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Pharmacokinetics and dosage regimen of florfenicol in co-administration with paracetamol in cross bred calves

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ABSTRACT

The pharmacokinetics of florfenicol were investigated in cross-bred calves treated with a single intravenous administration (20 mg/kg) following a single intramuscular injection of paracetamol (50 mg/kg)**.** The concentration of florfenicol in the plasma was estimated by microbiological assay technique, using *E. coli* as the test organism. The drug reached a maximum concentration of 31.5 ± 1.45 µg/mL in the plasma at 1 min, and this rapidly declined to 15.6 ± 0.46 µg/mL at 30 min. It was detected in the plasma above the minimum inhibitory concentration up to 12 h after administration. The disposition pattern of florfenicol followed the two-compartment open model. Florfenicol was fairly distributed from the blood to the tissue compartment as evidenced by the moderate values of the distribution coefficient, α (2.23 ± 0.18 per h) and the ratio of K_{12} /K_{21} (0.82 ± 0.1). The values of AUC and Vd_{area} were 54.8 ± 1.51 µg/mL.h and 1.5 ± 0.06 L/kg respectively**.** The elimination half-life, MRT and total body clearance were 2.84 ± 0.07 h, 3.61 ± 0.06 h and 0.37 ± 0.01 L/kg/h, respectively. Florfenicol at a dose of 20 mg/kg body weight IV at 12 h interval is sufficient to maintain T>MIC above 80% for bacteria with MIC values ≤1.0 µg/mL. The favourable pharmacokinetic profile of florfenicol with rapid distribution, high AUC, large Vd_{area} and 12 h dosing interval suggest that florfenicol may be an appropriate antibacterial when prescribed with paracetamol in cross-bred calves.

Key words: calves, dosage, florfenicol, paracetamol, pharmacokinetics

Introduction

Florfenicol (D-threo-2,2-dichloro-N-[1-(fluoromethyl)-2-hydroxy-2-[4-methyl sulfonyl) phenyl] ethyl]-acetamide) is a synthetic derivative of chloramphenicol. The clinical use of chloramphenicol in food-producing animals has been banned because of the serious adverse effects produced by its residues in human beings, including bone marrow suppression, aplastic anemia and hemolytic anemia (RAMACHANDRAN, 2000). Florfenicol, a

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monofluorinated analogue of thiamphenicol, which was approved for veterinary use in cattle in the USA in 1996, possesses antibacterial activity against a wide spectrum of bacterial strains, including enteric bacteria that are resistant to chloramphenicol and thiamphenicol. Florfenicol has distinct advantages over the parent drug chloramphenicol, it has improved antibacterial spectrum activity against some chloramphenicol resistant strains of bacteria (MARTEL, 1994), and unlike chloramphenicol, its use in food producing animals does not carry the risk of inducing aplastic anemia through residues in human beings (PAPICH and RIVIERE, 2001). Florfenicol has been demonstrated to be active *in vitro* and *in vivo* against *Pasteurella hemolytica, Pasteurella multocida* and *Haemophilus somnus* (LOBELL et al., 1994). It has been shown to be efficacious in the treatment of bovine respiratory disease (SHIN et al., 2005), undifferentiated fever (BOOKER et al., 1997) and bacterial meningitis in calves (DeCRAENE et al., 1997), urinary and genital tract infections, and bacterial infections in general. Antibacterials and analgesic drugs are used most frequently in multiple prescriptions and it is well documented that concurrently administered drugs may affect the absorption, distribution, biotransformation and excretion of one or both (BENET et al., 1996). The co-administration of NSAIDs with antibacterials has been associated with pharmacokinetic interactions in bovines (CHAUDHARY and SRIVASTAVA, 1999; DUMKA et al., 2008; SHARMA and UL HAQ, 2012). Paracetamol, a non-narcotic analgesic, antipyretic agent is routinely used in veterinary practice (BOOTH, 1995) and has been reported to alter the disposition of oxytetracycline (MANNA et al., 1993), cefotaxime (SHARMA and SRIVASTAVA, 1997) and levofloxacin (DUMKA, 2007) in ruminants. The pharmacokinetic studies of florfenicol have been conducted in cattle (DeCRAENE et al., 1997; SOBACK et al., 1995; GILLIAM et al., 2008), horses (McKELLAR and VARMA, 1996), cats, dogs (PAPICH and RIVIERE, 2001; PARK et al., 2008), pigs (KIM et al., 2008), rabbits (KOC et al., 2009), sheep (REGNIER et al., 2013), alpacas (HOLMES et al., 2012), and chickens (CHANG et al., 2010).

