J. vet. Pharmacol. Therap. 18, 61–67, 1995.

The effects on the pharmacokinetics of intravenous ceftiofur sodium in dairy cattle of simultaneous intravenous acetyl salicylate (aspirin) or probenecid

T. WHITTEM
D.A. FREEMAN*
D. HANLON &
K. PARTON

Department of Veterinary Clinical Sciences, Massey University, Palmerston North, New Zealand;
**Current address is c/o Professional Services, Fort Dodge Laboratories, 800 5th Street N.W., Fort Dodge, Iowa 50501-0510, USA*

Whittem, T., Freeman, D.A., Hanlon, D., Parton, K. The effects on the pharmacokinetics of intravenous ceftiofur sodium in dairy cattle of simultaneous intravenous acetyl salicylate (aspirin) or probenecid. *J. vet. Pharmacol. Therap.* 18, 61–67.

Ceftiofur sodium is a third-generation cephalosporin antibiotic. It is possible that non-steroidal anti-inflammatory drugs such as acetyl salicylate (aspirin) may be used concomitantly with ceftiofur sodium in dairy cattle. Therefore this study evaluated potential pharmacokinetic interactions between ceftiofur sodium and aspirin. In addition, this study evaluated the potential for interaction between ceftiofur and its active metabolites and the organic anion transporter. The organic anion transporter substrate used in this evaluation was probenecid. Ten healthy, non-pregnant, non-lactating dairy cows were used in a randomized complete three-way crossover design. In repeated experiments all cows were administered: (1) 2 mg of ceftiofur sodium per kg body weight by intravenous bolus or (2) 10 mg of probenecid per kg body weight by intravenous bolus, followed immediately by 2 mg of ceftiofur sodium per kg body weight by intravenous bolus or (3) 26 mg of aspirin per kg body weight by intravenous bolus, followed immediately by 2 mg of ceftiofur sodium per kg body weight by intravenous bolus. For treatment with ceftiofur sodium alone, the mean volume of distribution at steady-state $V_{d(ss)}$ was 0.2 ± 0.06 L/kg, the mean volume of distribution by the area method $V_{d(area)}$ was 0.38 ± 0.22 L/kg, mean residence time (*MRT*) was 6.5 ± 1.8 h, mean residence time in peripheral tissues (MRT_p) was 2.6 ± 1.0 h, total body clearance (*Cl*) was 0.032 ± 0.013 L/kg/h and elimination rate constant (β) was 0.097 ± 0.044 h^{-1} (mean ± standard deviation). No statistically significant changes were detected as a result of preceding treatment with aspirin. Preceding treatment with probenecid resulted in a decrease in both *Cl* (0.007 ± 0.005 L/kg/h) and MRT_p (0.89 ± 0.45 h). These results suggest that ceftiofur or its metabolites may interact with the organic anion transporter, but that consideration of alterations to dose and dose interval may not be necessary when ceftiofur sodium is administered to the cow concomitantly with a single dose of aspirin.

(Paper received 10 November 1993; accepted for publication 25 April 1994)

T. Whittem, Department of Veterinary Clinical Sciences, Massey University, Private Bag, Palmerston North, New Zealand

INTRODUCTION

Ceftiofur sodium is a third-generation cephalosporin antibiotic with a broad spectrum of activity, including activity against gram-positive and gram-negative aerobes and some anaerobic bacteria. Ceftiofur sodium is registered in several countries. Owing to the antibiotic's high efficacy against *Pasteurella haemolytica*, *Pasteurella multocida* and *Haemophilus somnus* (Anonymous, 1991; Jaglan *et al.*, 1992) ceftiofur sodium is labelled for use in bovine respiratory disease. In beef cattle, ceftiofur sodium is used primarily to treat 'shipping fever', an acute bronchopneumonia that often occurs following transport to feed lots (Sweeney & Smith, 1990). In dairy cattle, ceftiofur sodium is indicated for the treatment of enzootic calf pneumonia (Sweeney & Smith, 1990; Anonymous, 1991). Ceftiofur sodium has been proposed for the treatment of bovine mastitis because of its broad antimicrobial spectrum (Soback *et al.*, 1989; Owens *et al.*, 1990) but it is not licensed for this indication.

Non-steroidal anti-inflammatory drugs (NSAIDs) are indicated as an adjunct to antimicrobial therapy for infections with bacteria which elaborate endotoxins. In dairy cattle, the use of NSAIDs such as phenylbutazone, flunixin or acetyl salicylate (aspirin) is often associated with the treatment of coliform mastitis (Ziv, 1992), pneumonia (Selman *et al.*, 1986), and neonatal septicaemia. For practical purposes, single doses of these NSAIDs are frequently

used at the initiation of a therapeutic regimen. Therefore, it is likely that NSAIDs may be used concomitantly with ceftiofur sodium in dairy cattle, especially at the onset of treatment.

