Safety of Ketoprofen in Cow calves following repeated intravenous administration

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Abstract

Ketoprofen is a non steroidal anti-inflammatory drug (NSAID) used for its anti-inflammatory, analgesic and antipyretic properties in Veterinary Medicine. The present study was planned to assess safety of ketoprofen (3 $mg.kg^{-1}$) after repeated intravenous administration at 24 hours interval for five days in six crossbred cow calves (6-12 months age and weighing between 60-122 kg). Ketoprofen in calves was found safe based on evaluation of haematological (Hb, PCV, TLC and DLC), blood biochemical (AKP, ACP, AST, ALT, LDH, Total bilirubin, Serum Creatinine, BUN, Serum total protein, Serum albumin and Blood glucose) parameters.

Keywords: Ketoprofen, Cow calves, Safety, Intravenous

Introduction

Ketoprofen is an aryl propionic acid derivative, non steroidal anti-inflammatory drug (NSAID). It is a strong non-selective inhibitor of cyclooxygenase (COX). It has powerful anti-inflammatory, analgesic and antipyretic properties (Boothe, 2001). Ban on use of Diclofenac sodium in bovines and other domestic animals, made it necessary to find alternative NSAID for use in domestic animals. Ketoprofen has emerged as a good therapeutic substitute for treating musculoskeletal disorders and painful conditions in bovines.

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 and joint diseases of the horse and dog, as well as for the control of traumatic and postoperative pain in all species (Lees *et. al*., 2004).

Ketoprofen is given by intravenous and parenteral routes in cattle, cats, dogs and horses. It is recommended that ketoprofen treatment should be limited to a maximum of five consecutive days to reduce the risk of gastrointestinal effects (Thompson, 2006). Side effects like gastrointestinal ulceration, hepatopathies, haematological alteration, photo-sensitivity 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 cattle are lacking. As the drug is used parenterally in domestic animals, safety data following its repeated administrations are needed. 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 materializing 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 multiple intravenous administration of Ketoprofen in calves.

Materials and Methods

The present study was carried out on six healthy crossbred (Holstein-Friesian x Kankrej) male calves (6-12 months and weighing between 60 to 122 kilograms) at Instructional Farm, College of Veterinary Science and Animal Husbandry, Anand Agricultural University, Anand. The calves were housed in experimental calf pen, two weeks prior experiment for acclimatization. The animals were fed concentrates, green fodder and roughage and had free access to water. All essential and standard managemental measures were adopted to keep the calves free from stress. The study was approved by the Institutional Animal Ethics Committee (IAEC), College of veterinary Scince and animal Husbandry, Anand.

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Table-1. Hematological parameters (Mean ± S.E.) after intravenous administration of ketoprofen (3 mg.kg^{-1} repeated at 24 hr interval) in calves.

Parameters	Days					
	0	1	2	3	4	5
Haemoglobin (%)	10.95 ± 0.26^a	10.87 ± 0.18^a	11.02 ± 0.16^a	10.98 ± 0.19^a	10.82 ± 0.32^a	10.87 ± 0.24^a
PCV (%)	34.67 ± 0.33^a	34.17 ± 0.31^a	35.17 ± 0.31^a	35.00 ± 0.37^a	34.67 ± 0.49^a	34.83 ± 0.31^a
TLC (per cmm)	8333.33± 245.85^a	8433.33± 192.64^a	8366.67± 276.49^a	8416.67± 253.53^a	8466.67± 292.88^a	8483.33± 263.84^a
Neutrophil (%)	23.17 ± 0.60^a	23.33 ± 0.84^a	22.67 ± 0.99^a	21.83 ± 0.87^a	21.50 ± 0.50^a	21.67 ± 0.61^a
Lymphocyte (%)	72.50 ± 0.99^a	73.00 ± 0.89^a	73.17 ± 0.95^a	74.17 ± 1.05^a	75.00 ± 0.63^a	74.67 ± 0.67^a
Eosinophil (%)	2.00 ± 0.37^a	2.17 ± 0.40^a	2.83 ± 0.31^a	2.33 ± 0.33^a	1.17 ± 0.31^a	1.83 ± 0.17^a
Monocyte (%)	1.50 ± 0.22^a	1.00 ± 0.37^a	0.83 ± 0.17^a	1.00 ± 0.26^a	1.50 ± 0.22^a	1.33 ± 0.21^a
Basophil (%)	0.83 ± 0.31^a	0.50 ± 0.22^a	0.50 ± 0.22^a	0.67 ± 0.21^a	0.83 ± 0.31^a	0.50 ± 0.22^a

Number of calves in each group (n) = 6
Similar superscript (a) indicates non-significant differences ($p<0.05$)

Ketoprofen injection [Neoprofen (100 mg/ml), Vetnex Ranbaxy Fine Chemicals Limited, New Delhi] was administered at the dose rate of 3 mg kg^{-1} intravenously in calves 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 1st (24 h), 2nd (48 h), 3rd (72 h), 4th (96 h) and 5th day (120 h) for haematological [Hemoglobin (Hb), Packed cell volume (PCV), Total leukocytes count (TLC) and Diffrential leukocytes count (DLC)] and serum biochemical analysis [Alkaline phosphatase (AKP), Acid phosphatase (ACP), Aspartate aminotransferase (AST), Alanine transaminase (ALT), Lactate dehydrogenase (LDH), Total bilirubin, Serum creatinine, Blood urea nitrogen (BUN), Serum total protein, Serum albumin and Blood glucose]. Serum was collected and stored at -20ºC 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 Clinical Chemistry Analyzer (Junior Selectra, Vital Scientific, Netherland). The data generated from the safety profile study were compared by Least Square Difference test using SPSS software (version 12.0.1).