However, there is no information available on the influence of simultaneously administered paracetamol on the pharmacokinetic behavior of florfenicol in animals. In view of the paucity of such pharmacokinetic data, the present study was undertaken to determine the pharmacokinetics and the appropriate dosage regimen of florfenicol in cross-bred calves after its single intravenous (iv) administration upon co-administration with paracetamol.

Materials and methods

Experimental animals. The study was conducted on four male cross-bred calves of about one year age and weighing 80-120 kg. The animals were acclimatized to the experimental conditions for 2 weeks prior to the commencement of the experiment. During the experimental period, the animals were maintained on green fodder and wheat straw, and water was provided *ad libitum*. The average day temperature in the shed was about

25 ^{0}C during the experiment. The experimental protocol followed the ethical guidelines on the proper care and use of animals and had been approved by the institutional animal ethics committee.

Drug administration. Florfenicol (RF 30%, Ranbaxy Laboratories, India) was administered by i.v. injection into the jugular vein of calves at the dose rate of 20 mg/kg. The dose of florfenicol used in the study was comparable to the dosage used in camel, sheep, goats (ALI et al., 2003; REGNIER et al., 2013), pigs (LIU et al., 2003) and cows (SOBACK et al., 1995). Paracetamol (Bromol, Martin and Brown Pharmaceuticals, India) was administered at the dose rate of 50 mg/kg, by single intramuscular injection in the lateral neck region immediately prior to administration of florfenicol.

Blood sampling. Blood samples (6 mL) were collected into heparinized glass centrifuge tubes by contralateral jugular venipuncture at 1, 2.5, 5, 7.5, 10, 15, 30 and 45 min and at 1, 2, 3, 4, 6, 8, 10, 12 14 and 24 h of administration of florfenicol. Plasma was separated by centrifugation at 1300 g and stored at -20 ^{0}C until analyzed for florfenicol, which was usually done on the day after collection.

Analytical procedure. The concentration of florfenicol in plasma samples was estimated by microbiological assay technique using *Escherichia coli* (MTCC 739) as the test organism. The test organism was cultured on antibiotic medium no. 1 at 37 ^{0}C for 24 h, and a suspension was prepared in sterile normal saline. 20 mL of molten seed layer, containing bacterial suspension, was poured onto a Petri dish with the help of Cornwell Continuous Pipetting Device (Becton Dickinson, New Jersey, USA). Preliminary experiments were conducted to determine the actual amount of bacterial suspension to be used in the preparation of the seed layer. After solidification of the media, six wells were punched at equal distance, with the help of a punching device (developed and standardized in our laboratory). The samples were thawed at room temperature and suitably diluted with phosphate buffer. The alternate three wells were filled with one plasma or urine sample and the remaining three wells with a reference solution of florfenicol (0.5 μg/mL). These assay plates were incubated at 35 ^{0}C for 8 h. At the end of incubation, the diameter of the zone of inhibition of each well was measured. For each sample, 9 replicates were analyzed and correlated with the zone of inhibition of the reference solution. The concentration of florfenicol in the samples was calculated as μg/mL of plasma. This method estimated the level of parent drug and its active metabolites having antibacterial activity. The assay could detect a minimum of 0.125 μg/mL of florfenicol. The standard curve of florfenicol was linear between 0.125 and 2.5 μg/mL drug concentration (DUMKA and SINGH, 2013).

Pharmacokinetic analysis. The pharmacokinetic parameters were calculated manually for each animal by the regression technique (GIBALDI and PERRIER, 1982). The mean pharmacokinetic variables were obtained by averaging the variables calculated for drug disposition after intravenous drug administration to each animal.

The minimum inhibitory concentration (MIC_{90}) of florfenicol against most of the susceptible bacterial pathogens of cattle has been reported to be less than 1 µg/mL, including *Actinobacillus,, Pasteurella, Mannheimia* and *Bordetella,* with mean MIC values of 0.47-0.53 against bovine *Pasteurella* isolates (SHIN et al., 2005; HORMANSDORFER and BAUER, 1998). In the current study, a concentration of 1.0 µg/mL was considered to be the average MIC_{90} of florfenicol against most of the pathogens for veal.

The time for which the plasma drug levels remain above or equal to the minimal inhibitory concentration (MIC) value was calculated using the formula:

$$\%T>MIC = \ln\left[\frac{D}{Vd_{area} \times MIC}\right] \times \left[\frac{t_{1/2\beta}}{\ln(2)}\right] \times \left[\frac{100}{DI}\right]$$

where T>MIC is the time interval (per cent) during which the plasma concentration is above or equal to the MIC values, ln is the natural logarithm, D is the proposed dose, Vd_{area} is the volume of distribution, $t_{1/2\beta}$ is the terminal elimination half-life, and DI is the dose interval.