Probenecid (Cunningham *et al.*, 1981, Weiner, 1992), several cephalosporins (Ziv *et al.*, 1979; Arvidsson *et al.*, 1981; Carbon *et al.*, 1984; Dromer *et al.*, 1985; Guerrini *et al.*, 1985; Soback *et al.*, 1987) and several NSAIDs (Carbon *et al.*, 1984; Weiner, 1992) are substrates for the organic anion transporter of the renal proximal convoluted tubule in many species. Transport of these xenobiotics by the organic anion transporter is a saturable process, and therefore concomitant use of these drugs could lead to competitive inhibition of renal secretion or distribution within tissues. This competitive inhibition of transport processes could lead to alterations of each drug's pharmacokinetics. Since it is possible that NSAIDs and ceftiofur sodium may be used concomitantly, knowledge of a potential pharmacokinetic interaction would assist in correction of dose requirements and facilitate necessary adjustment to food product withholding times recommended on the basis of single drug use.

The objectives of this study were to: (1) examine the pharmacokinetics of ceftiofur sodium and its active metabolites in dairy cattle; (2) examine the potential for ceftiofur sodium and its active metabolites to interact with the organic anion transporter; and (3) examine potential pharmacokinetic interactions between ceftiofur sodium and its active metabolites and aspirin in a clinically relevant dose regimen. The null hypotheses for this study were that the apparent volume of distribution at steady-state ($V_{d(ss)}$, the apparent volume of distribution by the area method ($V_{d(area)}$), the total body mean residence time (*MRT*), the mean residence time in peripheral tissues (MRT_p), total body clearance (*Cl*) and elimination rate constant (β) for ceftiofur sodium and its active metabolites after a single intravenous dose are not altered by either (1) the archetypical anion pump substrate, probenecid or (2) simultaneous single-dose intravenous administration of aspirin at the labelled therapeutic dose rate.

MATERIALS AND METHODS

Aspirin (Vetalgine, Sanofi Animal Health, France) as DL-lysine-acetyl salicylate was a gift from Techvet Laboratories (Otahuhu, Auckland, New Zealand) and ceftiofur sodium (Naxcel Sterile Powder, The Upjohn Company, Kalamazoo, MI, USA) was a gift from Upjohn New Zealand (Ellerslie, Auckland, New Zealand). Probenecid was obtained from Sigma (St Louis, MO, USA); *Providencia alcalifaciens* (ATCC 9886) and all other chemicals and reagents were of the best available source.

Aspirin was dissolved according to labelled instructions in sufficient Water for Injection (BP) to achieve a final concentration of 220 mg/mL. Ceftiofur sodium was dissolved according to labelled instructions in sufficient Water for Injection (BP) to achieve a final concentration of 50 mg/mL. Probenecid was suspended in 10 mmol/L NaH_2PO_4 pH 7.4 and the pH was adjusted by addition of 0.1 N NaOH to achieve dissolution. The solution was diluted with deionized water to a final concentration of 50 mg/mL probenecid in 5 mmol/L NaH_2PO_4 at pH 7.8. This solution was filtered through a 0.45μm filter prior to use.

Ten healthy, non-pregnant, non-lactating dairy cows were selected from the Department of Veterinary Clinical Science's teaching herd. A randomized complete three-way crossover design was used, with a 2 week washout period between successive experiments. Randomization of treatment order was achieved by lottery. In repeated experiments all cows were administered: (1) 2 mg/kg ceftiofur sodium by intravenous bolus; (2) 10 mg/kg probenecid by intravenous bolus, followed immediately by 2 mg/kg ceftiofur sodium by intravenous bolus; or (3) 26 mg/kg aspirin by intravenous bolus, followed immediately by 2 mg/kg ceftiofur sodium by intravenous bolus. These doses for both ceftiofur sodium and aspirin were the recommended, labelled doses.

A jugular venecatheter was placed into each jugular vein under light sedation with xylazine the day before each experiment. These catheters were flushed with 5 mL of 155 mmoL/L NaCl containing 25 IU/mL heparin. Catheters were flushed with 5 mL of 155 mmol/L NaCl prior to and between administrations of the test drugs. Test drugs were administered through one jugular catheter and blood was collected through the opposite jugular catheter at 0, 5, 10, 20, 30, 45, 60 and 90 min after injection and at 2, 3, 4, 5, 6, 8, 10, 12 and 24 h after injection. Serum was harvested and frozen at −80°C until analysis. A ceftiofur standard for assay was also prepared as follows: ceftiofur sodium was added to drug-free, pooled bovine serum to achieve a concentration of 100 mg/L and was frozen at −80°C with the samples.

