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Comparative Pharmacokinetic Studies on Ampicillin in Camels, Sheep and Goats

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Abstract: Kinetics of long-acting ampicillin injected intravenously (IV) at a dose of 4.166 mg kg^{-1} were determined in eight each of camels, sheep and goats. The disposition of ampicillin was described by two-compartment open model. Two elimination half-lives were recorded for the camel (90 min and 33.6 h), whereas in sheep and goat were 101, 103 min, respectively. The peak plasma concentration was 0.80, 0.28 and 0.26 μg ml^{-1} at 5 min in camel, sheep and goat, respectively. The volume of distribution were 2.52, 8.53 and 8.82 for the camels, sheep and goats, respectively. In sheep and goats value of value $t_{1/2}$, v_d and clearance have been found similar but different from camel, indicating exclusive distribution and substantial storage which were consistent with oxytetracycline lipophilicity and the large fat content of camel body.

Key words: Camel, goat, sheep, pharmacokinetic, ampicillin

Introduction

Ampicillin is a broad spectrum aminopenicillin which is extensively used in the treatment of bacterial diseases in animal species (Escudero *et al.*, 2002). Ampicillin in common with cell wall synthesis and disrupting bacterial cell wall integrity (Tomasz, 1979; Russell and Chopra, 1990). It is used for the treatment of many bacterial infections caused by Gram-positive and Gram-negative organisms, their wide safety margin and relatively low price make this penicillin a popular choice for the treatment of animal infections (Baggot and Prescott, 1987; Vaden and Riviere, 2001). The drug has been shown to be effective in the treatment of many conditions including respiratory, urinary tract, meningitis, skin and synovial infections or septicaemia (Baggot and Prescott, 1987 ; Furr, 1989; Dowell *et al.*, 1999; Ehinger and Kietzmann, 2000; Vaden and Riviere, 2001). There are wide variations in the recommended dosage for ampicillin and it may be appropriate to adjust the dose for specific cases depending on the severity of the infections, susceptibility of the pathogens and the site of infection (Sarasola and Mckellar, 1994; Ehinger and Kietzmann, 2000; Escudero *et al.*, 2002; Vaden and Riviere, 2001; Ortiz *et al.*, 2002). Several studies have down shown that the Pharmacokinetic behavior, optimal dosage, plasma half-life, renal clearance and urinary excretion of the investigated drugs were different under indigenous when compared with values given in the literature or in the

product inserts supplied by manufacturers. For example drug manufactures give no specific recommendations for the camel. Therefore, the doses used clinically in this species are in general extrapolated from doses recommended for large domestic species. This is not without danger, because toxic effects sometimes occur in camels which are given certain drugs at doses apparently harmless to other species (Homeida *et al.*, 1981; Ali *et al.*, 1996; Al-Dughaym *et al.*, 1998). This study was planned to investigate pharmacokinetics of ampicillin in camels, sheep and goats following IV injections of a single dose (5 mg kg^{-1}).

Materials and Methods

Animals: Eight clinically healthy male and female (4 each) of camels (*Camelus dromedarius*), aged 3-6 years and weighed between 200-320 kg, goats of Ardi breed aged 3-4 years and weighed between 45-55 kg and sheep of Neimi breed aged 2-3 years and weighed between 60-65 kg were used in this study. The animals were allowed to rest for certain time to make sure none of them had received any medication for at least 8 weeks prior ampicillin administrations, Water, hay and concentrate supplements were provided *ad libitum*.

Drugs administration: A ampicillin (Sigma, UK) solution was administered as a bolus intravenously (IV) injection at a dose of 4.166 mg kg^{-1} body weight to animal tested.

Blood samples were collected from the jugular vein in heparinized tubes prior to drugs administration and at 5,10,15, 30 and 45 min., 1, 2, 3, 4, 5, 6, 7, 8, 10, 24, 48, 72, 96 and 120 h after drug administration, The blood samples were allowed to clot, serum was separated by centrifugation (120 x g for 5 min) and was stored at -20 °C until analysis. A ampicillin was estimated by the method of Ali (1981). Trichloracetic acid was used for deproteinization and acidification of samples. Fluorescence was measured in spectrophotometer (Pyunicam, England) at wavelength of 320 nm.