Results

The mean plasma levels of florfenicol at different time intervals, following its single intravenous administration after intramuscular administration of paracetamol, are presented in an semilogarithmic scale in Fig. 1. The pharmacokinetics are adequately described by the equation: $Cp = Ae^{-\alpha t} + Be^{-\beta t}$

where Cp is the plasma concentration of florfenicol at time t, e is the base of the natural logarithm, A and B are zero-time plasma concentration intercepts of the biphasic disposition curve and α and β are hybrid rate constants related to the slopes of the distribution and elimination phases, respectively.

On concomitant administration of florfenicol and paracetamol, the mean plasma concentration of florfenicol at 1 min following its intravenous administration was 31.5 ± 1.45 µg/mL, which declined to 0.37 ± 0.01 µg/mL at 24 hours and the drug was detected above the minimum inhibitory concentration (MIC_{90}) up to 12 h of administration.

Various kinetic determinants that describe the distribution and elimination pattern of florfenicol, after its intravenous injection in combination with paracetamol, were calculated. They are presented in Table 1.

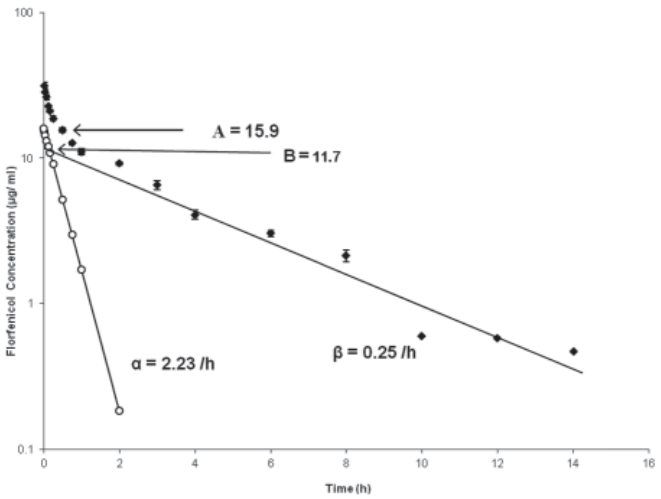

Fig. 1. Semilogarithmic plot of plasma concentration-time profile of florfenicol following its single intravenous injection of 20 mg/kg body weight subsequently after a single intramuscular injection of paracetamol (50 mg/kg). Values are presented as mean ± SE of 5 animals. The data was analyzed according to two-compartment open model. A and B are zero-time plasma drug concentration intercepts of the regression lines of distribution and elimination phases, respectively. Distribution (α) and elimination (β) phases are represented by regression lines. The calculated points (o) of distribution phase were obtained by feathering technique.

Table 2 shows the calculated % T>MIC for microorganisms of different susceptibilities to florfenicol for 8, 12 and 24 h dosing intervals, based on the estimated pharmacokinetic parameters obtained following IV injection in calves following a single intramuscular injection of paracetamol.

Table 1. Pharmacokinetics of florfenicol (20 mg/kg) after its intravenous injection following single intramuscular injection of paracetamol (50 mg/kg)

Parameter	Unit	Mean ± SE
A	μg/mL	15.9 ± 1.31
$t_{½\alpha}$	h	0.32 ± 0.02
B	μg/mL	11.7 ± 0.61
$t_{½\beta}$	h	2.84 ± 0.07
K_{12}/K_{21}	Ratio	0.82 ± 0.10
AUC	μg/mL.h	54.8 ± 1.51
AUMC	μg/mL.h^2	197.6 ± 4.74
Vd_{area}	L/kg	1.50 ± 0.06
fc	Ratio	0.49 ± 0.03
P/C	Ratio	1.06 ± 0.12
C_p^o	μg/mL	27.6 ± 1.05
K_{el}	/h	0.51 ± 0.02
Cl_B	L/kg/h	0.37 ± 0.01
MRT	h	3.61 ± 0.06
td	h	15.1 ± 0.39

A and B, zero-time plasma drug concentration intercepts of the regression lines of distribution and elimination phases, respectively; α and β, distribution and elimination rate constants, respectively; $t_{½\alpha}$, absorption half-life; $t_{½\beta}$, elimination half-life; AUC, area under the plasma concentration-time curve; AUMC, area under the first moment of plasma concentration-time curve; Vd_{area}, apparent volume of distribution; fc, fraction of drug in central compartment; P/C, ratio of drug present in central versus peripheral compartments; K_{el}, first order elimination rate constant from central compartment; Cl_B, total body clearance of drug; Cpº, plasma drug concentration at time zero after intravenous dose; MRT, mean residence time; td, total duration of pharmacological effect.

