclofenac was best described by a two compartment open pharmacokinetic model. Elimination half life ($t_{1/2}\beta$), area under plasma concentration time curve (AUC), mean residential time (MRT), micro-rate constant of drug transfer from central to peripheral (K_{12}) and peripheral to central compartment (K_{21}) were noted as 2.97 ± 0.53 h, 19.40 ± 2.98 mg.L^{-1}h, 2.62 ± 0.61 h, 1.710 ± 0.141 $h^{-1}$and 0.514 ± 0.041 h^{-1}, respectively. Volume of distribution (Vd^{area}) and total body clearance (Cl_B) were 0.49 ± 0.11 L.kg^{-1} and 1.91 ± 0.33 ml.kg^{-1}.min^{-1}, respectively. Rate constant drug elimination from central compartment (Kel), fraction of drug available for elimination from central compartment (Fc) and approximate tissue to plasma concentration ratio (T H" P) were noted as 2.509 ± 0.884 h^{-1}, 0.13 ± 0.02 and 8.16 ± 2.21, respectively. Low Vd_{area}, K_{21} and Cl_B with high K_{12}, MRT supports high protein binding and localisation of diclofenac.

KEY WORDS: Pharmacokinetics, Diclofenac, HPLC, I.V., Goat

INTRODUCTION

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID), widely used in therapeutics, that exhibits potent analgesic and anti-inflammatory properties (Todd *et al.*, 1988). It is approved for the long-term treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis, and also for the short-term treatment of acute musculoskeletal injury, postoperative pain and dysmenorrhoea (Brogden *et al.*, 1980). Diclofenac is predominantly eliminated via hepatic biotransformation with less than 1% of the dose being excreted unchanged via the kidneys because it have high (more than 90 %) plasma protein binding (Chan et al., 2006). The major primary metabolite of diclofenac is 42 -hydroxydiclofenac (42 -OH diclofenac), with 32 -OH- and 52 -OH-diclofenac being minor metabolites (Stierlin, *et al.*, 1979). Both diclofenac and its hydroxylated metabolites undergo glucuronidation and sulphation.The pharmacokinetics of diclofenac has been studied in man (Willis et al., 1979), minipig (Oberle et al., 1994), rat (Peris-Ribera et al., 1991), camel (Wasfi, *et al.*, 2003), sheep (Altaher, *et al.*, 2005 and Rahal *et al.*, 2008) and buffalo calves (Kumar *et al.*, 2003). The purpose of present study is to determine the pharmacokinetics and urinary excretion of diclofenac in goats after its intravenous administration.

MATERIALS AND METHODS

The experiment was carried out on five clinically healthy female goats (*Capra hircus*) of non-descript breed weighing between 20 to 22 kg. The animals were housed in animals shed with concrete floor, provided with dry fodder, concentrate feed and greens apart from grazing for 5 to 6 hours. Water was provided *ad lib*. Diclofenac (Versatan@-Ranbaxy, India) was administered in jugular vein of healthy goats at the dose rate of 2 mg.kg^{-1} b.wt. Blood samples were withdrawn in sterilised heparinised test tubes from contralateral jugular vein at 0.042, 0.083, 0.167, 0.25, 0.33, 0.50, 0.75,

1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 h after intravenous administration of the drug. Plasma samples were separated after centrifugation at 3000 rpm for 15 minutes at room temperature. Samples of urine were collected at the above noted time intervals as well as at 24, 30, 36 and 48 h after drug administration, Collection of urine samples were done by introducing a Foley's catheter (No. 12) into urethra. Samples were stored at -20^{0}C. Concentration of drug in plasma and urine were analysed by High Performance Liquid Chromatography (HPLC) as described by El-Sayed et al. (1988) with minor modifications. The plasma concentration–time data following i.v. administration of diclofenac was best described by a two compartment open pharmacokinetic model (Kumar et al., 2003).

RESULTS AND DISCUSSION

The mean plasma and urine levels of doclofense at various time intervals (from 0.042 h. to 12 h in plasma and 0.042 h to 48 h in urine) after its single i.v. administration (2 mg.kg^{-1} b.wt.) in healthy goats were found between 56.35 ± 10.07 to 0.08 ± 0.03 and 1.68 ± 0.24 to 0.38 ± 0.08 ìg.ml^{-1}, respectively. The peak plasma concentration was noted to be 56.35 ± 10.07 ìg.ml^{-1} at 0.042 h while in case of urine it was noted to be 95.64 ± 15.33 ìg.ml^{-1} at 0.50 h.

Table 1: Kinetic parameters of diclofenac in healthy goats following single I.V. dose of 2 mg.kg^{-1}.

