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The Pharma Innovation

ISSN (E): 2277-7695
ISSN (P): 2349-8242
NAAS Rating: 5.23
TPI 2022; SP-11(9): 1618-1621

www.thepharmajournal.com
Received: 22-07-2022
Accepted: 25-08-2022

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Pharmacokinetics of ketoprofen following single dose intravenous administration in Black Bengal goats

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Abstract
Ketoprofen (KTP) is a non-steroidal anti-inflammatory drug (NSAID) frequently used in veterinary practice for the treatment of various inflammatory conditions. The present study was conducted to evaluate the disposition kinetics of KTP in healthy Black Bengal goats following single intravenous administration at the dose rate of 3 mg. kg^{-1} body weight. Blood samples were collected in pre-heparinized tubes before drug administration and at time intervals of 0.042, 0.083, 0.167, 0.25, 0.333, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12 and 24 hours post drug administration. KTP in plasma was estimated by high performance liquid chromatography (HPLC). On the basis of a semi-log plot of the plasma drug concentration versus time curve, the pharmacokinetic parameters of KTP were estimated by two-compartment open model which provided best results for the experimental data. The mean plasma concentration of the drug at 0.042 h was found to be 9.08±0.45 µg.ml^{-1}. The drug was detectable in all the five animals upto 6 h. The distribution rate constant (α) of 3.135±0.231 h^{-1} and elimination rate constant (β) of 0.619±0.039 h^{-1} was found. The mean distribution half-life ($t_{1/2}$ α) and elimination half-life ($t_{1/2}$ β) values of the drug were observed to be 0.23±0.02 and 1.13±0.07 h, respectively. The mean values of Vd_{area} and total body clearance (Cl_B) were observed to be 0.86±0.05 L. kg^{-1} and 8.75±0.31 ml.kg^{-1}. min^{-1}, respectively. The drug appeared in urine at 0.042 h with a mean value of 0.12±0.08 µg.ml^{-1} was maintained upto 24 h with a mean value of 0.02±0.02 µg.ml^{-1}. The mean peak urine concentration of 98.77±9.69 µg.ml^{-1} was observed at 0.75 h.

Keywords: Ketoprofen, pharmacokinetics, intravenous administration, HPLC, Black Bengal goats

1. Introduction
Ketoprofen, an effective non-steroidal anti-inflammatory drug (NASID) may act as an alternative to diclofenac since the use of diclofenac caused extinction of vultures in most part of India [1]. Ketoprofen possesses powerful anti-inflammatory, analgesic and antipyretic properties. When ketoprofen is used concomitantly with primary antibacterial agent, it significantly improved recovery in gram-negative clinical mastitis in dairy cows [2]. Ketoprofen is a propionic acid derivative, it is a non-selective COX inhibitor [3] that prevents the synthesis of prostanoids [4], which are major mediators of acute and chronic inflammatory conditions. Ketoprofen may also exhibit centrally -mediated, anti-nociceptive activity [5, 6], elicited via supraspinal and spinal receptors [7]. Ketoprofen has provided effective analgesia for clinical conditions in dog, such as osteoarthritis [8], castration [9], joint pain [10] and orthopedic procedures [11, 12]. Kinetic study of ketoprofen in lactating goats [13] after i.v. administration and the pharmacodynamic chiral pharmacokinetics and PK-PD modeling of ketoprofen [14] studies have been reported. However, there is lack of pharmacokinetic studies of ketoprofen in small ruminants, particularly in Black Bengal goats. Hence, the present study was undertaken with the objective to evaluate the disposition kinetics of Ketoprofen in Black Bengal goats after single intravenous administration.

2. Materials and Methods
2.1 Animals and Drugs
In the present study, five clinically healthy female goats of Black Bengal breed between 20 to 24 months of age and 18-22 kg body weight were used. The goats were housed in the animal shed in the Department of Veterinary Pharmacology and Toxicology, Bihar Veterinary College, Patna. The goats were maintained on dry fodder concentrate and green grasses apart from routine grazing of about 4 to 5 hours.

Neoprofen®, an injectable commercial preparation containing ketoprofen in concentration of 100 mg.ml^{-1} was used in present study.

2.2 Experimental design
Ketoprofen @ dose rate of 3 mg. kg^{-1} was administered in each of five healthy goats by intravenous (i.v) route. The samples of various biological fluids were collected after i.v. administration of drugs in healthy goats. The samples of plasma and urine were collected at 2.5, 5, 10, 15, 20, 30, 45 min and 1, 1. 5, 2, 3, 4, 5, 6, 8, 10, 12 and 24 h. Samples of urine were collected further up to 48 h (at 30, 36 and 48 h). For the purpose of separating the plasma, samples were centrifuged at 3000 rpm for 15 minutes. After that, plasma and urine samples were stored at -20 °C in a refrigerator till analysis.

