



## RESEARCH ARTICLE

### Impact of Multiple Intravenous Administrations of Ketoprofen on Blood Profile in Cow Calves

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#### ABSTRACT

Ketoprofen is an aryl propionic acid derivative, non steroidal anti-inflammatory drug (NSAID) administered by intravenous and other parenteral routes in domestic animals. Side effects like gastrointestinal ulceration, hepatopathies, haematological alterations, photosensitivity and renal diseases, have been reported in domestic and laboratory animals following long term administration of ketoprofen. It was found that there is a lack of literature on the safety of ketoprofen in the target species like cattle. Therefore the present study was planned to evaluate the safety of ketoprofen following its multiple intravenous administration in cow calves. The present study was carried out on six healthy male cow calves of 6-12 months and weighing between 76 to 117 kilograms. Ketoprofen injections were administered at the dose rate of 3 mg/kg intravenously in calves and repeated at 24 hours interval for 5 days. Blood samples were withdrawn from jugular vein into sterile heparinized (2 ml) and non-heparinized (5 ml) test tubes at 0 day (before drug administration) and on 1<sup>st</sup> (24 h), 2<sup>nd</sup> (48 h), 3<sup>th</sup> (72 h), 4<sup>th</sup> (96 h) and 5<sup>th</sup> day (120 h) for haematological [Hb, PCV, TLC and DLC] and serum biochemical [SAP, ACP, AST, ALT, LDH, Total bilirubin, Serum creatinine, BUN, Serum total protein and Serum albumin] analysis. The mean values of all haematological and blood biochemical parameters in treated animal do not differ significantly ( $P < 0.05$ ) when compared to control samples. It is concluded that administration of ketoprofen by intravenous route continuously for 5 days in calves was found safe.

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#### INTRODUCTION

Administration of anti-inflammatory and antipyretic agents to alleviate signs of inflammation is a standard therapeutic approach. However the ban on widely used NSAID like diclofenac sodium in bovines and other domestic animals in India necessitates finding alternative therapeutic substitute for treating musculoskeletal disorders and painful conditions in bovines. In such conditions in veterinary practice, ketoprofen has emerged as a good therapeutic substitute for treating inflammatory conditions in bovines. It is a strong non-selective inhibitor of cyclooxygenase (COX). It has powerful anti-inflammatory, analgesic and antipyretic properties (Lees, 2009). In veterinary practice, ketoprofen is used to lower

body temperature in animals with fever, to relieve respiratory signs in calf and piglet pneumonias and to relieve pain in conditions as diverse as equine colic, joint diseases of the horse and dogs and for the control of traumatic and postoperative pain in all species (Lees *et al.*, 2004).

Ketoprofen is given by intravenous and other parenteral routes in cattle, cats, dogs and horses. Side effects like gastrointestinal ulceration, hepatopathies, haematological alteration, photosensitivity and renal disease, have been reported in domestic and laboratory animals following long term administration of ketoprofen (Collins *et al.*, 1998; Jerussi *et al.*, 1998; Cabre *et al.*, 1998; Narita *et al.*, 2005; Luna *et al.*, 2007). Most of the safety and toxicity studies are conducted in laboratory

animals following intravenous administration. However, the data on safety of repeated administration of ketoprofen in target species like cattle are lacking. Pharmacokinetic data and pharmacokinetic-pharmacodynamic relationship of ketoprofen in cattle are reported (Landoni *et al.*, 1995; De Graves *et al.*, 1996; Igarza *et al.*, 2004). But that there is lack of literature on safety of ketoprofen in the target species like cattle. Therefore the present study was planned to evaluate safety of ketoprofen following its multiple intravenous administration in cow calves.

## MATERIALS AND METHODS

The present study was carried out on six healthy male cow calves (Kankrejbreed) calves of 6-12 months age group and weighing between 76 to 117 kilograms at Livestock Research Station, Anand Agricultural University, Anand. The calves were housed in experimental calf pen two weeks prior to experiment for acclimatization. The animals were fed concentrates, green fodder and roughage and had free access to water. All essential and standard management measures were adopted to keep the calves free from stress. The study was approved by the Institutional Animal Ethics Committee (IAEC), College of Veterinary Sciences and Animal Husbandry, Anand.

