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PHARMACOKINETICS AND TOLERANCE OF CHLORAMPHENICOL AND FLORFENICOL IN CAMELS

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ABSTRACT

The pharmacokinetic of chloramphenicol and florfenicol following intravenous administration of 5 mg/kg body weight was studied in camels. The plasma concentration versus time were best described by a two-compartment open model. Significantly higher volume of distribution, shorter half-life and body clearance were observed for chloramphenicol compared to florfenicol. Mean volume of distribution, half-life and body clearance were 0.921 L/kg, 100 minutes and 0.018 ml/minute/kg, respectively for chloramphenicol and 0.732 L/kg, 138 minutes and 0.0037 ml/minutes/kg, respectively for florfenicol. Animals treated intramuscularly with chloramphenicol in a dose up to 40 mg/kg for 3 successive days showed inappetance, dullness and some haematological and biochemical alterations. Florfenicol given at a dose of 200 mg/kg intramuscularly for 3 days was well tolerated. It is recommended that use of chloramphenicol should be limited in camel unless there is no other effective antibiotic, and that florfenicol could be a good substitute.

Key words : Camel, chloramphenicol, florfenicol, pharmacokinetic, tolerance

In veterinary medicine, the use of chloramphenicol is restricted to non-food producing animals. It should be used to treat individuals rather than a group of animals (Yolande, 2001). It is active against rickettsial and chlamydial infections, majority of anaerobes, most of the Gram-positive aerobes, and non-enteric aerobes. Clinical use of chloramphenicol has declined because of serious adverse effects which include - bone marrow suppression, aplastic anemia and hemolytic anemia (Ramachandran, 2000). Toxic effects in animals are uncommon. However, young animals and cats are the most sensitive to intoxication (Watson, 1980). Florfenicol, a fluorinated analogue of chloramphenicol, shares the general properties of the parent substance but is less liable to produce serious adverse effects (Ramachandran, 2000). The kinetics and tolerance of chloramphenicol have been studied in goats (Etuk and Onyeyili, 2005; Etuk *et al*, 2005), neonatal calves (Burrows *et al*, 1984), mare (Gronwall *et al*, 1986) and cats (Watson, 1980). Like wise florfenical have been studied in goats, horses, cattle, sheep and camels (McKellar and Varma, 1996; Varma *et al*, 1998; Atef *et al*, 2001; Ali *et al*, 2003), but kinetics and toletrance of both drugs have never been compared in camels. This study is planned to investigate these parameters in the camels.

Materials and Methods

Pharmacokinetic studies

Animals and Preparations

Eight adult camels (*Camelus dromedarius*) were used for pharmacokinetic studies of chloramphenicol and florfenicol. The animals had free access to food and drinking water. Jugular vein of animals was canulated under strict aseptic conditions with plastic canula No. 90 (Portex Ltd, England) for administration of drugs and collection of blood samples.

Drug administration

A single dose of chloramphenicol succinate (Chloromycetin succinate, Parke-Davis, Pontypool, UK) or florfenicol (Nuflor, Schering-Plough, LaGrindoLiere, France) was injected intravenously (i.v) at a dose of 5 mg/kg body weight.

Collection of blood samples

Blood samples (5ml) were collected in heparinised tubes at 0, 5, 10, 15, 30 minutes and at 2, 4, 6, 9 and 12 hours, post-treatment. The blood samples were centrifuged at 2000 x g and the plasma was separated and stored at -20°C for analysis.

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Chloramphenicol and florfenicol analysis

Drug concentrations were measured in the blood by a bioassay technique using *Bacillus subtillis* as the test organism as described by Arret *et al* (1971) and Entenza *et al* (1999). Aliquots of 100 µl from either standard or unknown samples were added in triplicate to the wells in the assay dish. The lower detectable limit of chloramphenicol and florfenicol was 0.05 µg/ml. The inter-assay coefficient of variations were < 8% (n=10) for the range 0.10 to 10 µg/ml. The plasma chloram-phenicol and florfenicol versus time data were analysed by using WinNonlin (Pharsight Corporation 299 California Avenue, Palo Alto., CA, USA). A two-compartment open model with first order absorption provided the best fit of individual animal data based on the Akaike information criterion.

