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Safety Assessment of Marbofloxacin Following Repeated Intramuscular Administration in Goats

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Abstract

Marbofloxacin (MB) is an extended spectrum, third generation fluoroquinolone, developed exclusively for the use in veterinary medicine. The safety assessment was done to evaluate the clinical impact of marbofloxacin after repeated intramuscular administration in goats. Safety of drugs is important and changes in serum biochemical and/or hematological markers could provide an early indication of cellular toxicity. The drug was administered at the dose of 2 mg/kg for 5 days by intramuscular route in six healthy, non-lactating Beetal goats, 1.5-2 yrs of age. Haematological (TLC, TEC, Hb, PCV, MCV, MCH and MCHC) and serum biochemical parameters viz. liver function test (LFT) and kidney function test (KFT) (ALT, AST, ALP, GGT, BUN, creatinine, total proteins and albumin) were determined and analyzed to establish the safety profile of marbofloxacin. The hematological and biochemical parameters were found to fluctuate within normal range during treatment period and no significant alterations ($p < 0.05$) were found in the mean values. The results indicated that intramuscular administration of marbofloxacin in goats at the dose of 2 mg/kg for 5 days seems to be safe.

Keywords: Marbofloxacin, repeated administration, safety assessment, goats

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Introduction

Antimicrobials are amongst the most commonly used drugs in veterinary medicine for treatment of mild to severe infections. The search for new antimicrobial drugs with greater potency, improved safety and broader spectrum of activity has led to the introduction of many new drugs. It will not be a matter of exaggeration to call decades after 1980's as an era of fluoroquinolones when its use increased both in human as well as veterinary medicine. Marbofloxacin (MB) is 9-fluoro-2,3-dihydro-3methyl-10(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido (3,2,1-ij) (4,1,2) benzoxadiazine-6 carboxylic acid, third generation fluoroquinolone, which has been developed exclusively for use in the veterinary medicine.[1] It is structurally related to other FQs such as enrofloxacin and danofloxacin and shares the same mechanism of action. Like other fluoroquinolones, marbofloxacin has a broad antibacterial spectrum, which includes many gram-negative microorganisms, some gram-positive bacteria and *Mycoplasma spp*.[2,3,4] and kills most sensitive pathogens by a concentration-dependent mechanism.[5] Marbofloxacin is licensed in many countries, including India, for use in cattle, pigs, dogs, horses and cats for the treatment of respiratory,

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urinary tract, soft tissue and dermatological infections. However, extra-label use of MB may be extended to minor species, such as sheep and goats, because respiratory diseases in these species are major causes of morbidity, mortality and economic loss. Safety of drugs is important and changes in serum biochemical and/or hematological markers could provide an early indication of cellular toxicity. Thus effect of repeated drug administration on the haematological and biochemical profile should be assessed before recommending the drug for clinical application. Clinical trials of MB for the treatment of bovine and porcine pneumonias have established its clinical efficacy under field conditions at a dose rate of 2 mg/kg.[6,7] Thus the present study we planned to evaluate biochemical and hematological parameters in healthy adults goats after repeated intramuscular administration of marbofloxacin for five days.

Materials and Methods

Drug and Chemicals

Marbofloxacin was used as 10% injectable aqueous solution (Marbocyl®, Vetoquinol UK Limited). VetScan HM5 Hematology Reagent Packs (Abaxis) were used for hematological analysis and serum biochemical analysis was performed using Autospan Liquid Gold Analytical Kits (Span Diagnostics Ltd.).

Experimental animals

Six healthy female, non-lactating Beetal goats, weighing 30-35 kg and aged 1.0-1.25 years, were used in the research study. They were housed in a ventilated barn in individual pens separated by wire mesh barriers to maintain social contact. Goats were housed in Animal house, Dept. of Pharmacology and Toxicology, GADVASU Ludhiana. They were kept under close observation before the commencement of experiment and were acclimatized to the environment. Animals were given antibiotic free pelleted small ruminant diet, procured from Dept. of Animal Nutrition, green fodder and *ad libitum* water. The experimental protocol was reviewed and approved by the Institutional Animal Ethics Committee of the Guru Angad Dev Veterinary and Animal sciences University, Ludhiana.

Experimental Design

Marbofloxacin was administered at the dose of 2 mg/kg body weight for 5 days by intramuscular route alternatively into left and right gluteal muscle. Blood samples were collected from jugular vein of goats into sterilized plain and EDTA added collection tubes on day 0 (pre-treatment) and day 5, for serum biochemical and hematological analysis. The samples were analyzed in AbaxisVetscan HM5 Hematology Analyzer and Microlab 300 Automated Clinical Chemistry Analyzer for assessment of hematological [Total leucocytic count (TLC), Total erythrocytic count (TEC), hemoglobin (Hb), Packed cell volume (PCV), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH) and mean Corpuscular Hemoglobin Concentration (MCHC)] and serum biochemical parameters viz. liver function test (LFT) and kidney function test (KFT)[alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyltranspeptidase (GGT), blood urea nitrogen (BUN), creatinine, total proteins and albumin].

