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A Review on Flunixin Meglumine

[1] Faiza Hassan, [2] Sidra Altaf, [3] Misbah Ijaz, [4] Muhammad Tahir Mohy-ud-din

[1, 2, 3] Institute Of Pharmacy, Physiology & Pharmacology

[4] Department of Clinical Medicine & Surgery, Faculty of Veterinary Science, University of Agriculture. Faisalabad, Pakistan

Abstract
Flunixin meglumine is important Non-steroidal anti-inflammatory drugs (NSAIDs) use in veterinary medicine. This drug is routinely used in livestock animal. Flunixin act by inhibiting cyclooxygenase (COX) enzyme and blocks the formation of certain inflammatory mediators and prostaglandins. Flunixin can interact with certain drugs and may alter the pharmacokinetics of other drugs.

Keywords: Flunixin Meglumine, cyclooxygenase, pharmacokinetics

1. Introduction

Flunixin meglumine

Non-steroidal anti-inflammatory drugs (NSAIDs) are also important class of veterinary medicines for most of mammalian animal species. In recent years, their clinical uses have tremendously increased (Rantala *et al.,* 2002) [11]. NSAIDs alleviate pain and inflammation without the immunosuppressive and metabolic side effects associated with corticosteroids. Flunixin meglumine, being NSAID, is routinely and commonly used in veterinary practice as an analgesic, antipyretic and anti-inflammatory drug (Vane and Botting, 1996) [13]. Use of flunixin in different ruminant species, for the treatment of various inflammatory conditions like endotoxemia, mastitis and musculoskeletal disorders, has been reported (Rantala *et al*., 2002) [11]. It exhibits its action by inhibiting the enzyme cyclooxygenase (COX). The COX plays role in arachidonic acid cascade and converts it to prostaglandins. Flunixin blocks the formation of prostaglandins and inflammatory mediators by stopping COX (Landoni *et al.,* 1995) [8].

Drug Interaction

Effect of flunixin administration on pharmacokinetic aspects of sulphadimidine was studied by El-Banna (1999) [3] in clinically healthy (control) and flunixin-medicated horses after a single intravenous and oral administration of 100 mg/kg body weight. Plasma sulphadimidine concentration was determined by high-performance liquid chromatography (HPLC). Following the intravenous injection, all plasma sulphadimidine data were best approximated by a two-compartment open model using sequential, weight non-linear regression. Flunixin induced a 67% increase in the rate of sulphadimidine return to the central compartment from peripheral tissues (K_{21}) and there were a trend to a 30% increase in K_{12}. The sulphadimidine elimination half-life was decreased 21%, the Vdss was reduced by 18% and MRT was decreased by 20%. Following the oral administration, sulphadimidine was rapidly absorbed in control and Flunixin-medicated horses with absorption half-lives ($t_{1/2}$ abs) of 0.5 and 0.43 hours respectively. The peak plasma concentration (C_{max}) was 93.7 and 109 micrograms/ml attained at (t_{max}) 2.36 and 1.9 hours respectively. The elimination half-life after oral administration ($t_{1/2}$ abs) was shorter in flunixin pre-medicated horses than in control ones. The systemic bioavalability percentages (F%) of sulphadimidine after oral administration of 100 mg/kg body weight was 79.3 and 71.2% in control and flunixin medicated horses, respectively. Therefore care should be exercised in the use of sulphadimidine in equine patients concurrently treated with flunixin.

