sured by diarrhea and the presence of blood in the feces was compared, the coccidia-coronavirus infected calves were more severely affected ($p < 0.05$) than calves that received only coronavirus. Calves that had received only coccidia oocysts appeared more severely affected than calves that had received only coronavirus but differences were not significant. Calves in each replicate were euthanatized and necropsied 9 days after coronavirus inoculation. Calves that had received either coccidia alone, or coccidia and coronavirus had more severe lesions of mucosal degeneration and epithelial necrosis than calves that had received only coronavirus ($p < 0.05$). Lesions, however, were generally most severe in calves that had received coccidia and coronavirus. In 4 calves fibrinopurulent typhlitis and/or colitis was present; 3 of these observations were made in calves that received coccidia and coronavirus. Results from this project suggest that although coronavirus infection in young calves is very common and may, on occasion be quite mild, when combined with *E. bovis* infection, the resultant disease may be more severe than infection with either coronavirus or *E. bovis* alone.

Ibuprofen Therapy in Lactating Dairy Cows

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Introduction

Ibuprofen is a phenylpropionic acid derivative that inhibits prostaglandin biosynthesis by cyclo-oxygenase inhibition, a property common to the nonsteroidal anti-inflammatory drugs. Ibuprofen may produce anti-inflammatory effects by additional mechanisms of action, which may be of considerable importance. Ibuprofen's role as an iron chelator may be one such mechanism of action. Chelation of iron may inhibit the Fenton reaction, to reduce the formation of extremely toxic hydroxyl radicals from less toxic hydrogen peroxide and superoxide radicals. In addition, ibuprofen has been demonstrated to influence inflammatory cells, the neutrophil in particular. Ibuprofen has been demonstrated to alter the clinical course of endotoxemia and septicemia in man and domestic species and may have potential in the therapy of endotoxic conditions of dairy cows, including coliform mastitis, bacterial pneumonia, septic metritis, and acute diarrhea.

The purpose of this study was to evaluate the pharmacokinetic properties of ibuprofen in lactating dairy cows and then to study the clinical effect of ibuprofen during experimental endotoxin-induced mastitis.

Materials and Methods

Pharmacokinetic studies

Healthy lactating Holsltein cows ($n = 6$) were treated intravenously with ibuprofen at 25 mg/kg by jugular vein catherization. After a one week washout period, cows were treated with 25 mg/kg ibuprofen per os. Jugular blood and milk samples were collected at 0, 15, 30, 45, 60, 90, 120, 240, 360 and 480 minutes after ibuprofen administration. Milk and serum were analyzed for ibuprofen concentration by high performance liquid chromatography. Intravenous data were analyzed with a two compartment open pharmacokinetic model (PETDR).

Endotoxin studies

Acute mastitis was induced in healthy lactating Holstein dairy cows by intramammary inoculation of 1 mg *E. coli* 026.B6 endotoxin. Cows were randomly assigned to ibuprofen (25 mg/kg iv, $n = 6$) or saline control (iv, $n = 6$) treatment groups. Treatments were given as a rapid bolus one time, by jugular catheterization at 2 hours post-endotoxin administration. Data were analyzed with a repeated measures design (SAS).

Results

Pharmacokinetic studies

Mean serum ibuprofen concentrations after intravenous ($n = 6$) and oral ($n = 6$) ibuprofen administration are graphically displayed in Figure 1. The serum half-life of elimination of ibuprofen was 1.57 $\pm$0.14 hours. There was a 14.6 $\pm$5.1 minute time lag after the oral administration of 25 mg/kg ibuprofen, before ibuprofen appeared in serum. Peak serum ibuprofen concentrations after oral administration occurred at 2 hours. The bioavailability (F) of orally administered ibuprofen was 91 $\pm$11%. Additional pharmacokinetic parameters are listed in Table 1.

Ibuprofen was present in milk shortly after oral and intravenous ibuprofen administration. Peak milk ibuprofen levels were .64 $\pm$0.21 mcg/ml and occurred 30 minutes after intravenous treatment. Ibuprofen was not detectable in milk after 2 hours post intravenous treatment. Low levels of ibuprofen were detectable in milk after oral adminis-

Figure 1. Mean Serum concentrations following the administration of 25 mg/kg ibuprofen in lactating dairy cows (n = 6).