Samples were assayed by microbiological assay according to the method of Bennett *et al.* (1966) using *Providencia alcalifaciens* as the test organism. To minimize the effect of interassay variation, all samples for each cow from one experiment were assayed together. Data were analysed by least-squares linear regression of the logarithm of the ceftiofur standard concentration vs. the diameter of the growth inhibition zone. It was recognized that this assay fails to distinguish between ceftiofur sodium and its active metabolites, and therefore results were expressed as serum ceftiofur-equivalent activity in mg/L.

Serum ceftiofur-equivalent activity vs. time data from 30 min after injection to 24 h after injection were analysed by a non-linear weighted least-squares curve-fitting method using the computer program Microsoft Excel v. 4.0 on a Macintosh computer. Using Akaike's information criterion to select the best-fitting model (Yamaoka *et al.*, 1978), a two-compartment open model provided the best fit to the (post 20 min) data in all cows. Analyses were run for each data set independently.

The following pharmacokinetic parameters for each data set were calculated from the ordinate axis intercepts and the rate constants for the distribution and elimination phases of the serum ceftiofur-equivalent activity vs. time curves (respectively A and α and B and β) according to previously reported pharmacokinetic formulae: the serum ceftiofur-equivalent activity at any time t ($C(t)$), the apparent volume of the central compartment (V_c), the apparent volume of distribution at steady-state ($V_{d(ss)}$), the elimination half-life ($t_{1/2}$) (Gibaldi & Perrier, 1975). The area under the serum ceftiofur-equivalent activity vs. time curve from time zero to infinity (*AUC*), the area under the 'first moment curve' of the serum

ceftiofur-equivalent activity vs. time from time zero to infinity (*AUMC*) and the total body mean residence time (*MRT*) were calculated using the computer program Minim (Purves, 1992) on a Macintosh computer by the log-trapezoidal method. The apparent volume of distribution according to the area method ($V_{d(area)}$), the total body clearance (*Cl*) (Ritschell, 1986) and the mean residence time in peripheral tissues (MRT_p) (Veng-Pedersen, 1989) were calculated according to previously reported model-independent methods.

The apparent volume of distribution at steady-state, total body mean residence time, mean residence time in peripheral tissues, total body clearance and elimination rate constant are the parameters of clinical interest for potential interaction between the test drugs, as alteration of these parameters might necessitate changes to dose, dose interval or food product withholding times. Most of these parameters probably do not conform to a normal population distribution (Whittem, 1993) and therefore descriptive statistics used included the mean, median, standard deviation about the mean and interquartile ranges. The 95% confidence interval for the mean was also calculated, based on Student's *t*-distribution.

The formulated null hypotheses excluded any need to compare the results obtained between the two pretreatments: probenecid was used solely to probe the question of organic anion transporter competition and aspirin was used to probe the question of whether it causes a clinically important interaction. Therefore, only pairwise comparisons were appropriate between each treatment and ceftiofur alone. Since examination of the descriptive statistics and the skewness and kurtosis coefficients for each parameter confirmed non-normal population distributions for most parameters, Wilcoxon's sign-ranked test for paired data was used for these comparisons with the acceptable probability for α error set at $P < 0.05$. Since the calculation of the probability of β-error is not possible using this non-parametric test, power for accepting the null hypotheses was calculated using Student's *t*-distribution, acknowledging that the values so determined should be interpreted with care.

RESULTS

The microbiological assay for ceftiofur was linear between 0.1 and 5.0 mg/L with the correlation coefficient (r^2) always exceeding 0.99. The intra-assay coefficient of variation was 5.81 ± 1.9% (mean ± standard deviation, $n = 14$) and the inter-assay coefficient of variation was 8.7% ($n = 10$) at 5 mg/L. The assay detection limit was defined as 0.1 mg/L. Recovery from fortified serum was determined as 100%. The assay parameters were not altered significantly by the inclusion in the serum for dilution of either 100 mg/L aspirin or 100 mg/L probenecid.

All the serum ceftiofur-equivalent activity vs. time curves for all cows showed an increase in ceftiofur-equivalent antimicrobial activity during the first 20 min after injection. This finding was unexpected. When curve fitting by non-linear unweighted or weighted least-squares methods to the expression

$$C(t) = Ae^{-\alpha t} + Be^{-\beta t} - Ce^{-k_m t}$$

was performed, where *C* is a constant and k_m is the rate constant for the initial increase in ceftiofur equivalent, the estimates for k_m and *C* were unstable and highly correlated ($r^2 \geq 0.95$). This instability was due to insufficient data points during the first 20 min after injection, and permitted multiple minima for the sum of squared residuals. Therefore no result for *C* or k_m could be obtained by these methods. Since the time to maximum serum concentration of ceftiofur-equivalent activity was approximately 20 min in all cases, further model-dependent data analysis was performed on the serum ceftiofur-equivalent activity–time curves only for the time points subsequent to 20 min after injection. Assuming that this early kinetic event was 97% completed by 20 min, k_m was estimated from a half-time of approximately 4 min. The curves of 'best fit' shown in Figs 1 and 2 are based on the equation above, fixing k_m at 0.173/min, with the estimate for *C* constrained to create a positive *y*-axis intercept.

