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. Animals treated intramuscularly with chloramphenicol in a dose up to 40 mg/kg for 3 successive days showed inappetance, dullness and some hematological and biochemical alterations. Florfenicol given at a dose of 200 mg/kg for 3 days was well tolerated. It is suggested that further studies using higher doses of florfenicol and its effect on bone integrity should be performed to confirm its safety in this species.

KEY WORDS: Pharmacokinetic, tolerance, chloramphenicol, florfenicol, camel.

Introduction

Chloramphenicol is a broad-spectrum bacteriostatic antibacterial. Chloramphenicol is used in the treatment of human *Salmonella typhi* infection (typhoide). 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, the majority of anaerobes, most Gram-positive aerobes, and non-enteric aerobes. Enterobacteriaceae are intrinsically susceptible but inactive against *Pseudomonas* spp. (Yolande, 2001). The clinical use of chloramphenicol has declined because of the serious adverse effects associated with its administration, which include: bone marrow suppression, aplastic anemia and hemolytic anemia (Ramachandran, 2000). Bone marrow suppersion has been the most important adverse effect associated with chloramphenicol administration to people. This involves inhibition of erythroid and granulocytic colony forming unit and plastic anaemia (IARC, 1990). Toxic effects in animals are uncommon. However, young animals and cats are the most sensitive to intoxication (Waston, 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). Information regarding pharmacokinetics and their side-effect of Chloramphenicol and its analogue Florfenicol have not been studied in Arabian camels. This study is planned to investigate pharmacokinetic and tolerance of Chloramphenicol and floerfenicol in Arabian camels.

MATERIALS AND METHODS

Pharmacokinetic Studies:

Animals and Preparations:

For study of pharmacokinetic of chloramphenicol and florfenicol, eight camels (*Camelus dromedarius*) were used for each drug. The animals had free access to food and drinking water. Each animal was weighed before the start of each experiment. Animals were canullated under strict aseptic conditions with plastic canulla No. 90 (Portex Ltd, England) for administration of drugs and collection of blood samples.

Drugs 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 of 5ml were collected in heparinizied 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 × g and the plasma was separated and stored at –20 ^{o}C until analysis.

Chloramphenicol and florfenicol analysis:

Drugs concentrations were measured in the blood by a bioassay technique, using *Bacillus subtillis* as test organism as described by Entenza, *et al*. (1999).

B. 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 2kg of mixture of barley and wheal bron with hay, water was proired *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) with chloramphenicol succinate at a dose of 4, 20 and 40 mg/kg

body weight daily for 3 successive days, respectively. Animals in group 6 and 7 were injected i.m. with florfenicol at a dose 20, 100 and 200 mg/kg body weight daily for 3 successive days, respectively.

All animals were observed for clinical signs. Blood was collected on days 1, 3 and 7 of experiment. Blood was either collected into heporinized tubes for haematological measurment or into plain tubes to obtain serum for biochemical measurements.

Serum total protein, 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 heparized samples were analysed within 24 h of collection for haematology variable including Total leucocytes count (TLC), red blood cells (RBC), haemoglobin (Hb) and packed cell volume (PCV) using veterinary Automated Haematology (Roche Products, Herts, UK).

Statistical analysis:

Student's t-test for paired data was used to determine whether there was significant difference between the mean values (Kirkwood, 1988). The probability value $P < 0.05$ was accepted significant.

RESULTS

A. Pharmacokinetics studies:

The experimental data show that the disposition curve for chloramphhenicol and florfenicol could fit a two compartment open model. The disposition curves which show the decline in serum concentration as a function of time are shown in Figure 1 for chloramphenicol and florfenicol.

Pharmacokinetic parameters that describe the dispostion of the drug 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.

B. Tolerance studies:

Results of tolerance studies are shown in Table 2 and 3. Only camels in Group 4 which recived 40 mg/kg body weight ate less, became dull and had a depressed appetite on days 3 and 7 of the experimental period. Haemotological changes due to chloramphenicol or florfenicol treatment are shown in Table-2. PCV, significantly ($P < 0.5$) increased, RBC, Hb and TLC significantly ($P < 0.05$) decreased in these animals (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 at a dose of 5 mg/kg body weight produced high serum concentration of antibiotics in the camel exceeding the widely accepted 5 and 1 μg/ml minimal inhibitory concentration values for chloramphenicol and florfenicol, respectively (Burrows *et al*., 1984; Soback *et al*., 1995). Such concentrations were maintained for 3 and 9 hours for chloramphenicol and florfenicol, respectively. Florfenicol has been reported to have greater *invitro* activity against pathogenic bacteria than chloramphenicol (Neu and Fu, 1980; Syriopoulou *et al*., 1981). The present study show that florfenicol had a longer elemination half-life and lower clearance than chloramphenicol. Lower values of $t_{1/2}$ and body clearance were reported in equines (Gronwall *et al*., 1986; Baggot, 1995; Mckellar and Varma, 1996). Lower value of $t_{1/2}$ of chloramphenicol and florfenicol were also reported in goats (Abdullah and Baggot, 1989; Atef *et al*., 2001). 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 longer volume of distribution than florfenicol in the camel, and therefore may distribute into tissue compartments more readily (Baggot, 1977).