Table 2. Calculated %T>MIC for florfenicol based on the estimated pharmacokinetic parameters obtained after IV injection 20 mg/kg body weight following single IM injection of paracetamol (50 mg/kg) in calves for 8, 12 and 24 h dosing interval

Microorganism susceptibility (mg/mL)	%T>MIC		
	24	12	8
0.25	67.9	135.8	203.7
0.5	56.1	112.1	168.2
1.0	44.2	88.4	132.7
1.5	37.3	74.6	111.9
2.0	32.4	64.8	97.2

Discussion

The evaluation of the results on the observed plasma levels of florfenicol administered with paracetamol indicated that the data may be best fitted to a two-compartment open model. The disposition pattern of florfenicol has also been reported to follow the two-compartment open model in goats, calves, camel and sheep (ALI et al., 2003; LANE et al., 2004; DeCRAENE et al., 1997) after intravenous administration. The plasma concentration of florfenicol at 1 min was 63 fold higher than the MIC of florfenicol.

The distribution half-life of florfenicol was 0.32 ± 0.02 h, indicating rapid distribution from the central to the peripheral compartments, however it was shorter than the $t_{½\alpha}$ of 0.47 ± 0.07 h obtained after administration of florfenicol alone in calves (DUMKA and SINGH, 2013). In agreement with the present finding, short distribution half-lives of 0.37 h and 0.069 h have been reported following intravenous injection of florfenicol in pigs (LIU et al., 2003) and sheep (LANE et al., 2004), respectively. The excellent distribution of florfenicol in various tissues and body fluids was reflected by the large Vd_{area} of 1.50 ± 0.06 L/Kg in the present study, but this value was lower than the Vd_{area} of 1.99 ± 0.16 L/Kg after administration of florfenicol alone in calves (DUMKA and SINGH, 2013). A high value for the volume of distribution (1.86 L/Kg) was also reported for florfenicol in sheep (SHEN et al., 2004). However, the present finding was more than the corresponding values reported in rabbits (0.57 L/Kg), sheep (0.50 L/Kg) and pigs (1.2 L/Kg) for volumes of distribution of florfenicol (LIU et al., 2003; LANE et al., 2004; ABD-EL-ATY et al., 2004). The excellent tissue penetration of florfenicol was also reflected by the high P/C ratio in the present study (1.06 ± 0.12), however this value was lower than the P/C ratio of 1.55 ± 0.19 following administration of florfenicol alone in calves (DUMKA and SINGH, 2013). The present finding is supported by the attainment of a high lacrimal fluid-to-plasma concentration ratio of 32.5 to 40.2% after extravascular administration of florfenicol in ewes (REGNIER et al., 2013).

Consistent with the high AUC of florfenicol in calves (54.8 ± 1.51 μg/mL.h) observed in the present study, which was higher than the AUC of 40.3 ± 1.70 μg/mL.h after administration of florfenicol alone in calves (DUMKA and SINGH, 2013), high values of AUC of florfenicol have also been reported, such as 51.83 μg/mL.h in alpacas (HOLMES et al., 2012), 64.86 μg/mL.h in pigs (LIU et al., 2003), 76.31 and 62.45 μg/mL.h in sheep (SHEN et al., 2004; ALI et al., 2003), 60.61 μg/mL.h in camels and 74.07 μg/mL.h in goats (ALI et al., 2003).

The elimination half-life of florfenicol administered with paracetamol in calves in the present study (2.84 ± 0.07 h) was similar to the $t_{½\beta\ of}$ 2.76 ± 0.16 h obtained after administration of florfenicol alone in calves (DUMKA and SINGH, 2013), indicating the rapid elimination of the drug from the body. Comparable values for elimination half-lives of florfenicol were reported in sheep (1.01 h), calves (3.2 h) and pigs (2.91 h)