The pharmacokinetic parameters for ceftiofur sodium and metabolite activity following single intravenous bolus of 2 mg/kg ceftiofur sodium are presented in Table 1. These parameters following a single intravenous bolus injection of aspirin or probenecid are presented in Tables 2 and 3 respectively. Owing to laboratory error, data for five cows' probenecid treatments were lost. Therefore Table 3 presents only the data from the remaining five cows.

Preceding treatment with probenecid resulted in statistically significant alterations in MRT_p and *Cl*. Power to accept the null hypotheses for each of $V_{d(ss)}$, $V_{d(area)}$, *MRT* or β was 0.92, 0.94, 0.94 and 0.86 respectively.

Preceding treatment with aspirin did not result in statistically significant alterations to any parameter. Power to accept the null hypotheses for $V_{d(ss)}$, $V_{d(area)}$, *MRT*, MRT_p, *Cl* or β was 0.87, 0.90, 0.95, 0.94, 0.92 and 0.92 respectively.

DISCUSSION

The initial 20 min rise in serum ceftiofur-equivalent activity was unexpected, as such a rise is atypical for intravenous bolus doses of most drugs. Since the half-time for this phase of the curve approximates estimates of the half-time for metabolism of ceftiofur to its major metabolite, desfuroylceftiofur (Brown *et al.*, 1991), it is likely that the apparent increase in ceftiofur-equivalent activity is a function of ceftiofur's metabolism. Accepting the assumption that this effect is due to metabolism, four explanations for the phenomenon are possible. First, it is possible that ceftiofur is less potent than desfuroylceftiofur for *Providencia alcalifaciens*, and that the equipotency of ceftiofur and this metabolite previously reported (Brown *et al.*, 1991) applies only to some bacteria. Alternatively, it is possible that ceftiofur and desfuroylceftiofur are synergistic *in vitro* for *Providencia alcalifaciens*. Synergism for some test organisms has previously been demonstrated between a third-generation cephalosporin, cefotaxime, and its major metabolite (Neu, 1982). Third, it is possible that the early increase in serum ceftiofur-equivalent activity observed in this study was due to unequal loss of potency by ceftiofur and its various active metabolites during storage at −80°C prior to assay. These three possible explanations have been examined and found not to be true, but the final expla-

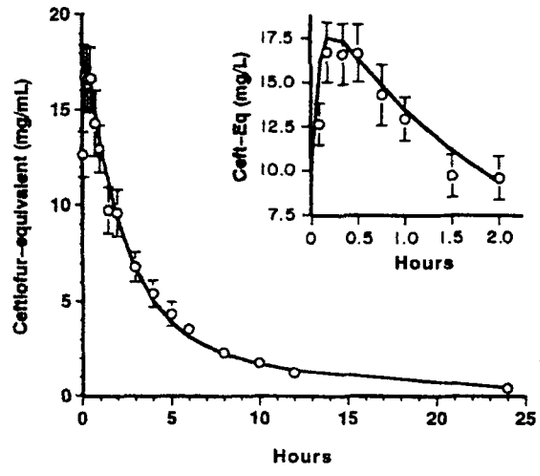

Fig 1. Mean ± SEM for serum ceftiofur equivalent activity in mg/L versus time from zero to 24 h after single intravenous bolus injection of 2 mg/kg ceftiofur sodium to non-pregnant, non-lactating dairy cattle (n = 10). Inset: Mean ± SEM for serum ceftiofur equivalent activity in mg/L versus time from zero to 2 h.