Tolorance studies

Twenty one male and female camels aged 4-5 years and weighing 300-400 kg body weight were used. They were fed daily with 2 kg of mixture of barley and wheat bran with hay, water was provided *ad libitum*.

Animals were divided randomly into 7 groups of 3 animals each. Animals in group 1 were kept as untreated control. Animals in group 2, 3 and 4 were injected intramuscularly (i.m) chlorampheni-col succinate at a dose of 4, 20 and 40 mg/kg body weight daily for 3 successive days, respectively. Animals in group 5, 6 and 7 were injected i.m. florfenicol at a dose 20, 100 and 200 mg/kg body weight daily for 3 successive days, respectively.

All the animals were observed for clinical signs. Blood samples were collected on days 1, 3 and 7 of experiment in heparinised tubes for haematological measurment and into plain tubes to obtain serum for biochemical measurements.

Serum total proteins, glucose, aspartate aminotransferase, lactic dehydrogenase, creatine kinase and blood urea nitrogen were determined by Clinical Chemistry Analyser (Roche Products, Herts, UK) using specific kits. The heparinised samples were analysed within 24 hours of collection for haematology variables including total leucocytes count (TLC), red blood cells (RBC), haemoglobin (Hb) and packed cell volume (PCV) using veterinary Automated Haematology (Roche Products, Herts, UK).