2.3 HPLC assay of Ketoprofen
The concentrations of ketoprofen in plasma and urine were estimated by HPLC method [15]. The HPLC equipment consisted of a HPLC pump, a dual wavelength absorbance detector, a rheodyne manual injector with a 200 µl loop size and a data module. Chromatographic separations were performed using C18 column (3.9 × 150 mm size). The flow rate was 1 ml. min^{-1}, the effluent was monitored at 257 nm, loop size was 200 µl, injection volume was 400 µl, chart speed was 0.25 mm. min^{-1} and the detector sensitivity was monitored at 2.000 area under full scale (A.U.F.S). The mobile phase comprised of water with orthophosphoric acid (pH 3.2): acetonitrile: methanol (52:35:13% v/v).

2.4 Pharmacokinetic analysis
The pharmacokinetic parameters of ketoprofen were calculated after its single i.v. administration from semi-log plot of plasma drug concentration versus time curve. The experimental data were analyzed by using two compartment open model for ketoprofen (i.v. route) [16-18].

$C_p = A_e^{-\alpha t} + B_e^{-\beta t}$……..(Two compartment model)

Where e is the base of natural logarithm and C_p is the drug concentration in plasma at time 't'.

2.5 Statistical Analysis
Statistical analysis was done by using single factor Anova [19].

3. Result and Discussion
Plasma concentrations of ketoprofen at various time intervals following single intravenous dose of 3 mg. kg^{-1} in goats have been shown in Table 1. The drug was detectable in goats upto 8 h and the mean plasma concentration was 0.016±0.01 µg.ml^{-1}. The drug was not detected at 10 h in any of the goats. The mean peak urine concentration of 98.77±9.69 µg.ml^{-1} was observed at 0.75 h.

Plasma and urine drug concentrations versus time profile has confirmed the two-compartment open model. Table 2 shows the values of different kinetic parameters.

Distribution half-life ($t_{½}\alpha$) of 0.07 h noted for ketoprofen in H.F cows [19] was found to be lower as compared to the $t_{½}\alpha$ value noted in the present study (0.22±0.02 h) in goats. This shows that ketoprofen may be distributed comparatively slower in goats as compared to H.F cows. The elimination rate constant, β of 0.619±0.039 h^{-1} and elimination half-life, $t_{½}\beta$ of 1.13±0.07 h was noted in present study. Lower value of elimination half-life ($t_{½}\beta$) of 0.32±0.14 h in goats [13], 0.42±0.08 h in calf [20], 0.48 h in H.F cows [19] were noted after i.v administration. Higher value of $t_{½}\beta$ of 1.63 h in mare [21], 1.88 h in camels [22] were noted after i.v. administration of ketoprofen. The total body clearance (Cl_B) of 8.75±0.31 ml. kg^{-1}. min^{-1}. was observed after single i.v administration of ketoprofen. A low Cl_B value of 5.50±0.50 ml. kg^{-1}. min^{-1} in calf [20] was observed. The value reported in goats (12.33±2.00 ml. kg-1. min^{-1}) in a study [13] is comparatively higher than the present study. The KTP in Black Bengal goats can be repeated after 12 hours because the drug was not detected in plasma at 12 hour.

We conclude that ketoprofen administered @ dose rate of 3 mg/kg i.v. maintained its therapeutic concentration in urine for a period of 24 h. Hence, the drug can be used @ 3 mg/kg i.v. every 12 hourly in clinical cases where commonly pain, pyrexia and other inflammatory conditions are observed.

Table 1: Plasma and Urine concentrations (µg/ml) of Ketoprofen in healthy goats following single i.v. administration of ketoprofen (3 mg/kg).

Time (h)	Mean Plasma Conc. ± S.E.M	Mean Urine Conc. ± S.E.M
0.042	9.08±0.45	0.12±0.08
0.083	6.86±0.38	5.19±1.42
0.167	5.09±0.38	12.64±2.57
0.25	4.35±0.40	30.69±7.56
0.333	3.66±0.13	58.66±4.65
0.50	2.94±0.07	76.58±6.48
0.75	1.90±0.27	98.77±9.69
1	1.21±.0.06	81.23±6.73
1.5	0.97±0.02	43.52±6.54
2	0.68±0.03	23.93±3.33
3	0.41±0.07	10.74±1.57
4	0.25±0.04	6.35±1.91
5	0.11±0.02	2.84±1.37
6	0.05±0.01	1.20±0.56
8	0.016±0.01	0.46±0.17
10	N.D	0.28±0.15
12		0.07±0.04
24		0.02±0.02

N.D = Non-detectable

Table 2: Kinetic parameters of ketoprofen in healthy goats after single intravenous dose of 3 mg/kg (calculated by two compartment model).

