Pharmacokinetics and anti-inflammatory effects of intravenous and transdermal flunixin meglumine in healthy goats

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Introduction

Flunixin meglumine is a non-steroidal anti-inflammatory drug (NSAID) used for its antipyretic, analgesic, and anti-inflammatory properties in multiple mammalian species. In the United States (US), cattle are the only food-producing ruminant species that have an approved flunixin meglumine label. A new transdermal (TD) formulation of flunixin meglumine has been developed for use in cattle and has recently been released for use in cattle in the US.

Selection of drugs for use in goats, in the US, is problematic due to the paucity of labeled products. More specifically, there are no NSAIDs labeled for use in goats in the US. Dosing, routes of administration, and indications for use of NSAIDs are extrapolated from cattle. Understanding the pharmacokinetics and pharmacodynamics of NSAIDs in goats is critical to minimizing negative side effects of the drugs and mitigating tissue residues to ensure a safe food supply. The objective of this study was to determine the pharmacokinetic properties and anti-inflammatory effects of intravenous and transdermal flunixin meglumine in healthy goats.

Materials and Methods

This study was conducted using a randomized crossover design. Eight, similarly sized, adult female Boer goats, were administered flunixin meglumine intravenously into a jugular vein at a dose of 1.0 mg/lb (2.2 mg/kg). Following a 10-day washout period, does were administered flunixin meglumine transdermal at a dose of 1.5 mg/lb (3.3 mg/kg). Blood samples were collected at predetermined times from 0-48 h for the intravenous portions and 0-72 h following transdermal dosing. Plasma drug concentrations were determined using liquid chromatography with mass spectroscopy. Pharmacokinetic analysis was completed using non-compartmental methods. The individual animal pharmacokinetic values were calculated and the descriptive statistics (geometric mean, minimum, median and maximum values) reported. Bioavailability was calculated for topical administration using the following equation: [Topical AUC/Topical Dose]/[IV AUC/IV Dose]

At predetermined time points, 1 ml of whole blood was spiked with *E. coli* lipopolysaccharide to stimulate prostaglandin E2 (PGE2) production. Prostaglandin E2 concentrations were determined using a commercially available ELISA.

Results

No adverse reactions were seen following topical administration of flunixin. Mean elimination/terminal half-life (T½) after IV administration was 6.0 h (range 4.7 - 9.2 h) resulting from a mean apparent volume of distribution (Vz) of 584.1 ml/kg (range, 357.1 - 1092 ml/kg) and plasma clearance (CL) of 67.11 ml/kg/h (range, 45.57 - 82.35 ml/kg/h). The mean Cmax, Tmax, and T½ for flunixin following TD administration was 0.13 ug/ml (range, 0.05 - 0.19 ug/ml), 11.4 h (range, 6.0 - 36.0 h) and 43.1 h (16.0 62.5 h), respectively. The mean bioavailability for TD flunixin was calculated as 24.8%. Intravenous flunixin at 1.0 mg/lb (2.2 mg/kg) suppressed PGE2 for 24 hours. Transdermal flunixin at 1.5 mg/lb (3.3 mg/kg) suppressed PGE2 by 50% for up to 36 hours starting at 4 h post-administration.

Significance

All goats tolerated topical administration of flunixin meglumine TD. Efficacy of IV and TD flunixin was measured by PGE2 inhibition. Both IV and TD flunixin lowered PGE2 concentrations. A single dose of flunixin given at 1.0 mg/lb (2.2 mg/kg) IV provides 24 hours of anti-inflammatory effects. To overcome the low bioavailability and increase the antiinflammatory suppressive effects of TD flunixin, a higher dose may be warranted. Further studies are needed to determine the underlying cause of the poor bioavailability, prolonged absorption, and tissue residue profiles for TD flunixin.