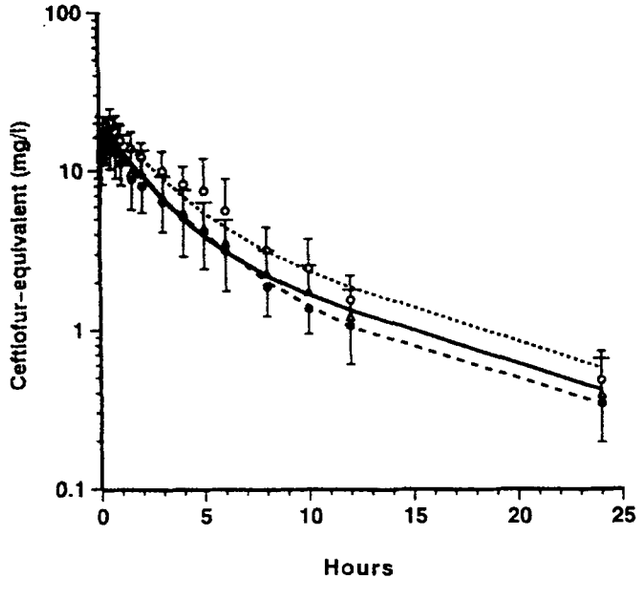

Fig 2. Mean + SD for serum ceftiofur equivalent activity in mg/L versus time in hours after single intravenous bolus injection of 2 mg/kg ceftiofur sodium (1) alone (△) (n = 10), (2) when preceded by a single intravenous bolus injection of 26 mg/kg aspirin (●) (n = 10) and (3) when preceded by a single intravenous bolus injection of 10 mg/kg probenecid (○) (n = 5).

nation, that the apparent volume of distribution for the metabolite desfuroylceftiofur is less than that of the parent drug, is true. This explanation is supported by the observation of this phenomenon when using alternative assay methods such as high-performance liquid chromatography (HPLC) (S.A. Brown, personal communication).

In model-dependent analysis for calculation of V_c, $V_{d(ss)}$ and $t_{1/2}$, the changing apparent volume of distribution during the first 20 min necessitated use of only those data points subsequent to 20 min post injection. Although model-independent methods were used to calculate the $V_{d(area)}$, Cl, MRT and MRT_p and utilized all the data time points it is important to consider that an assay of biological activity was used to analyse the samples. It is therefore necessary to emphasize that estimated values for all pharmacokinetic parameters are composite values for all assayed drug and metabolites together. Since it is the degree and duration of antimicrobial activity that is of interest to veterinary clinicians, the use of an antimicrobial assay in the context of this work's aims was appropriate.

The MRT and $t_{1/2}$ for ceftiofur-equivalent activity reported herein were greater than those reported previously for lactating dairy cattle (6.48 and 7.12 h vs. 5.06 and 3.61 h respectively) (Soback *et al.* 1989). However, in their work Soback *et al.* (1989) examined the elimination phase only to 8 h post injection, and their assay detection limit for serum was 0.78 mg/L. It is probable therefore that their estimates for the terminal elimination rate constant were not as accurate as those of the study presented here, where samples were collected to 24 h post injection and where the assay used had a lower detection limit. An alternative explanation has been proposed by Brown *et al.* (1991), who demonstrated that the $t_{1/2}$ of total desfuroylceftiofur when analysed by HPLC was 9.65 ± 1.97 h. They proposed that differences in $t_{1/2}$ determined by different assay methodologies may be due to the effects of protein binding on the assay results (Brown *et al.*, 1991). However, the serum $t_{1/2}$ reported herein is in closer agreement with the value reported by Brown *et al.* (1991) than the value reported by Soback *et al.* (1989). This difference is despite the assay methodology of this work being similar to that of Soback *et al.* (1989) and distinct from that of Brown *et al.* (1991). Therefore, it is more likely that the difference in reported values is due to a higher number of sample time points and a longer duration of sample collection, since these factors result in better definition of the terminal elimination rate constant.

Ceftiofur and all its major metabolites possess a carboxylic acid moiety (Jaglan *et al.*, 1992), and therefore may be present in biological fluids as organic anions. Thus, these xenobiotics are potential substrates for the organic anion transporters of the renal proximal tubule and other tissues. These xenobiotics may be partially excreted or resorbed by active transport across the epithelia of the proximal convoluted tubule, and distribution to or from peripheral tissues may be assisted in part by organic anion transporters. Probenecid is an archetypical substrate for the organic anion transporter. In this study probenecid increased the Cl and decreased MRT_p for ceftiofur and its metabolites, indicating the possibility of altered tissue distribution and/or elimination. Although other interactions such as alteration to plasma protein binding cannot be ruled out, these changes to the pharmacokinetics of ceftiofur sodium and its metabolites may have been due to competition for transport by the organic anion transporter. Nevertheless, aspirin did not alter the pharmacokinetics of ceftiofur and its metabolites. Ceftiofur sodium and its metabolites demonstrate unusual protein binding, possibly because of an exposed sulphydryl group (Brown *et al.*, 1991). It is possible that this characteristic reduced their access to the organic anion transporter. Alternatively, it is possible that the alkaline urine expected in the mature dairy cow may

Table 1. Pharmacokinetic parameters for ceftiofur and its active metabolites in cattle after a single intravenous bolus dose of 2 mg/kg ceftiofur sodium ($n = 10$).