Parameter	Mean ± S.E.M
A (µg/ml)	5.64±0.95
B (µg/ml)	2.46±0.24
C $^{o}_{p}$ (µg/ml)	8.10±0.74
α (h^{-1})	3.135±0.231
$t_{1/2}$ α (h)	0.23±00.02
β (h^{-1})	0.619±0.039
$t_{1/2}$ β (h)	1.13±0.07
AUC (mg/L.h)	5.72±0.18
AUMC (mg/L.h^2)	7.02±0.39
MRT (h)	1.22±0.04
K_{12} (h^{-1})	0.958±0.159
K_{21} (h^{-1})	1.383±0.111
Kel (h^{-1})	1.414±0.112
Fc	0.45±0.06
T≈P	1.36±0.32
Vdc ($L.kg^{-1}$)	0.38±0.03
Vd_B ($L.kg^{-1}$)	1.26±0.12
Vd_{area} ($L.kg^{-1}$)	0.86±0.05
Vdss ($L.kg^{-1}$)	0.64±0.03
Cl_B (ml. kg^{-1}. min^{-1})	8.75±0.31

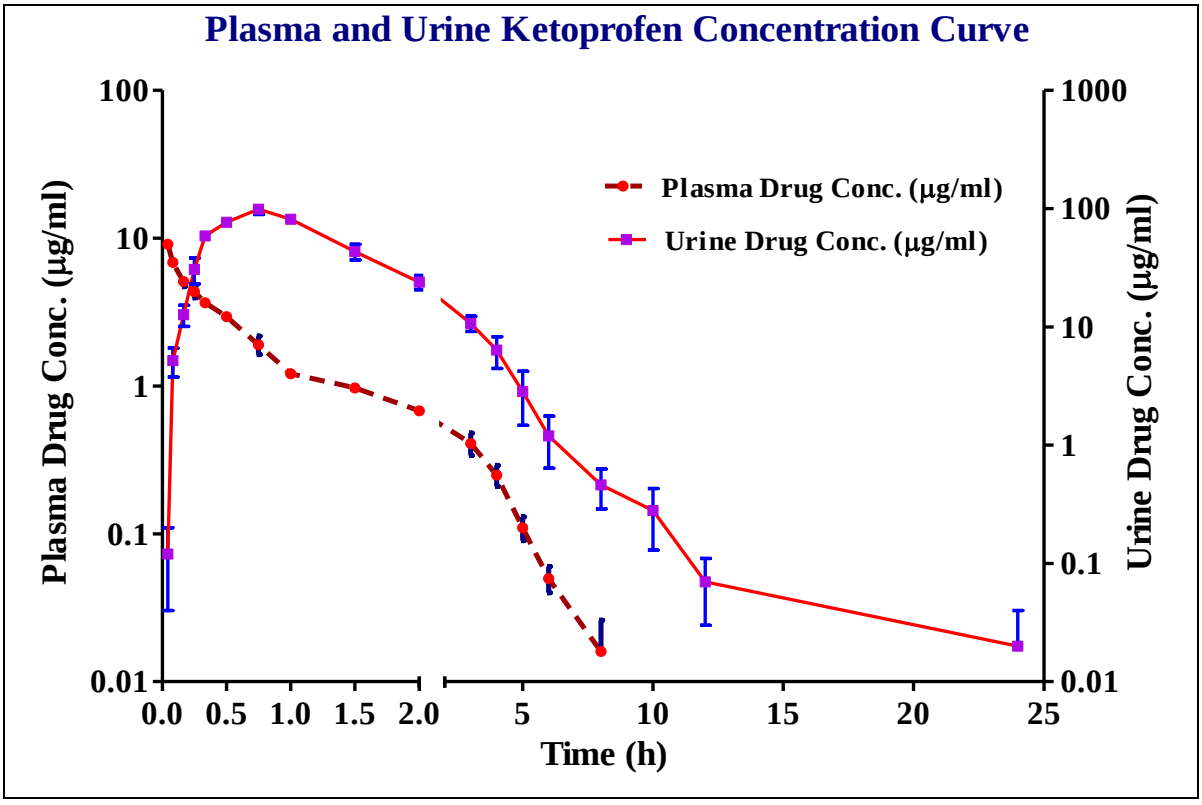

Fig 1: Plasma and Urine Drug concentrations (µg/ml) versus Time profile curves following single intravenous administration of Ketoprofen @ 3 mg/kg b.wt. in healthy goats (n=5).

4. Acknowledgement
Authors are grateful to Bihar Veterinary College, Patna for providing necessary support to accomplish this work which is a part of post graduate research study of the first author.

5. Conflict of interest
The authors declare no conflict of interests.

6. Author's Contribution
DK performed the experiment and analyzed the results. VKG assisted in experiments and analysis of samples. NK drafted the manuscript. NK and CJC designed the experiment.

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