Pharmacokinetic analysis: Kinetic parameter were calculated. Mean values and variables were calculated. Analysis of variance (ANOVA) was performed with species as treatments. When a significant F value was obtained, Duncan's Multiple Range Test was used to determine which species is different from the other in case of significant results.

Results

The mean peripheral plasma concentration of ampicillin in camels, sheep and goats receiving a single IV dose of 4.166 mg kg^{-1} body weight of Na-ampicillin versus time are best filled to a two-compartment open model (Fig. 1).Values of the kinetic parameter which describe the disposition of ampicillin in the 3 animals are presented in Table 1. Two elimination half-lives were recorded for the camel (t $_{1/2}$ β_1= 90 minutes and t$_{1/2}$ β_2=33.6 h). Elimination half-lives in sheep and goat were 101 and 103 min., respectively. The disappearance of Na-ampicillin from plasma in the 3 species was steep and reflects the processes involves in the distribution of the drug from central to peripheral compartment with a t$_{1/2}$ α of 18.9, 19.9, and 20.3 minutes in camels, sheep and goats, respectively.

In camel there was an increase of ampicillin plasma concentration about 4-5 h post-injection reached a maximum of 0.4 µg ml^{-1} at 8 h post-injection and then declined thereafter producing a trough-like pattern. The new half-life of this elimination phase was 33.3 h. Such pattern was absent in plasma of sheep and goat. The volume of distribution was 2.5 in camels, 8.5 in sheep and 8.8 L kg^{-1} in goat.

Discussion

Compared with other penicillin group, ampicillin is less ionized, more lipid soluble and thus penetrate cell membrane more readily, in addition to its wide spectrum of antibacterial activity (Brander *et al.*, 1985). The pharmacokinetic of ampicillin in camels characteristically demonstrates a longer half-life especially at the latter part
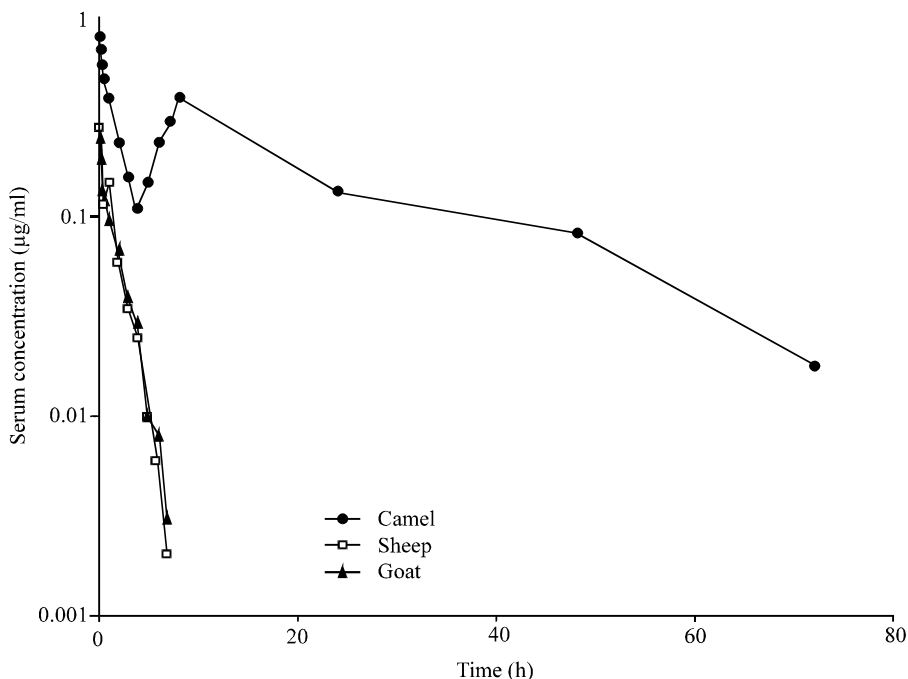

Fig. 1: The semilogarthmic plot of ampicillin sodium concentration in plasma Versus time following IV administration of a single dose of 4.166 µg kg^{-1} To camel, sheep and goats. (n=8 each)