Drugs with a volume of distribution of 0.7L/kg or greater generally distribute well throughout the total body water and this feature is unlikely to limit the therapeutic efficacy of florfenicol (Rang and Dale, 1991). 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 repeated doses of 200mg/kg. Similar observation were reported for 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, TIC and serum protein and glucose. Similar hematological observations have been reported for cats (Watson and Middleton, 1978). Milder hematological effects after a dministration of 225 mg/kg have been observed in dogs (Watson, 1977).

Among domestic animals cats and newborn animals are considered most susceptible to chloramphenicol intoxicosis because of defecient glucuronide conjugation mechanism, the major metabolic pathway for chloramphenicol (Ref.). Camels, too have relatively lower activity of gluconyl transferase enzyme responsible for this metabolic inactivation (Elsheikh *et al*., 1988).

In conclusion, the present study domenstrates that florfenicol has a number of pharmacokinetic characterstics including longer half-life and could be well tolerated by animals more than chlorampenicol. Further studies regarding higher dose level and bone marrow effects should be carried out to confirm its safety in this species.

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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	
	Chloramphenicoal	Florfenical
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	0.0305 ± 0.00612
$t_{1/2}$ α (min)	8.1 ± 1.5	12.2 ± 2.1
$t_{1/2}$ β (min)	100 ± 15	138 ± 20
$V_{d\ (area)}$ (L/kg)	0.921 ± 0.051	0.732 ± 0.021
Cl_B (Ml/min/kg)	0.018 ± 0.005	0.0037 ± 0.0012

C_o = Initial concentration in plasma calculated from the serum of coefficents (A & B); α and β = distribution and elimination constant; $t_{1/2}$ α and $t_{1/2}$ β = distribution and elimination half-lives; $V_{d\ (area)}$ = volume of drug distribution; Cl_B = total body clearance

Table-2: Haematological values of camels treated intramuscularly (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.
* Significant deference ($P < 0.5$).

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 ± 03	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.

* Significant deference ($P < 0.05$).

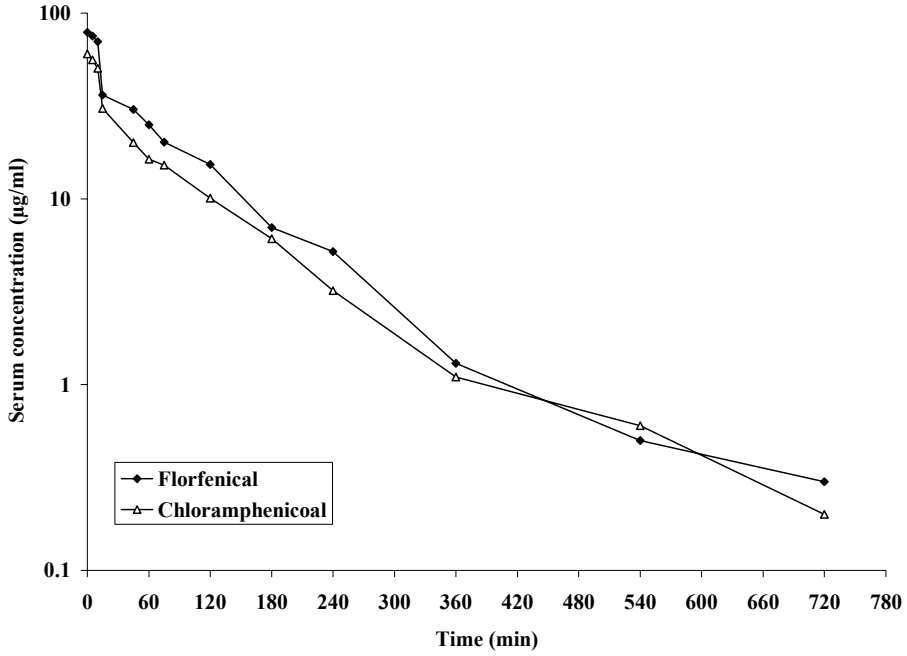

Fig 1: Mean semi-log serum concentrations of chloramphenicol and florfenicol versus time following intravenous (i.v) administration of a single dose of 5 mg/kg body weights to healthy camels. (n. = 8 each).

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الحرائك الدوائية والتحمل للكلورمفينيكول و الفلورفينيكول في الجمال

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الملخص

تم قياس الحرائك الدوائية للكلورمفينيكول و الفلورفينيكول في الجمال بعد حقنها بالوريد بجرعة مقدارها ٥ ملجرام للكيلوجرام. ولقدتم وصف العلاقة بين تركيز الأدوية والوقت المناسب لأختفائها من البلازما بمطابقة موديل الحيزين الحرائكي. فقد كان حجم الانتشار اكبر وعمر النصف والمعدل التصفوي أقصر للكلورمفينيكول بالمقارنة مع الفلورفينيكول. عند حقن هذه الحيوانات بالكلورمفينيكول بجرعة مقدارها ٤٠ ملجرام للكيلوجرام في العضل لمدة ثلاثة ايام متتالية، كانت شبه متوقفه عن الأكل بالأضافة الى بعض التغييرات في المعايير الدموية والبيوكيميائية. أما بالنسبةللفلورفينيكول بعد حقنه بجرعة مقدارها ٢٠٠ ملجرام للكيلوجرام فلم يحدث أي تغييرات. وتم أقتراح أعطاء جرعات اكبر للفلورفينيكول ودراسة تأثيراته على نخاع العظام لتأكد من سلامة استعماله في هذا الحيوان.