Ogino *et al.* (2002) investigated the pharmacokinetic interaction of flunixin meglumine and enrofloxacin in dogs. Three treatment protocols were adopted and a wash out period of 4 week was given between each treatment that is flunixin is given alone subcutaneously (1 mg/kg); simultaneous administration of flunixin (1mg/kg subcutaneously) and enrofloxacin (5mg/kg subcutaneously); and enrofloxacin administered alone (5 mg/kg through subcutaneous route). Blood was collected at different intervals that are 0.5, 0.75, 1, 1.5, 2, 3, 5, 8, 12, and 24 hours after injection from cephalic vein. Pharmacokinetic parameters were estimated from plasma drug concentration. Results showed significant increase in the elimination half life (29%) and in the area under curve (32%). After co-administration of flunixin and enrofloxacin a significant decrease (23%) in the elimination rate constant of flunixin from the central compartment was observed as compared to flunixin alone. Similarly a noteworthy change was observed in elimination half-life of enrofloxacin in combine treatment of enrofloxacin and flunixin as compared to enrofloxacin alone. The observed reduction in clearance of drug in case of concurrent administration of flunixin and enrofloxacin revealed that both drugs interact with each other during the elimination phase. Therefore, it was concluded that care should be taken in the parallel use of flunixin and enrofloxacin in dogs to avoid untoward reactions of drug.

Lockwood *et al.* (2003) [10] demonstrated the clinical efficacy of flunixin, ketoprofen and carprofen as adjunct to the antibiotics for the treatment of bovine respiratory disease. Three different non-steroidal anti-inflammatory drugs (NSAIDS) were assessed in combination with ceftiofur for the treatment of natural infection of bovine respiratory disease. Sixty-six mixed-breed beef cattle suffering from pyrexia and moderate dyspnoea were selected and randomly divided into four groups according to treatment. All received intramuscular injection of ceftiofur at a dose rate of 1-1 mg/kg for three days. Out of all four groups, three groups were also given a single additional dose of either flunixin at the rate of 2-2mg/kg through intravenous injection or ketoprofen @ 3 mg/kg by intravenously or carprofen at the dose

rate of 1-mg/kg subcutaneously. In the first 24 hours, the pyrexia in animals treated with a NSAID was lowered significantly more as compared to group receiving ceftiofur alone. Decrease in pyrexia was significant 2 to 4 hours post treatment in the groups receiving flunixin and ketoprofen as compared to the animals receiving carprofen. No significant differences were observed between all the groups regarding depression, dyspnoea, illness scores and coughing. Lung consolidation was also less with NSAID as compared to animals with ceftiofur alone.

Therapeutic efficacy of ceftiofur and flunixin for amelioration of bronchopneumonia in weaners was evaluated (Halloy *et al.*, 2006) [6]. The weaner pigs were divided into four groups, 5 animals in each. Lipopolysaccharides of Escherichia coli were inoculated in all animals intra-tracheally and then, after 24 hours, $10x10^9$ colony forming units of non-virulent strain of *Pasteurella multocida* type A were also given. The animals of group 1 were treated with intramascular injection of ceftiofur @ 3mg/kg b.wt. for consecutive five days. Flunixin @ 2 mg/kg b.wt. in combination with ceftiofur was given to animals of group 2 for five days. Animals of group 3 were kept untreated. Group 4 was control *i.e.* animals were not inoculated with lipopolysaccharides and *Pasteurella multocida*. It was observed that animals of untreated group showed coughing, hyperthermia and reduced weight gain as compared to treated animals where symptoms disappeared in 2-3 days. No significant difference was observed between animals of first and second groups. After inoculation, up to 15 days, continuous increase in numbers of inflammatory cells was observed in bronchoalveolar fluid of animals of group 3 while the numbers were reduced to baseline after 15 days in treated animals of both groups. Lung lesions volume was also significantly less in treated groups. However, no additional significant effect was observed with combined use of flunixin and ceftiofur.