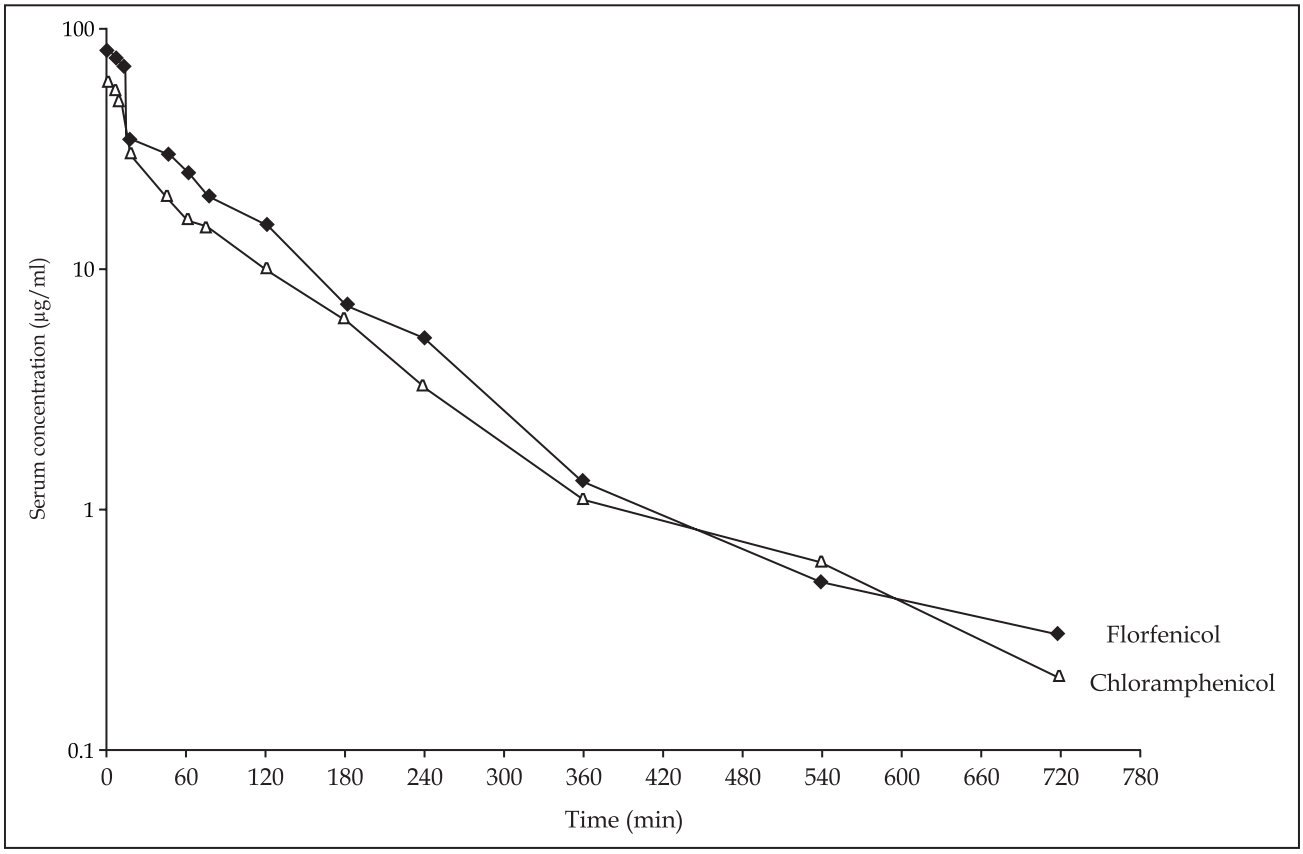

Fig 1. Mean semi-log serum concentrations of chloramphenicol and florfenicol versus time following intravenous (i.v) administration of a single dose of 5 mg/kg body weights to healthy camels. (n = 8 each).

Table 1. Pharmacokinetic parameters describing the disposition of chloramphenicol and florfenicol in camels after a single intravenous (i.v) bolus of 5 mg/kg body weight (n = 8 each).

Disposition Parameters	Values	
	Chloramphenicol	Florfenicol
C_o (µg/ml)	60.3±9.2	78.6±12.1
α (min^{-1})	0.08121±0.021	0.0035±0.00121
β (min^{-1})	0.0044±0.001	0.00305±0.00612
$t_{½}$ α (min)	8.1*±1.5	12.2*±2.1
$t_{½}$ β (min)	100*±15	138*±20
$V_{d\ (area)}$ (L/kg)	0.921*±0.051	0.732*±0.021
Cl_B (ml/min/kg)	0.081*±0.005	0.0037*±0.0012

C_o = Initial concentration in plasma calculated from the serum of coefficents (A and B);
α and β = distribution and elimination constant;
$t_{½}$ α and $t_{½}$ β = distribution and elimination half-lives;
$V_{d\ (area)}$ = volume of drug distribution;
Cl_B = total body clearance.
* P < 0.5

Table 2. Haematological values of camels treated intramus-cularly (i.m) with chloramphenicol (C) or florfenicol (F).

Drugs	Blood parameters				
	Day	PCV (p/L)	RBC (10^{12}/L)	Hb (gd/L)	TLC (10^9/L)
Group-1 0 mg/kg (control)	1	29.1±2.1	7.6±0.3	11.6±0.3	10.1±0.1
	3	30.2±1.6	7.4±0.4	11.1±0.3	10.2±0.3
	7	28.1±1.7	7.6±0.3	11.4±0.3	10.3±±0.4
Group-2 4 mg/kg (C)	1	29±1.4	7.7±0.2	11.5±0.2	10.4±0.4
	3	28±2.1	7.8±0.1	12.1±0.3	10.3±0.2
	7	30.1±2.1	7.6±0.1	12.5±0.2	10.1±0.3
Group-3 20 mg/kg (C)	1	29.2±1.9	7.9±0.2	12.1±0.1	10.4±0.1
	3	28±1.4	7.4±0.1	11.6±0.2	10.5±0.1
	7	30±1.2	7.6±0.1	11.3±0.2	10.4±0.2
Group-4 40 mg/kg (C)	1	29±1.3	7.6±0.3	11.6±0.1	10.3±0.1
	3	32.1±1.9	7.3±0.1	10.1±0.3	9.5±0.1
	7	33*±1.4	5.6±*0.1	9.3*0.3	8.3*±0.1
Group-5 20 mg/kg (F)	1	30±1.5	7.6±0.2	11.3±0.2	10.3±0.2
	3	29±2.1	7.4±0.2	12.1±0.1	10.1±0.1
	7	29±1.6	7.5±0.1	11.4±0.2	10.2±0.1
Group-6 100 mg/kg (F)	1	29±1.6	7.3±0.2	11.6±0.1	10.4±0.2
	3	30±1.5	7.6±0.1	11.5±0.1	10.1±0.1
	7	30±1.6	7.5±0.2	12.1±0.3	10.3±0.2
Group-7 200 mg/kg (F)	1	30.1.7	7.7±0.2	12.3±0.1	10.2±0.2
	3	31±1.6	7.6±0.1	11.9±0.1	10.4±0.2
	7	31±1.9	7.6±0.1	11.8±0.2	10.2±0.1