Parameter	Mean	Median	SD	CV	First quartile	Third quartile	CI(95)
$C(0)$ (mg/L)	18.9	17.3	5.8	0.30	14.9	23.2	3.6
α (/h)	0.483	0.421	0.205	0.42	0.367	0.497	0.127
β (/h)	0.097	0.087	0.044	0.45	0.068	0.134	0.027
A (mg/L)	15.0	14.7	6.2	0.41	10.1	19.6	3.8
B (mg/L)	3.9	3.4	2.5	0.64	2.3	5.5	1.6
V_c (L/kg)	0.115	0.116	0.036	0.31	0.086	0.134	0.022
$V_{d(ss)}$ (L/kg)	0.200	0.181	0.062	0.31	0.150	0.253	0.038
$V_{d(area)}$ (L/kg)	0.382	0.288	0.224	0.59	0.245	0.413	0.139
Cl (L/kg/h)	0.032	0.028	0.013	0.41	0.025	0.035	0.008
AUC (mg·L/h)	72.4	70.8	27.5	0.38	57.7	79.6	17.0
$AUMC$ (mg·L/h ^{2})	491.9	401.8	269.5	0.55	310.1	670.2	167.0
MRT (h)	6.48	6.05	1.76	0.27	5.34	6.83	1.09
MRT_p (h)	2.65	2.63	1.01	0.38	2.30	2.94	0.63
$t_{1/2}$ (h)	7.12*	7.98	–	–	5.18	10.19	–

*Harmonic mean.

SD is the standard deviation, CV is the coefficient of variation and CI (95) is the 95% confidence interval surrounding the mean, based on Student's t-distribution.

Note that the SD, CV and CI (95) are potentially misleading for markedly skewed population distributions, and should therefore be interpreted with caution.

Table 2. Pharmacokinetic parameters for ceftiofur and its active metabolites in cattle after a single intravenous bolus dose of 2 mg/kg ceftiofur sodium preceded by a single intravenous bolus dose of 26 mg/kg acetyl salicylate (asprin) ($n = 10$)

Parameter	Mean	Median	SD	CV	First quartile	Third quartile	CI (95)
$C(0)$ (mg/L)	17.0	17.7	3.0	0.18	14.8	19.4	1.9
α (/h)	0.520	0.383	0.500	0.96	0.279	0.445	0.310
β (/h)	0.076	0.074	0.045	0.59	0.043	0.095	0.028
A (mg/L)	14.8	15.4	3.1	0.21	11.9	17.6	2.0
B (mg/L)	2.1	2.5	1.2	0.57	0.9	3.0	0.7
V_c (L/kg)	0.122	0.113	0.026	0.21	0.104	0.137	0.016
$V_{d(ss)}$ (L/kg)	0.253	0.212	0.100	0.39	0.199	0.244	0.062
$V_{d(area)}$ (L/kg)	0.558	0.442	0.314	0.56	0.389	0.582	0.195
Cl (L/kg/h)	0.036	0.032	0.019	0.52	0.026	0.037	0.012
AUC (mg·L/h)	63.8	61.8	20.5	0.32	53.7	77.4	12.7
$AUMC$ (mg·L/h^2)	433.2	425.0	171.5	0.40	340.9	558.1	106.3
MRT (h)	6.57	6.84	1.22	0.19	6.36	7.46	0.76
MRT_p (h)	2.78	2.62	0.78	0.28	2.28	3.44	0.48
$t_{1/2}$ (h)	9.10*	9.54	–	–	7.35	16.29	–

*Harmonic mean.

SD is the standard deviation, CV is the coefficient of variation and CI (95) is the 95% confidence interval surrounding the mean, based on Student's t-distribution.

Note that the SD, CV and CI (95) are potentially misleading for markedly skewed population distributions, and should therefore be interpreted with caution.

No statistically significant differences from control (ceftiofur alone) were detected using Wilcoxon's signed-rank test for paired samples ($P < 0.05$).

decrease the potential for probenecid or aspirin to affect organic anion transporter secretion of ceftiofur at the basolateral membrane of the proximal convoluted tubule. The effect of probenecid on secretion of cefsulodin in the rabbit (Dromer *et al.*, 1985) and on aspirin in humans (Weiner, 1992) is minimal with alkaline urine, since alkaline urine reduces the resorption of each anionic xenobiotic from the urinary ultrafiltrate (Weiner, 1992). Finally, the harmonic mean of the serum $t_{1/2}$ of aspirin in these cows was 0.51 h (T. Whittem, unpublished data). This relatively rapid elimination may have reduced the time available for its potential interaction at the organic anion transporter. While repeated or higher doses of aspirin may lead to an alteration of ceftiofur sodium pharmacoki-