following a single intravenous dose (DeCRAENE et al., 1997; LIU et al., 2003; LANE et al., 2004). The total body clearance of florfenicol in calves (0.37 ± 0.01 L/Kg/h), although lower than the Cl_B of 0.50 ± 0.018 following administration of florfenicol alone in calves (DUMKA and SINGH, 2013), was higher than the values reported for Cl_B of 0.162 L/Kg/h in cattle (SOBACK et al., 1995), 0.26 L/Kg/h in sheep (SHEN et al., 2004), 0.33 L/Kg/h in camels (ALI et al., 2003) and 0.172 L/Kg/h in calves (ADAMS et al., 1987). The MRT (3.61 ± 0.06 h) of florfenicol obtained in present study was higher than 2.93 ± 0.059 h following administration of florfenicol alone in calves (DUMKA and SINGH, 2013) and the values of MRT reported in calves camels, sheep, goats and rabbits. The values of MRT reported in camels, sheep, goats and rabbits were 2.71 ± 0.31 h, 2.34 ± 0.25 h, 2.11 ± 0.23 h and 1.69 h, respectively (ALI et al., 2003; ABD-EL-ATY et al., 2004). The alterations in the pharmacokinetic parameters of $t_{½\alpha}$, Vd_{area}, P/c ratio, AUC, $t_{½\beta}$, Cl_B and MRT observed in the present study from the corresponding values of these variables obtained after administration of florfenicol alone in calves may be due to the influence of co-administration of paracetamol on the pharmacokinetic constants of IV florfenicol. The findings of the present study are supported by the reports whereby simultaneous administration of paracetamol altered the disposition of levofloxacin and ceftizoxime in cross bred calves (DUMKA, 2007; SINGH et al., 2008). Further, similar alterations in the pharmacokinetics of levofloxacin and gatifloxacin were found upon co-administration of another NSAID, meloxicam in bovines (DUMKA et al., 2008 and 2010).

Florfenicol acts as a time-dependent bactericidal drug. The most important pharmacodynamic/pharmacokinetic parameter for this type of drug is the length of the time during which drug remains above the MIC_{90} value. It is generally recommended that T>MIC should be at least 50% of the dosage interval to ensure an optimal bactericidal effect (TOUTAIN and LEES, 2004). The purpose of the present study was to calculate and modify the dosage regimen of florfenicol for concomitant administration with paracetamol in cross-bred calves. The experimental data presented here shows that florfenicol at a dose of 20 mg/kg body weight IV at 12 h interval is sufficient to maintain T>MIC above 80% for bacteria with MIC values ≤1.0 µg/mL and above 60% for bacteria with MIC values ≤ 2.0 µg/mL. This dosage regimen meets the pharmacokinetic-pharmacodynamic criteria predicting a successful therapy for susceptible bacteria with MIC ≤2.0 µg/mL. The favourable pharmacokinetic profile of florfenicol with rapid distribution, high AUC, large Vd_{area} and 12 h dosing interval suggest that florfenicol may be an appropriate antibacterial when prescribed with paracetamol in cross-bred calves.

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SAŽETAK

Istraživana je farmakokinetika jednokratno intravenski primijenjenog florfenikola (20 mg/kg) u križane teladi nakon jednokratne intramuskularne primjene paracetamola (50 mg/kg)**.** Koncentracija florfenikola u plazmi bila je procijenjena mikrobiološkim testom uporabom bakterije *E. coli* kao testiranog organizma. Lijek je dosegao maksimalnu koncentraciju od 31,5 ± 1,45 µg/mL u plazmi za jednu minutu da bi se njegova koncentracija vrlo brzo, već za 30 minuta, spustila na 15,6 ± 0,46 µg/mL, a potom se u plazmi nalazio iznad minimalne inhibicijske koncentracije do 12 sati nakon primjene. Dispozicija florfenikola odvijala se po modelu dvostrukog odjeljka. Florfenikol se lako proširio iz krvi u tkiva što je dokazano na osnovi umjerenih vrijednosti koeficijenta raspodjele, α (2,23 ± 0,18 na sat) i omjera K_{12}/K_{21} (0,82 ± 0,1). Vrijednost AUC iznosila je 54,8 ± 1,51 µg/mL/h, a $Vd_{površine}$ 1,5 ± 0,06 L/kg**.** Poluživot izlučivanja iznosio je 2,84 ± 0,07 h, MRT 3,61 ± 0,06 h, a sveukupni tjelesni klirens 0,37 ± 0,01 L/kg/h. Intravenska primjena florfenikola u dozi od 20 mg/kg tjelesne mase u razmaku od 12 sati dovoljna je za održavanje T>MIC iznad 80% za bakterije s vrijednostima minimalne inhibicijske koncentracije MIC ≤1,0 µg/mL. Povoljan farmakokinetički profil florfenikola s brzom raspodjelom, visokim AUC, širokim $Vd_{površine}$ i 12 h intervalom doziranja pokazuje da on može imati odgovarajući antibakterijski učinak u križane teladi kada se primjenjuje s paracetamolom.

Ključne riječi: telad, doziranje, florfenikol, paracetamol, farmakokinetika