Tohamy (2011) [12] determined the pharmacokinetic interactions of flunixin and orbifloxacin in buffalo calves. Twelve healthy buffalo calves were used to study the effect of flunixin as a non-steroidal anti-inflammatory drug on some pharmacokinetic aspects of orbifloxacin as a fluoroquinolone antimicrobial. After intravenous injection of orbifloxacin alone and in combination with flunixin, there is no significant changes in the half-lives of distribution and elimination ($t_{0.5(\alpha)}$ and $t_{0.5(\beta)}$), volumes of distribution at steady state (Vd_{ss}), Mean residence time (MRT) and total body clearance (Cl_B) as evidenced from the values of 0.14 and 0.13 h, 4.98 and 4.95 h, 1.10 and 1.04 L kg^{-1}, 6.8 and 6.8 h, 0.16 and 0.15 L kg^{-1} h^{-1}, respectively. Following intramuscular administration, the maximum concentrations (C_{max}) 1.6 and 1.6 µg mL^{-1} were achieved at a maximum times (t_{max}) 1.30 and 1.31 h, respectively. No significant changes were detected in absorption ($t_{0.5(ab)}$) and elimination ($t_{0.5(el)}$) half-lives and mean residence time (MRT) as a result of orbifloxacin co-administration with flunixin. The intramuscular bioavailability was 91.9 and 90.5% for orbifloxacin alone and in combination with flunixin, respectively. The result of *in-vitro* protein binding study indicated that 17.8% of orbifloxacin was bound to calve's serum proteins. This data conclude that orbifloxacin administered intravenously and intramuscularly to buffalo calves at a dose rate of 2.5 mg kg^{-1} was characterized by extensive absorption and high systemic bioavailability. Also, no significant alterations have been recorded in serum concentrations and pharmacokinetic parameters of orbifloxacin in buffalo calves by simultaneous administration with flunixin and thus, dose regimens for orbifloxacin need not be altered when the two drugs are used in combination.

Enrofloxacin adversely alters the pharmacokinetic profile of flunixin when given concomitantly (Abo-El-Soodu and Al-Anati, 2011) [1]. The researchers administered the flunixin alone and in combination with enrofloxacin in healthy calves and studied the pharmacokinetics aspects of flunixin. Calves were divided into two groups. Group I received intramascular injection of flunixin (2.2mg/kg) alone. A combination of flunixin @ 2.2mg/kg and enrofloxacin @ 2.5mg/kg was administered in animals of group II through intramuscular route. High performance liquid chromatography (HPLC) method was used to determine the plasma concentration of flunixin. Results Showed significant alterations in pharmacokinetics of flunixin due to enrofloxacin. It delayed the absorption and accelerated the elimination of flunixin. There was a significant increase in concentration of flunixin when given in combination with enrofloxacin as compared to administration of flunixin alone. The hepato-renal functions were also adversely affected by giving the combination of both drugs. In conclusion, co-administration of flunixin and enrofloxacin should not be the part of any prescription for calves.

El-Hewaity (2014) [4] investigated the influence of flunixin on the disposition kinetic of cefepime in goats. The pharmacokinetic profile of cefepime (10 mg/kg b.w.) was studied following intravenous and intramuscular administration of cefepime alone and coadministered with flunixin (2.2 mg/kg b.w.) in goats. Cefepime concentrations in serum were determined by microbiological assay technique using *Escherichia coli* (MTCC 443) as test organism. Following intravenous injection of cefepime alone and in combination with flunixin, there are no significant changes in the pharmacokinetic parameters. Following intramuscular injection of cefepime alone and in combination with flunixin, the maximum serum concentration was significantly increased in flunixin coadministered group compared with cefepime alone. However, no significant changes were reported in other pharmacokinetic parameters. The result of in vitro protein binding study indicated that 15.62% of cefepime was bound to goat's serum protein. The mean bioavailability was 92.66% and 95.27% in cefepime alone and coadministered with flunixin, respectively. The results generated from the study suggested that cefepime may be coadministered with flunixin without change in dose regimen. Cefepime may be given intramuscularly at 12 h intervals to combat susceptible bacterial infections.