Table 3. Pharmacokinetic parameters for ceftiofur and its active metabolites in cattle after a single intravenous bolus dose of 2 mg/kg ceftiofur sodium preceded by a single intravenous bolus dose of 10 mg/kg probenecid ($n = 5$)

Parameter	Mean	Median	SD	CV	First quartile	Third quartile	CI (95)
$C(0)$ (mg/L)	22.0	20.4	3.9	0.17	19.6	23.0	3.4
α (/h)	0.310	0.359	0.078	0.25	0.226	0.360	0.068
β (/h)	0.074	0.091	0.035	0.47	0.043	0.101	0.030
A (mg/L)	19.5	17.4	4.8	0.25	17.1	21.9	4.2
B (mg/L)	2.6	1.8	1.7	0.65	1.5	3.3	1.5
V_c (L/kg)	0.093	0.098	0.014	0.15	0.087	0.102	0.012
$V_{d(ss)}$ (L/kg)	0.149	0.146	0.024	0.16	0.146	0.151	0.021
$V_{d(area)}$ (L/kg)	0.346	0.333	0.124	0.36	0.275	0.348	0.109
Cl (L/kg/h)	0.023†	0.023	0.008	0.34	0.016	0.025	0.007
AUC (mg·h/L)	96.9	86.3	33.3	0.34	80.0	121.4	29.2
$AUMC$ (mg·h^2)	624.4	582.6	281.5	0.45	499.3	782.9	246.7
MRT (h)	6.23	6.45	1.00	0.16	6.24	6.75	0.88
MRT_p (h)	1.91 †	2.22	0.53	0.28	1.53	2.32	0.47
$t_{1/2}$ (h)	9.39*	7.62	–	–	6.86	16.12	–

*Harmonic mean.

† Differs significantly from control (ceftiofur alone) using Wilcoxon's signed-rank test for paired samples ($P \leq 0.05$).

SD is the standard deviation, CV is the coefficient of variation and CI (95) is the 95% confidence interval surrounding the mean, based on Student's *t*-distribution.

Note that the SD, CV and CI (95) are potentially misleading for markedly skewed population distributions, and should therefore be interpreted with caution.

netics, this work has demonstrated that the potential for influence on ceftiofur's excretion rate by aspirin is not realized at clinically relevant single doses.

This study determined that the mean residence time in the peripheral tissues for all ceftiofur and metabolite molecules, irrespective of whether or not they are distributed to the tissues (MRT_p), was not altered by aspirin in the administered regimen. These data support the suggestion that a single dose of aspirin concomitant with ceftiofur sodium may not affect the necessary food product withholding time for ceftiofur sodium. Nevertheless, since this pharmacokinetic parameter is a mean value and assumes that the peripheral tissues are a homogeneous kinetic space (Veng-Pedersen, 1989), conclusions about tissue residue times cannot be steadfastly accepted without tissue residue studies.

In conclusion, these results suggest that ceftiofur or some of its active metabolites may be substrates for the organic anion transporter. Nevertheless, alterations to dose or dose interval may not be indicated when ceftiofur sodium is administered to the cow concomitantly with a single dose of aspirin.

ACKNOWLEDGMENTS

The authors wish to acknowledge the contribution of Dr R. Marshall and the technical assistance of Ms V. Tilson and L.C. Cullinane. The authors also wish to acknowledge the assistance of Dr S.A. Brown for his helpful review of the manuscript. This study was supported by the Massey University Research Foundation.

REFERENCES

Anonymous (1991) Naxel brand of ceftiofur sodium sterile powder, manufacturer's product information. The Upjohn Company, Kalamazoo, MI.

Arvidsson, A., Borga, O. & Kager, L. (1981), Renal elimination of cefoxitin and effect of probenecid after single and repeated doses. *Journal of Antimicrobial Chemotherapy*, 7, 423–430.

Bennett, J.V., Brodie, J.L., Benner, E.J. & Kirby, W.M.M. (1966) Simplified, accurate method for antibiotic assay of clinical specimens. *Applied Microbiology*, 14, 170–177.

Brown, S.A., Jaglan, P.S. & Banting, A. (1991) Ceftiofur sodium: disposition, protein-binding, metabolism, and residue depletion profile in various species. (abstract mo.O.A2b). *Proceedings of the Fifth Congress of the European Association for Veterinary Pharmacology and Toxicology*, Eds Friis, C., Gyrd-Hansen, N., Nielsen, P. & Rasmussen, F. *Acta Veterinaria Scandinavica* (Suppl. 87) 97–99.