Ketoprofen injection [Neoprofen (100 mg/ml), Vetnex Ranbaxy Fine Chemicals Limited, New Delhi] was administered at the dose rate of 3 mg/kg intravenously in calves and repeated at 24 hours interval for 5 days. The animals were observed for any clinical abnormalities during the period of experiment. Blood samples were withdrawn from jugular vein into sterile heparinized (2 ml) and non-heparinized (5 ml) test tubes at 0 day (before drug administration) and on 1<sup>st</sup> (24 h), 2<sup>nd</sup> (48 h), 3<sup>rd</sup> (72 h), 4<sup>th</sup> (96 h) and 5<sup>th</sup> day (120 h) for haematological [Hemoglobin (Hb), Packed cell volume (PCV), Total leukocytes count (TLC) and Differential leukocytes count (DLC)] and serum biochemical analysis [Alkaline phosphatase (SAP), Acid phosphatase (ACP), Aspartate aminotransferase (AST), Alanine transaminase (ALT), Lactate dehydrogenase (LDH), Total bilirubin, Serum creatinine, Blood urea nitrogen (BUN), Serum total protein and Serum albumin]. Serum was collected and stored at -20°C for biochemical analysis. Hb estimation and TLC were done by Automated Hematology Analyzer (CA 620 VET, Boule Medical, Sweden). PCV and DLC were carried out manually. All the biochemical

parameters were estimated using standard assay kits (Anamol Laboratories Pvt. Ltd., Palghar, India) with the help of automated Clinical Chemistry Analyzer (Junior Selectra, Vital Scientific, Netherland). The data generated from these safety profile study were compared by student t test using SPSS software (version 12.0.1).

## RESULTS

The values of hematological and serum biochemistry parameters evaluated after intravenous administration of the drug at the dose rate of 3 mg/kg body weight repeated at 24 hours interval in calves are presented in Table 1 and 2. No adverse reaction or toxic manifestations were exhibited in the present study.

## DISCUSSION

The mean values of Hb, PCV, TLC, and DLC observed in treated animal (24-120 h) do not differ significantly ( $P < 0.05$ ) when compared to control (0h) samples. Moreover, mean values of serum AKP, ACP, AST, ALT, LDH, total serum bilirubin, serum creatinine, BUN, total serum protein and serum albumin observed during treatment period (24-120 h) do not differ significantly ( $P < 0.05$ ) from the corresponding values observed in control (0 h) samples. It indicates that repeated administration of ketoprofen within therapeutic dosage regimen in calves was well tolerated. However, adverse effect of ketoprofen like gastrointestinal ulcers, hepatopathy and nephropathy were observed after long term administrations (25 to 90 days) of ketoprofen or when given repeatedly at high dose rates (Collinset *et al.*, 1998; Jerussiet *et al.*, 1998; Cabreet *et al.*, 1998; Naritaet *et al.*, 2005; Lunaet *et al.*, 2007).

Ketoprofen inhibits both COX-1 and COX-2 enzymes. COX-1 is a constitutive enzyme, involved in the synthesis of eicosanoids related to 'house keeping functions' while COX-2 is an inducible isoenzyme, involved in the production of eicosanoids related to the inflammatory response. Therefore, reduction in serum  $\text{TxB}_2$  is a measure of inhibition of COX-1, whilst decreased exudate  $\text{PGE}_2$  synthesis indicates inhibition of COX-2. The  $\text{IC}_{50}$  ratio (serum  $\text{TxB}_2$ : exudates  $\text{PGE}_2$ ) was 1.37 (Landoni *et al.*, 1995). The greater concentration required to inhibit  $\text{TxB}_2$  indicates a lesser likelihood of toxic reactions after ketoprofen administration in cattle which is in agreement with findings of the present study.

**Table 1:** Hematological parameters (Mean  $\pm$  S.E.) after intravenous administration of ketoprofen (3 mg/kg repeated at 24 hr interval) in calves.

Parameter	Days					
	0	1	2	3	4	5
Haemoglobin (g/dl)	10.88 $\pm$ 0.18	10.82 $\pm$ 0.21	11.05 $\pm$ 0.23	11.02 $\pm$ 0.19 <sup>a</sup>	11.15 $\pm$ 0.27	11.07 $\pm$ 0.25
Packed Cell Volume (%)	35.00 $\pm$ 0.52	34.83 $\pm$ 0.48	34.67 $\pm$ 0.42	35.17 $\pm$ 0.40	35.50 $\pm$ 0.62	35.50 $\pm$ 0.62
Total Leukocyte Count (per cmm)	8566.67 $\pm$ 154.20	8650.00 $\pm$ 183.94	8616.67 $\pm$ 219.72	8633.33 $\pm$ 170.62	8550.00 $\pm$ 133.54	8633.33 $\pm$ 154.20
Neutrophil (%)	22.00 $\pm$ 0.63	23.00 $\pm$ 0.68	22.17 $\pm$ 0.95	23.00 $\pm$ 0.52	22.00 $\pm$ 0.86	22.00 $\pm$ 0.68
Lymphocyte (%)	74.33 $\pm$ 0.88	73.50 $\pm$ 1.18	73.83 $\pm$ 1.58	72.67 $\pm$ 0.76	74.00 $\pm$ 0.93	74.67 $\pm$ 1.02
Basophil (%)	0.67 $\pm$ 0.21	0.83 $\pm$ 0.17	0.83 $\pm$ 0.31	0.67 $\pm$ 0.21	0.83 $\pm$ 0.17	0.50 $\pm$ 0.22
Eosinophil (%)	1.67 $\pm$ 0.21	1.83 $\pm$ 0.40	2.00 $\pm$ 0.37	2.33 $\pm$ 0.33	2.00 $\pm$ 0.45	1.83 $\pm$ 0.17
Monocyte (%)	1.33 $\pm$ 0.21	0.83 $\pm$ 0.17	1.17 $\pm$ 0.31	1.33 $\pm$ 0.33	1.17 $\pm$ 0.31	1.00 $\pm$ 0.26