Pharmacokinetics

Coakley *et al.* (1999) [2] conducted a study to determine the pharmacokinetics of flunixin meglumine in donkeys, mules, and horses. The objective of study was to compare serum disposition of flunixin meglumine after i.v. administration of a bolus to horses, donkeys, and mules. Three clinically normal horses, 5 clinically normal donkeys, and 5 clinically normal mules were selected. Blood samples were collected at time zero (before) and 5, 10, 15, 30, and 45 minutes, and at 1, 1.25, 1.5, 1.75, 2, 2.5, 2.75, 3, 3.5, 4, 4.5, 5, 5.5, 6, and 8 hours after i.v. administration of a bolus of flunixin meglumine (1.1 mg/kg of body weight). Serum was analyzed in duplicate by the use of high-performance liquid chromatography for determination of flunixin meglumine concentrations. The serum concentration-time curve for each horse, donkey, and mule were analyzed separately to estimate non-compartmental pharmacokinetic variables. Results showed

that mean (+/-SD) area under the curve for donkeys (646 +/- 148 minute x microg/ml) was significantly less than for horses (976 +/- 168 minute x micro g/ml) or for mules (860 +/- 343 minute x micro g/ml). Mean residence time for donkeys (54.6 +/- 7 minutes) was significantly less than for horses (110 +/- 24 minutes) or for mules (93 +/- 30 minutes). Mean total body clearance for donkeys (1.78 +/- 0.5 ml/kg/h) was significantly different from that for horses (1.14 +/- 0.18 ml/kg/h) but not from that for mules (1.4 +/- 0.5 ml/kg/h). Significant differences were not found between horses and mules for any pharmacokinetic variable. It was concluded that significant differences exist with regard to serum disposition of flunixin meglumine in donkeys, compared with that for horses and mules. Consequently, flunixin meglumine dosing regimens used in horses may be inappropriate for use in donkeys.

Pharmacokinetics and pharmacodynamic properties of flunixin after intravenous, intramuscular and oral administration was evaluated by Konigsson *et al*., 2003. Six Norwegian dairy goats were selected and administered with flunixin @ 2.2 mg/kg by three different routs *i.e.*i.v., i.m. and oral. Concentration of drug was analysed through HPLC and the PG synthesis was determined by quantifying plasma 15-ketodihydro-$PGF_{2\alpha}$ through radioimmuno-assay. The elimination half-lives for i.v., i.m. and oral were 3.6 (2.0-5.0), 3.4 (2.6-6.8), 4.3 (3.4-6.1) h respectively. The plasma concentration after oral administration showed double-peak that were in the same order of magnitude. For i.m. and p.o. routes bioavailability was 79 (53-112) and 58 (35%-120%) respectively. Plasma concentration of 15-ketodihydro-$PGF_{2\alpha}$ reduced after flunixin administration and was independent of the administration route.

The pharmacokinetics of flunixin meglumine after intravenous administration in angora rabbits was investigated by Elmas *et al*., 2004. Six healthy adult Angora rabbits were administered with bolus injection intravenously at two different doses (1.1 and 2.2 mg/kg b.wt.). Blood samples were collected at 10, 20, 30, 45 and 60 minutes, 2, 4, 6 and 8 hour post administration. Concentrations of drug in plasma were determined by HPLC. Pharmacokinetics was calculated by a two-compartment open model. It was observed that the area under the curve showed statistically significant differences between the two doses used ($P < 0.05$). Other parameters were statistically non-significant with both doses. It was suggested that the pharmacokinetic parameters of flunixin meglumine are dose independent at the dosage of 1.1-2.2 mg/kg b.wt. in Angora rabbits.

Lee *et al.* (2013) studied the Effect of body weight on the pharmacokinetics of flunixin meglumine in miniature horses and quarter horses. The purpose of this study was to determine whether miniature horses should receive a different dosage of flunixin meglumine than that used typically in light-breed horses. A standard dose of flunixin meglumine was administered intravenously to eight horses of each breed, and three-compartmental analysis was used to compare pharmacokinetic parameters between breed groups. The total body clearance of flunixin was 0.97 ± 0.30 mL/min/kg in miniature horses and 1.04 ± 0.27 mL/min/kg in quarter horses. There were no significant differences between miniature horses and quarter horses in total body clearance, the terminal elimination rate, area under the plasma concentration versus time curve, apparent volume of distribution at steady-state or the volume of the central compartment for flunixin ($P > 0.05$). Therefore, flunixin meglumine may be administered to miniature horses at the same dosage as is used in light-breed horses.

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