Carbon, C., Dromer, F., Brion, N., Cremieux, A.-C. & Contrepois, A. (1984) Renal disposition of ceftazidime illustrated by interferences by probenecid, furosemide, and indomethacin in rabbits. *Antimicrobial Agents in Chemotherapy*, 26, 373–377.

Cunningham, R.F., Israili, Z.H. & Dayton, P.G. (1981) Clinical pharmacokinetics of probenecid. *Clinical Pharmacokinetics*, 6, 135–151.

Dromer, F., Contrepois, A., Brion, N., Klein, C. & Carbon, C. (1985) Effects of urinary pH on renal interactions between probenecid and cefsulodin in rabbits. *Antimicrobial Agents in Chemotherapy*, 27, 660–662.

Gibaldi, M. & Perrier, D. (1975). *Pharmacokinetics*, pp. 45–89. Marcel Dekker, New York.

Guerrini, V.H., Filippich, L.J., English, P.B., Cao, G.R. & Bourne, D.W.A. (1985). Effect of probenecid on the pharmacokinetics of cefotaxime in sheep. *Journal of Veterinary Pharmacology and Therapeutics*, 8, 38–46.

Jaglan, P.S., Yein, F.S., Hornish, R.E., Cox, B.L., Arnold, T.S., Roof, R.D. & Gilbertson, T.J. (1992). Depletion of intramuscularly injected ceftiofur from the milk of dairy cattle. *Journal of Dairy Science*, 75, 1870–1876.

Neu, H.C. (1982). Antibacterial activity of desacetylcefotaxime alone and

in combination with Cefotaxime. *Reviews in Infectious Disease*, 4, S374–S378.

Owens, W.E., Xiang, Z.Y., Ray, C.H. & Nickerson, S.C. (1990). Determination of milk and mammary tissue concentrations of ceftiofur after intramammary and intramuscular therapy. *Journal of Dairy Science*, 73, 3449–3456.

Purves, R.D. (1992). Optimum numerical integration methods for estimation of area-under-the-curve (AUC) and area-under-the-moment-curve (AUMC). *Journal of Pharmacokinetics and Biopharmaceutics*, 20, 211-226.

Ritschell, W.A. (1986) *Handbook of Basic Pharmacokinetics. . . . Including Clinical Applications*, 3rd edn, pp. 191–247. Drug Intelligence Publications, Hamilton, IL.

Selman, I.E., Allan, E.M. & Dalgleish, R.G. (1986). The effects of flunixin meglumine and oxytetracycline therapy alone and in combination in calves with experimentally induced pneumonic pasteurellosis. *Proceedings of the 14th World Congress on Diseases of Cattle*, University College, Dublin, Ireland.

Soback, S., Ziv, G., Kurtz, B. & Paz, R. (1987) Clinical pharmacokinetics of five oral cephalosporins in calves. *Research in Veterinary Science*, 43, 166–172.

Soback, S., Ziv, G., Winkler, M. & Saran, A. (1989). Pharmacokinetics of ceftiofur administered intravenously and intramuscularly to lactating cows. *Israel Journal of Veterinary Medicine*, 45, 118–123.

Sweeney, C.R. & Smith, J.A. (1990). Diseases of the respiratory system. In *Large Animal Internal Medicine*. Ed. Smith, B.P., pp. 489–619. C.V. Mosby, Philadelphia.

Veng-Pedersen, P. (1989). Mean time parameters in pharmacokinetics. Definition, computation and clinical implications (Part I). *Clinical Pharmacokinetics*, 17, 345-366.

Weiner, I.M. (1992). Inhibitors of tubular transport of organic acids. In *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th edn. Eds Gilman, A.G., Rall, T.W., Nies, A.S. & Taylor, P. pp. 743–748. McGraw-Hill, New York.

Whittem, T. (1993) The population distribution of some pharmacokinetic parameters is not normal. A prediction based on computer modelling (abstract). In Proceedings of the Australasian Society for Clinical and Experimental Pharmacologists and Toxicologists (New Zealand Section) Annual Meeting. *New Zealand Medical Journal*, 106, 7.

Yamaoka, K., Nakagawa, T. & Uno, T. (1978). Application of Akaike's Information Criterion (AIC) in the evaluation of linear pharmacokinetic equations. *Journal of Pharmacokinetics and Biopharmaceutics*, 6, 165–175.

Ziv, G. (1992) Treatment of percute and acute mastitis. *Veterinary Clinics of North America: Food Animal Practice*, 8, 1–15.

Ziv, G., Nouws, J.F.M., Groothuis, D.G. & Van Miert, A.S.J.P.A.M. (1979) Effects of probenecid and milk on serum concentration of three oral cephalosporins in calves. *Refuah Veterinaria*, 35, 147–152.