Pharmacokinetics and milk elimination of flunixin meglumine in dairy cattle following different routes of administration

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Introduction

Flunixin meglumine (FLU) is a non-steroidal anti-inflammatory licensed for use in dairy cattle for treatment of inflammation in endotoxemia and control of pyrexia associated with bovine respiratory disease and acute bovine mastitis. FLU is labeled for intravenous (IV) administration at a dose of 1 mg/lb (2.2 mg/kg) every 24 hours or 0.5 mg/lb (1.1 mg/kg) every 12 hours. The milk withdrawal time is 36 hours. Currently, FLU is the second most common violative drug residue found in the dairy industry. The reason for the numerous illegal FLU drug residues remains unclear; however, administration by an unapproved route is one possible explanation. The administration of FLU by intramuscular (IM) or subcutaneous (SC) routes may prolong drug elimination and result in milk concentrations of the metabolite, 5-hydroxy flunixin (5OH), the marker residue for milk, to exceed the tolerance level of 2 ppb for > 36 hours. The objective of this study was to determine if the pharmacokinetics and milk residues of FLU and 5OH in lactating dairy cattle differed following IM and SC administration of FLU, compared with those following IV administration of FLU.

Materials and Methods

Twelve lactating Holstein cows were enrolled in a randomized crossover design study. Cows were assigned to one of two groups on the basis of milk production (< 44 lbs (20 kg)/day or ≥ 44 lbs (20 kg)/day). Within each group, cows were randomly allocated to receive FLU (0.5 mg/ lb; 1.1 mg/kg)) via IV, IM, or SC administration twice 12 hours apart. Blood samples were collected from the jugular vein prior to FLU administration; at 0.25, 0.5, 1, 2, 4, 8, and 12 hours after the first dose of FLU; and at 12 and 24 hours after the second dose of FLU. Composite milk samples were collected prior to FLU administration; at 1.5 and 12 hours after the first dose of FLU; and at 12, 24, 36, 48, 72, 84, and 96 hours after the second dose of FLU. After a 7-day washout period, each cow received FLU via another route of administration. Ultimately, all 12 cows received FLU by IV, IM, and SC administration. Concentrations of FLU were determined in plasma and milk samples via ultra-high-pressure liquid chromatography with mass spectrometric detection.

Results

In plasma samples, the terminal half-life ($t_{1/2ëz}$), mean transit time, and mean absorption time for FLU varied among the three routes of administration. FLU $t_{1/2ëz}$ was 3.42 hours, 4.48 hours, and 5.39 hours following IV, IM, and SC, respectively. The mean bioavailability of FLU following IM and SC administration was 84.5% and 104.2%, respectively. A population pharmacokinetic model by use of 5OH milk concentrations was developed. Both route of administration ($P < 0.001$) and milk production ($P < 0.1$) were identified as significant covariates. The proportion of 5OH-positive milk samples for each route of administration was compared with that for the other two routes of administration at each time point. Following IV administration, 5OH was undetectable in the milk of all cows 36 hours after the second dose of FLU; however, following both IM and SC administration, concentrations of 5OH above the tolerance limit were detected in the milk of one (8.33%) cow at 36 hours after the second dose of FLU.

Significance

The high number of FLU residues identified in both milk samples and cull dairy cows is at least partially related to administration of the drug by unapproved routes. Cows that received FLU by the approved IV route consistently had undetectable concentrations of 5OH in milk samples before the approved withdrawal time; however, FLU residues can persist beyond the approved withdrawal times following IM or SC drug administration. Cows producing < 44 lb (20 kg) of milk per day had altered clearance of FLU from milk, which may also contribute to violative FLU residues.