Statistical Analysis

The results for hematological and biochemical analysis were subjected to paired t-test between 1st day and 5th day values. The statistical significance was assayed at 5% ($p<0.05$) levels. The statistical calculations were carried out with IBM SPSS STATISTICS Version 20 software.

Results and Discussion

There were no adverse physical symptoms observed in any of the goatsduring the period of study. The hematological parameters were found to fluctuate within normal range (Table 1) and no significant alterations ($p < 0.05$) were found in the mean values observed on day 5from the corresponding pre-treatment (day 0) values. Moreover no indication of cellular toxicity (hepatotoxicity and renal toxicity) was observed as there were no significant alterations in LFT and KFT markers between day 0 and day 5 (Table 2). The results of our study are in agreement with the non-significant change in hematological and biochemical parameters following repeated administration of ciprofloxacin in calves, enrofloxacin in yak, levofloxacin in layer birds and moxifloxacin in human and rats.[8,9,10,11,12] However increase in total bilirubin, AST, WBC and lymphocytes were observed in rats administered fandofloxacin at higher oral dose of 125 mg/k.[13] Significant alterations in hematological and biochemical parameters following repeated administration of sinofloxacin in rats

Table 1. Hematological parameters before (day 0) and after repeated administration of marbofloxacin at the dose of 2 mg/kg for five days (Day 5) in goats (mean ± SE, n=6)

Parameters	Day 0	Day 5
TLC (103/µl)	7.60 ± 0.236	7.77 ± 0.193
TEC (106/µl)	13.63 ± 0.536	13.93 ± 0.561
Hb (g/dl)	8.95 ± 0.346	8.92 ± 0.266
PCV (%)	26.67 ± 0.882	25.83 ± 0.872
MCV (fl)	29.17 ± 0.792	28.67 ± 0.333
MCH (pg)	8.82 ± 0.414	8.912 ± 0.256
MCHC (g/dl)	29.37 ± 2.039	29.23 ± 1.958

Table 2. Serum biochemical parameters before (day 0) and after repeated administration of marbofloxacin at the dose of 2 mg/kg for five days (Day 5) in goats (mean ± SE, n=6)

Parameters	Day 0	Day 5
ALT (IU/L)	21.33 ± 2.186	23.17 ± 2.456
AST (IU/L)	70.83 ± 4.527	66.83 ± 3.683
ALP (IU/L)	217.5 ± 6.439	219.33 ± 7.699
GGT (IU/L)	15.48 ± 0.797	15.02 ± 0.784
BUN (mg/dl)	32.44 ± 2.987	31.67 ± 2.419
Creatinine (mg/dl)	0.788 ± 0.096	1.05 ± 0.164
Total protein (g/dl)	5.58 ± 0.326	5.68 ± 0.359
Albumin (g/dl)	3.27 ± 0.108	3.32 ± 0.123

and dogs and moxifloxacin in rats, mice and dogs are also reported.[14,15]

Although fluoroquinolones are relatively safer drugs, certain adverse effects such as gastrointestinal discomfort, hepatotoxic reactions, central nervous system effects, juvenile joint toxicity have been reported.[16] Fluoroquinolone use has been associated with drug-induced phototoxicity and retinal degeneration.[17,18,19] Repeated administration of fluoroquinolones has been found to produce significant alterations in the elimination characteristics resulting in accumulation of drug. Frydman*et al*[20] observed drug accumulation after repeated intravenous administration of pefloxacin for 10 days in human subjects. Similarly, Schneider *et al*[21] reported decrease in elimination rate and accumulation of marbofloxacin after repeated intramuscular administration for 3 days in cows. At higher doses, fluoroquinolones have been reported to follow dose dependent kinetics[22] and repeated administration has also been reported to increase the elimination half-life and volume of distribution of some fluoroquinolones.[23]Upon multiple dosing, ciprofloxacin, enoxacin and other fluoroquinolones have shown decrease in drug elimination and increase in volume of distribution from the first dose.[23,24] Since fluoroquinolones have a high volume of distribution[25] and their plasma concentrations are lower than tissue concentrations, thus accumulation of drug after repeated administration may lead to build up of fluoroquinolone concentration in tissues resulting into toxicity.Alterations in serum biochemical and/or hematological markers could provide an early indication of cellular toxicity.The results of present study showed that repeated intramuscular administration of marbofloxacin at the dose of 2 mg/kg for five days seems to be safe in goats as no change in early markers of cellular toxicity (LFT and KFT) was observed.

Conflict of Interest

None Declared

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