

Pharmacokinetics and Milk Depletion of Meloxicam and Gabapentin in Lactating Holsteins

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Introduction

There is an urgent need for safe and effective treatments to prevent and mitigate pain in food-producing ruminants. Two excellent candidates for this purpose are meloxicam, a non-steroidal anti-inflammatory drug, and gabapentin, an analogue of the neurotransmitter GABA that was originally developed as an anti-epileptic. Gabapentin is currently used to control neuropathic pain in humans. Neither of these drugs are approved for use in cattle, and bovine practitioners must comply with the requirements of the Animal Drug Use Clarification Act (AMDUCA, 1994) to use them in an extralabel manner in their patients. One of the AMDUCA requirements is the availability of scientific data on which to base an appropriate withdrawal interval to prevent harmful residues from entering the food chain. The purpose of this study was to generate such data for milk following co-administration of meloxicam and gabapentin to lactating Holstein cows.

Materials and Methods

A pharmacokinetic study was conducted in 12 mid-lactation Holstein dairy cows. The cows were randomly assigned to two groups. One group received a low dose of gabapentin (4.5 mg/lb; 10 mg/kg) and the other group received a higher dose (9 mg/lb; 20 mg/kg). Both groups received meloxicam at a dose of 0.45 mg/lb (1 mg/kg). The drugs were administered orally in gelatin capsules using a balling gun. The two doses of gabapentin were used to ascertain whether transport of this drug across the mammary epithelium became saturated at the higher clinical dose, because this drug is known to be a substrate of a low-capacity xenobiotic transporter. Blood and milk samples were collected from the animals at each

milking (3x daily) for seven days. Milk volumes were also recorded. Plasma and milk gabapentin and meloxicam concentrations were measured using a validated HPLC method. These data were analyzed by fitting them to a pharmacokinetic model with milk conceptualized as an excretory compartment to calculate the milk clearance of both drugs.

Results

Milk drug concentrations were below detectable levels by three days for both drugs in most animals. In general, meloxicam residues persisted for longer than gabapentin residues. The percentage of the dose excreted in the milk was low for both drugs (approximately 1 and 0.1% for meloxicam and gabapentin, respectively). A constant amount of gabapentin was excreted in the milk at the earlier time points, suggesting the movement of this drug across the mammary epithelium is mediated by a transporter that is saturated at higher plasma drug concentrations. Meloxicam milk excretion remained proportional to plasma concentrations throughout. No adverse reactions were reported in any of the animals.

Significance

Practitioners will be able to use the results of this study to recommend appropriate milk withdrawal intervals following the extralabel use of either meloxicam and/or gabapentin in dairy cattle. Such withdrawal times for both drugs will likely be at least 72 hours (three days) or longer, depending on the dose. The percentage of the gabapentin dose excreted in milk will not increase linearly with dose, likely due to transporter-mediated movement of this drug across the mammary epithelium.