PCV = Packed Cell Volume; RBC = Red Blood Cells Count;
Hb = Haemoglobin; TLC = Total Leucocyte Count. * P < 0.5.

Statistical analysis

Student's t-test for paired data was used to determine whether there was significant difference between the mean values (Kirkwood, 1988).

Results

Pharmacokinetic studies

Fig 1 shows the time versus concentration plot of the date points and the line predicted by the mean parameter values using a two-compartment model with first order absorption and elimination.

Pharmacokinetic parameters describing the dispostion of both the drugs are given in Table 1. Significantly (p < 0.05) higher volume of distribution and shorter half-life were reported for chloramphenicol compared to florfenicol. Longer body clearance was reported for florfenicol compared to chloramphenicol.

Tolerance studies

Results of tolerance studies are shown in table 2 and 3. Only camels in group 4 which received 40 mg/kg body weight ate less, became dull and had a depressed appetite on days 3 and 7 of the experimental period. Haematological changes due to chloramphenicol or florfenicol treatment are shown in Table 2. The PCV significantly (p < 0.5) increased while RBC, Hb and TLC significantly (p < 0.05) decreased in animals of group 4. Serum biochemical values showed decreased glucose and protein (p < 0.05) on days 3 and 7 of experimental period in group 4 compared to controls (Table 3). No other animals showed any clinical, haematological or serum biochemical changes.

Discussion

Intravenous administration of both chloramphenicol and florfenicol in camels at a dose of 5 mg/kg body weight produced high serum concentration of antibiotics in the camel exceeding above the widely accepted 5 and 1 mg/ml minimal inhibitory concentration values for chloramphenicol and florfenicol, respectively (Burrows *et al*, 1984; Soback *et al*, 1995). Plasma levels above the

Table 3. Serum biochemical values of camels treated intramuscularly (i.m) with chloramphenicol (C) or florfenicol (F).