Results and Discussion

After intravenous administration of the drug at the dose rate of 3 mg.kg^{-1} body weight repeated at 24 hours interval in calves, the determined values of hematological parameters and serum biochemistry were evaluated and are presented in Table 1 and 2. In the present study none of the calf exhibited clinical symptoms of adverse reaction or toxicity. The mean values of Hb, PCV, TLC, and DLC observed in treated animal (24-120 h) do not differ significantly ($P < 0.05$) from the corresponding values observed in control (0 h) animals. Also, mean values of serum AKP, ACP, AST, ALT, LDH, total serum bilirubin, serum creatinine, BUN, total serum protein, serum albumin and blood glucose observed at 0 h and during treatment period (24-120 h) do not differ significantly ($P < 0.05$) from the corresponding values observed in control (0 h) animals. 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 and observed after long term administrations (25 to 90 days) of Ketoprofen or when given repeatedly at high dose rates (Collins *et al.,* 1998; Jerussi *et al.,* 1998; Cabre *et al.,* 1998; Narita *et al.,* 2005; Luna *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 TxB_2 is a measure of inhibition of COX-1, whilst decreased exudate PGE_2 synthesis indicates inhibition of COX-2. The IC_{50} ratio (serum TxB_2: exudates PGE_2) was 1.37 (Landoni *et al*., 1995). The greater concentration required to inhibit 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-2. Biochemical parameters (Mean ± S.E.) after intravenous administration of Ketoprofen (3 mg.kg^{-1} repeated at 24 hr interval) in calves

Serum Biochemical Parameters	Days					
	0	1	2	3	4	5
AKP (IU/L)	272.04 ± 4.46^a	275.41 ± 4.62^a	274.22 ± 2.97^a	273.39 ± 3.83^a	277.67 ± 4.31^a	274.01 ± 4.73^a
ACP (IU/L)	2.18 ± 0.38^a	2.30 ± 0.31^a	2.26 ± 0.33^a	2.23 ± 0.30^a	2.44 ± 0.26^a	2.42 ± 0.26^a
AST (IU/L)	91.56 ± 3.56^a	89.76 ± 3.30^a	91.46 ± 3.97^a	90.85 ± 3.22^a	92.56 ± 3.59^a	92.95 ± 3.65^a
ALT (IU/L)	30.69 ± 1.17^a	32.16 ± 0.80^a	31.33 ± 1.15^a	32.56 ± 0.82^a	33.40 ± 1.07^a	33.39 ± 1.29^a
LDH (IU/L)	750.51 ± 9.19^a	752.45 ± 6.35^a	755.71 ± 8.11^a	750.00 ± 11.61^a	758.26 ± 13.23^a	762.95 ± 12.85^a
Total Bilirubin (mg/dl)	0.29 ± 0.01^a	0.27 ± 0.02^a	0.28 ± 0.01^a	0.31 ± 0.02^a	0.30 ± 0.02^a	0.29 ± 0.02^a
Creatinine (mg/dl)	1.20 ± 0.02^a	1.19 ± 0.01^a	1.19 ± 0.02^a	1.20 ± 0.01^a	1.19 ± 0.02^a	1.20 ± 0.01^a
BUN (mg/dl)	17.18 ± 0.28^a	17.22 ± 0.45^a	17.31 ± 0.33^a	17.26 ± 0.24^a	17.95 ± 0.17^a	17.89 ± 0.31^a
Total Protein (gm/dl)	6.68 ± 0.09^a	6.72 ± 0.12^a	6.70 ± 0.11^a	6.75 ± 0.13^a	6.73 ± 0.14^a	6.73 ± 0.09^a
Albumin (gm/dl)	3.07 ± 0.08^a	3.05 ± 0.08^a	3.02 ± 0.08^a	3.12 ± 0.10^a	3.10 ± 0.10^a	3.12 ± 0.08^a
Glucose (mg/dl)	64.23 ± 0.97^a	63.52 ± 1.35^a	64.31 ± 1.56^a	62.86 ± 1.41^a	64.76 ± 0.89^a	65.40 ± 0.83^a

Number of calves in each group (n) = 6
Similar superscript (a) indicates non-significant differences ($p<0.05$)

The results of the present study suggest that Ketoprofen has no adverse effects effect in calves following multiple intravenous administrations upto 5 days at the dose of 3 mg.kg^{-1} body weight. It is safe for treatment of inflammatory diseases and as an antipyretic and analgesic in calves.

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