Effect of age on the pharmacokinetics and pharmacodynamics of flunixin meglumine following intravenous and transdermal administration to Holstein calves

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Introduction

The objective of this study was to investigate the effect of age on the pharmacokinetics and pharmacodynamics of flunixin meglumine when administered by the intravenous and transdermal routes.

Materials and Methods

Eight Holstein male calves were administered flunixin meglumine via intravenous (1/0 mg/lb; 2.2 mg/kg) and transdermal (1.5 mg/lb; 3.33 mg/kg) routes at 2 months of age and then again at 8 months of age. Blood samples for flunixin and prostaglandin E2 determination were collected prior to dosing and at predetermined time points. Plasma flunixin concentrations were determined using high pressure liquid chromatography and mass spectroscopy. Flunixin pharmacokinetics were determined for each animal and respective age using noncompartmental analysis. PGE2 levels were determined using a commercial ELISA. The 50% inhibitory concentration (IC50) of PGE2 by flunixin was determined for each calf and age.

Results

Younger calves had a longer half-life (5.4 h vs, 3.5 h; P=0.0009), larger AUC (17.8 h*µg/mL vs 9.0 h*µg/mL; P=0.002), lower clearance (2.5 mL/min/kg vs. 4.1 mL/min/kg; P=0.002) and longer mean residence time (4.6 h vs 2.5 h; P=0.0003) after IV administration. Following transdermal dosing, the younger calves had higher maximum drug concentration (0.96 µg/mL vs 0.54 µg/mL; P=0.02), shorter mean residence time (9.1 h vs 15.7 h; P=0.006), and shorter mean absorption time (3.1 h vs 12.9 h; P=0.004). There was no effect of age on PGE2 percent inhibition following IV flunixin. Following transdermal flunixin administration, there tended to be an age effect on PGE2 inhibition (P=0.09) as calves had lower PGE2 levels at 2 months of age. Additionally, younger calves had a lower IC50 of flunixin on PGE2 (10.8 ng/mL vs 37.7 ng/mL; P=0.03).

Significance

Age influences the pharmacokinetics of flunixin after IV and transdermal dosing. Following IV administration, age-related pharmacokinetic differences are due to clearance of flunixin. The age-related differences following transdermal dosing are due to the absorption of the drug into the body. Further research on the effect of age and the anti-inflammatory effects of flunixin are needed. Following administration to younger calves, adjustments to dose and withdrawal period may be needed.