Drugs	Serum biochemical parameters						
	Day	TP (mg/dl)	Glu (mg/dl)	AST (IU/L)	LDH (IU/L)	CK (IU/L)	BUN (mg/dl)
Group-1 0 mg/kg (control)	1	5.3±0.3	122±10	6.3±0.4	139±12	68±3	6.6±0.5
	3	5.2±0.2	115±10	6.2±0.5	138±14	62±4	6.2±0.7
	7	5.4±0.2	112±11	6.4±0.6	133±16	64±6	6.7±0.8
Group-2 4 mg/kg (C)	1	5.5±0.2	110±11	6.5±0.4	125±12	71±8	6.3±0.3
	3	5.3±0.3	110±10	6.4±0.7	123±14	79±2	7.2±0.2
	7	5.4±0.1	112±9	6.5±0.5	131±16	73±4	6.3±0.4
Group-3 20 mg/kg (C)	1	5.5±0.1	116±10	6.4±0.6	134±16	65±6	6.4±0.5
	3	5.3±0.1	117±10	6.4±0.3	135±17	62±8	6.5±0.6
	7	5.2±0.2	110±10	6.5±0.4	136±14	64±5	7.1±0.6
Group-4 40 mg/kg (C)	1	5.3±0.3	110±10	6.6±0.1	132±19	65±3	6.8±0.2
	3	4.1*±0.2	93*±11	6.3±0.2	131±20	61±4	7.2±0.6
	7	4.0*±0.1	84*±11	6.4±0.7	131±12	63±5	6.6±0.4
Group-5 20 mg/kg (F)	1	5.1±0.2	109±9	6.6±0.4	132±13	64±5	6.6±0.5
	3	5.1±0.3	111±9	6.4±0.6	126±11	65±6	6.5±0.3
	7	5.3±0.1	112±9	6.3±0.5	122±12	66±3	6.3±0.2
Group-6 100 mg/kg (F)	1	5.3±0.1	112±11	6.5±0.3	124±14	67±4	6.6±0.2
	3	5.5±0.1	112±10	6.4±0.4	125±15	68±5	7.1±0.4
	7	5.3±0.2	111±10	6.6±0.1	126±14	71±2	6.6±0.5
Group-7 200 mg/kg (F)	1	5.1±0.2	112±11	6.4±0.1	124±16	62±2	6.8±0.6
	3	5.2±0.1	112±11	6.5±0.2	129±12	67±4	6.7±0.2
	7	5.3±0.2	110±11	6.4±0.5	128±13	68±3	6.8±0.4

TP = Total Protein; Glu = Glucose; AST = Aspertate Aminotransferase, LDH = Lactic Dehydrogenase; CK = Creatine Kinase; BUN = Blood Urea Nitrogen. * $P < 0.05$.

MIC values were maintained for 3 and 9 hours for chloramphenicol and florfenicol, respectively.

Present study revealed that florfenicol had a longer elimination half-life and lower clearance than chloramphenicol. Lower values of t½ and body clearance were reported in equines (Gronwall *et al*, 1986; Baggot, 1995; Mckellar and Varma, 1996). Lower value of t½ of chloramphenicol and florfenicol have also been reported in goats (Atef *et al*, 2001; Etuk *et al*, 2005). The longer half-life of chloramphenicol and florfenicol compared with other species may be due to lower concentration of glucurination process (Elsheikh *et al*, 1988) required for chloramphenicol metabolism manifested by camel compared to other species. However, chloramphenicol has a higher volume of distribution than florfenicol in the camel, and therefore may distribute into tissue compartments more readily (Baggot, 1977). The smaller volume of distribution of florfenicol than chloramphenicol in camels may be attributed to increase polarity conferred by sulfonyl methyl group compared to the nitro group of chloramphenicol (Bretzlaff *et al*, 1987).

In the present study florfenicol was well toleranced following even administration of very high doses of 200 mg/kg for three consecutive days. Similar observations have been reported in equines (Mckellar and Varma, 1996). Chloramphenicol given repeatedly at a dose of 40 mg/kg produced some toxic effect such as inappetance, dullness, increased PCV, decreased RBC, Hb, TLC and serum protein and glucose. Similar haematological observations have been reported for cats (Watson and Middleton, 1978). Milder haematological effects after administration of 225 mg/kg have been observed in dogs (Watson, 1977).

Among domestic animals cats and newborn animals are considered most susceptible to chloramphenicol toxicosis because these are defecient in glucuronide conjugation mechanism, the major metabolic pathway for chloramphenicol. Camels, too have relatively glucuronyl transferase enzyme activity (Elsheikh *et al*, 1988).

From the results of present study, it is apparent that florfenicol distributes well into different

body fluids and tissues and has longer biological half life. Good tolerance without any haemo-biochemical effects further adds to it superiority over chloramphenicol. However, further studies regarding higher dose level and bone marrow effects should be caried out to confirm its safety in this species.

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