Number of calves in each group (n) = 6; All the values do not differ significantly

**Table 2:** Serum biochemical parameters (Mean  $\pm$  S.E.) after intravenous administration of ketoprofen (3 mg/kg repeated at 24 hr interval) in calves.

Parameter	Days					
	0	1	2	3	4	5
Serum Alkaline Phosphatase (IU/L)	267.37 $\pm$ 3.25	271.63 $\pm$ 3.00	269.66 $\pm$ 3.41	271.79 $\pm$ 3.61	271.66 $\pm$ 3.31	269.03 $\pm$ 2.29
Serum Acid Phosphatase (IU/L)	2.42 $\pm$ 0.20	2.36 $\pm$ 0.22	2.29 $\pm$ 0.24	2.30 $\pm$ 0.23	2.35 $\pm$ 0.22	2.41 $\pm$ 0.20
AST/ SGOT (IU/L)	90.71 $\pm$ 2.68	89.25 $\pm$ 2.23	91.25 $\pm$ 2.72	90.21 $\pm$ 3.63	91.96 $\pm$ 2.92	91.52 $\pm$ 2.89
ALT/ SGPT (IU/L)	31.24 $\pm$ 0.89	31.30 $\pm$ 0.56	31.17 $\pm$ 0.66	31.40 $\pm$ 0.84	32.01 $\pm$ 0.47	31.31 $\pm$ 0.87
LDH (IU/L)	756.54 $\pm$ 10.16	756.42 $\pm$ 9.58	761.46 $\pm$ 9.21	763.67 $\pm$ 11.40	762.44 $\pm$ 10.54	758.05 $\pm$ 11.32
Total Serum Bilirubin (mg/dl)	0.28 $\pm$ 0.02	0.28 $\pm$ 0.01	0.28 $\pm$ 0.02	0.29 $\pm$ 0.02	0.28 $\pm$ 0.03	0.28 $\pm$ 0.02
Serum Creatinine (mg/dl)	1.19 $\pm$ 0.01	1.20 $\pm$ 0.01	1.20 $\pm$ 0.01	1.21 $\pm$ 0.01	1.22 $\pm$ 0.02	1.21 $\pm$ 0.02
B.U.N. (mg/dl)	16.41 $\pm$ 0.88	16.66 $\pm$ 0.78	16.90 $\pm$ 0.84	16.15 $\pm$ 0.94	16.33 $\pm$ 0.82	16.30 $\pm$ 0.68
Total Serum Protein (g/dl)	6.27 $\pm$ 0.07	6.23 $\pm$ 0.06	6.23 $\pm$ 0.08	6.27 $\pm$ 0.08	6.28 $\pm$ 0.08	6.27 $\pm$ 0.08
Serum Albumin (g/dl)	2.82 $\pm$ 0.07	2.83 $\pm$ 0.07	2.85 $\pm$ 0.06	2.83 $\pm$ 0.07	2.83 $\pm$ 0.07	2.85 $\pm$ 0.07

Number of calves in each group (n) = 6; All the values do not differ significantly

The results of the present study suggest that ketoprofen has no adverse effects effect in cow calves following multiple intravenous administrations upto 5 days at the dose of 3 mg/kg body weight. It is safe for treatment of inflammatory diseases and as an antipyretic and analgesic in cow calves.

### Conclusion

Ketoprofen in calves was found to be safe based on evaluation of haematological (Hb, PCV, TLC and DLC), blood biochemical (SAP, ACP, AST, ALT, LDH, Total bilirubin, Serum Creatinine, BUN, Serum total protein, Serum albumin and Blood glucose) parameters.

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