Kinetic Parameters (unit)	Values (mean ± S.E.M) n=5
A (µg. ml^{-1})	45.95 ± 21.13
B (µg. ml^{-1})	2.69 ± 0.65
Cp^{i} (mg. ml^{-1})	48.65 ± 21.24
α (h^{-1})	4.467 ± 0.827
$t_{1/2}\alpha$ (h)	0.17 ± 0.02
β (h^{-1})	0.262 ± 0.040
$t_{1/2}\beta$ (h)	2.97 ± 0.53
AUC (mg.L^{-1}h)	19.40 ± 2.98
AUMC (mg.L^{-1}h^2)	51.50 ± 17.56
MRT (h)	2.62 ± 0.61
K_{12} (h^{-1})	1.710 ± 0.141
K_{21} (h^{-1})	0.514 ± 0.041
Kel (h^{-1})	2.509 ± 0.884
Fc	0.13 ± 0.02
T ≈ P	8.16 ± 2.21
Vd_C (L.kg^{-1})	0.06 ± 0.01
Vd_B (L.kg^{-1})	0.90 ± 0.18

Vd^{area} ($L.kg^{-1}$)	0.49 ± 0.11
Vd_{ss} ($L.kg^{-1}$)	0.28 ± 0.06
Cl_B ($ml.kg^{-1}.min^{-1}$)	1.91 ± 0.33

A and B = extrapolated zero time plasma drug concentration during distribution and elimination phase, respectively; Cp^i = theoretical zero time concentration; α and β = distribution and elimination rate constant, respectively; $t_{1/2}\beta$ and $t_{1/2}\beta$ = distribution and elimination half life, respectively; AUC = area under plasma concentration time curve; AUMC = area under first moment of plasma concentration time curve; MRT = mean residential time; K_{12} and K_{21} = micro-rate constant of drug transfer from central to peripheral and peripheral to central compartment, respectively; Kel = rate constant drug elimination from central compartment; Fc = fraction of drug available for elimination from central compartment; T H" P = approximate tissue to plasma concentration ratio; Vd_C, Vd_B, Vd^{area}, and Vd_{ss} = volume of distribution from central compartment, elimination phase, AUC and steady state plasma level, respectively; Cl_B = total body clearance;

The mean values of various disposition kinetic parameters of diclofenac were calculated on the basis of plasma levels of diclofenac at different time intervals. Area under plasma concentration time curve (AUC) was noted to be 19.40 ± 2.98 $mg.L^{-1}h$ which is higher as compared to the report of Rahal et al. (2008) and Altaher, *et al.*, (2005) in sheep. The shorter distribution half life ($t_{1/2}\beta$) of 0.17 ± 0.02 h denotes that the drug is distributed at a faster rate. However higher $t_{1/2}\beta$ of 0.34 ± 0.08 h in buffalo calves was reported (Kumar et al., 2003).

The mean elimination rate constant (β) 0.262 ± 0.040 h^{-1} and elimination half life ($t_{1/2}\beta$) of 2.97 ± 0.53 h were noted for diclofenac after its single i.v. administration. The $t_{1/2}\beta$ observed in the present investigation is found to be higher in contrast to the report of Rahal et al. (2008) in sheep (1.03 ± 0.18 h) and lower as reported by Kumar et.al. (2003) in buffalo calves (4.06 ± 0.59 h). The value of $t_{1/2}\beta$ (2.97 ± 0.53 h) noted in the present study is more or less similar to that of 2.35 h in camel (Wasfi, *et al.*, 2003).The rate constant of drug transfer from central to peripheral (K_{12}), peripheral to central (K_{21}) compartment and rate constant of drug elimination from central compartment (Kel) were noted to be 1.710 ± 0.141 h^{-1}, 0.514 ± 0.041 h^{-1} and 2.509 ± 0.884 h^{-1}, respectively, after i.v. administration of diclofenac. Higher values of K_{12} and Kel as well as lower value of K_{21} are due to better retention of drug in central compartment so low K_{12} and high $K_{21.}$ Low Vd^{area} of 0.49 ± 0.11 $L.kg^{-1}$ in the present study denotes poor to moderate distribution of diclofenac in the body of goat which can be supported by higher MRT of 2.62 ± 0.61 h and higher T H" P of 8.16 ± 2.21. In the present study Vd^{area} , Vd_{ss} and Cl_B were found to be 0.49 ± 0.11 $L.kg^{-1}$, 0.28 ± 0.06 $L.kg^{-1}$and 1.91 ± 0.33 $ml.kg^{-1}.min^{-1}$ which are more or less similar to that reported by Altaher et al.(2005) as 0.39 ± 0.15 $L.kg^{-1}$, 0.20 ± 0.06 $L.kg^{-1}$and 1.47 ± 0.18 $ml.kg^{-1}.min^{-1}$, respectively. Diclofenac is localised or sequestrated in certain body compartments which can be supported by low value of Cl_B and higher values of MRT and T H" P with detection of diclofenac in urine beyond 48 h.

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