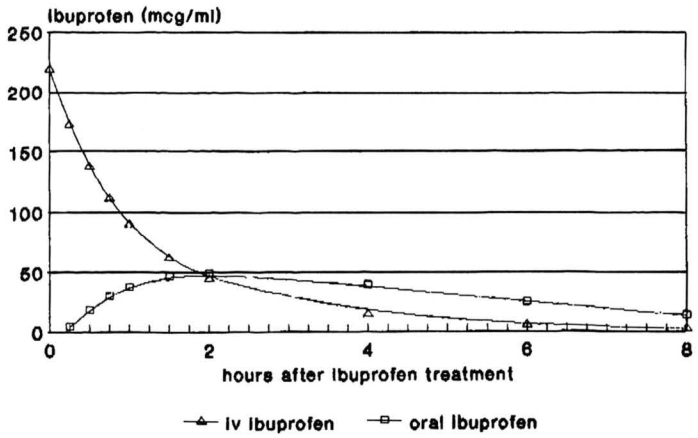

Table 1. Pharmacokinetic parameters of ibuprofen after an intravenous dose of 25 mg/kg in lactating dairy cows (mean ± standard deviation, n = 6).

Ibuprofen dosage, 25 mg/kg			
Intravenous		Per os	
Parameter	Mean ± S.D.	Parameter	Mean ± S.D.
VD (SS), L/kg	0.146 ± 0.018	Lag time, hrs	0.244 ± 0.085
CL (B), ml/kg/hr	87.7 ± 12.5	$t_{½absorp}$, hrs	0.881 ± 0.420
$t_{½(dist)}$, hrs	0.557 ± 0.082	F	0.912 ± 0.107
$t_{½(elim)}$, hrs	1.57 ± 0.14	AUMC, mcg/ml*hr^2	1030 ± 141
AUC, mcg/ml*hr	297 ± 44	AUC, mcg/ml*hr	268 ± 30
MRT, hrs	1.52 ± 0.15	MRT, hrs	3.87 ± 0.60

tration of ibuprofen, but most levels were below the limit of quantification.

Endotoxin studies

Rectal temperature, heart rate, respiratory rate and neutrophilic band cell counts increased significantly ($p < 0.05$) in the saline treated groups as compared to the ibuprofen treated group. Eosinophil numbers, serum phosphorous, sodium, and total carbon dixoide were significantly decreased ($p < 0.05$) in the saline treated group as compared to the ibuprofen group. Indices of renal, hepatic, and red blood cell damage were not increased following ibuprofen administration.

Discussion

Ibuprofen exhibits a pharmacokinetic profile that would be consistent with use in lactating dairy cows. Ibuprofen concentrations in milk were very low. This, in addition to the relatively short half-life of elimination of ibuprofen in dairy cows, would suggest that ibuprofen treated cows would present minimal risk of residue to consumers when used with appropriate caution.

Ibuprofen influenced the clinical course of endotoxin-induced mastitis. Ibuprofen did not appear to influence udder swelling, udder edema, or milk composition following endotoxin-induced mastitis. One 25 mg/kg dose of ibuprofen was well tolerated by lactating Holstein cows and no untoward effects were observed. **Ibuprofen is not currently approved for use in any food animal species.**

Challenge Model for *Escherichia coli* in the Colostrum Deprived Calf

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There is an increasing number of oral immunoglobulin and probiotic preparations commercially available for the bovine neonate. Advertisements for calf immunosupplements may be vague, confusing, or even misleading. Early ingestion of high quality colostrum provides the best defense against calf colisepticemia. Problems associated with modern management practices, the existence of low quality colostrum, and the relative economic significance of certain calves may justify the additional investment of oral immunoglobulins at birth. Objective information needed to evaluate the efficacy and cost effectiveness of these products is currently unavailable. Controlled challenge studies provide one mechanism for evaluation of these products.

In order for challenge studies to provide meaningful information they must produce consistent and reproducible results over time. The model developed by the authors involves three treatment groups: colostrum deprived calves, colostrum fed calves, and colostrum deprived calves fed one of the colostrum supplements to be evaluated. Colostrum deprived calves from attended parturitions are removed from their dam prior to suckling, transported to a