Table 1: Pharmacokinetic parameters of Na-ampicillin in camels, sheep and goat after a single IV bolus of 4.166 mg/kg body weight.(n=8 each)

Disposition Parameters	Camels	Sheep	Goat
$C_{max}(\mu g\ ml^{-1})$	0.80*	0.25	0.26
$T_{max}(min)$	50.00*	2.10	2.30
$A\ (\mu g\ ml^{-1})$	0.30	0.15	0.20
$B\ (\mu g\ ml^{-1})$	0.60*	0.20	0.15
$C_p^{o}\ (\mu g\ ml^{-1})$	0.90*	0.40	0.35
$T_{1/2}\ (\alpha)\ (min)$	18.90	19.90	20.30
$T_{1/2}\ (\beta 1)\ (min)$	90.00	101.00	103.00
$T_{1/2}\ (\beta 2)\ (h)$	33.30	-	-
$K_{12}\ (min^{-1})$	0.00692	0.00922	0.00997
$K_{21}(min^{-1})$	0.02703	0.01656	0.01846
$K_{el}(min^{-1})$	0.01045	0.01156	0.01237
$V_d\ (area)\ (L\ kg^{-1})$	2.5192*	8.5311	8.2216
$C_{1B}\ (ml/kg/min)$	0.0194	0.0611	0.0591

C_{max}	=	peak concentration
T_{max}	=	time of peak
A	=	zero-time intercept of distribution phase
B	=	zero-time intercept of elimination phase
C_p^{o}	=	plasma drug concentration at time zero after drug administration;
$t_{1/2}(\alpha)$	=	half-life of distribution phase;
$t_{1/2}(\beta_1)$,		
$t_{1/2}(\beta_2)$	=	elimination half-lives of phase I&II, respectively;
K_{12}	=	rate of transfer of drug from central to peripheral compartments;
K_{21}	=	rate of drug from peripheral to central compartments;
K_{cl}	=	elimination rate constant from central compartment;
$V_d\ (area)$	=	volume of drug distribution;
C_{1B}	=	total body clearance of the drug.

* statistically significant difference (P< 0.05).

of elimination curve and has a high volume of distribution which is similar to buffaloes (Khanikor *et al.*, 1986) indicating that there is very good penetration of the drug in the body compartments. However a much higher values of volume distribution was observed in sheep and goats. Pharmacokinetic values reported in the study for sheep and goats are similar to other studies else where (Mercer *et al.*, 1978).

Administrations ampicillin to camels resulted in two elimination half-lives and plasma levels showed a characteristic peak and trough profile as well as biphasic elimination after IV dosing indicating extensive tissue distribution and/or substantial storage, or both, which were consistent with ampicillin high polarity and large fat content of the camel body, The peak and trough phenomenon may result from absorption form the kidney or bladder as it has been shown that antibiotics are extensively reabsorbed form urinary tract in ruminant species (Nouws *et al.*, 1986). In addition it is demonstrated by morphometry that the nephron in the camel is twice as ling as that in the goat and sheep (Abdalla and Abdalla, 1979) confirming the suggestion that such phenomenon may occur as a result of anatomical difference.

The plasma levels of a drug are at least in part an index of drug's potential therapeutic efficacy (Gilman *et al.*, 1991). Therefore, it is very important to appreciate to what extent drug formulation for animal species affects the potential therapeutic results, i.e. The likelihood of a dose achieving plasma drug levels equal to or higher than minimum inhibitory concentration (MIC) for majority of pathogenic bacteria involved, The MIC for bacteria sensitive to ampicillin concentration is ranging between 0.01 and 0.2 $\mu g\ ml^{-1}$ (Hariharan and Barnum, 1974). This level was produced at 5 minutes post-injections in the 3 species and maintained above MIC for the whole period of sampling in camel (120 h) and for only 6 hours in sheep and goats, suggesting that a lower level dosage and frequency should be adopted for the camel. In conclusions, indigenous sheep and goats values of $t_{1/2}$, V_d and clearance have been found similar in ampicillin compared to their respective counterparts, Also, due to significant differences in pharmacokinetic parameters of ampicillin between different animal species (camel, sheep. goat), extrapolation of doses of drug from one species to another should be avoided.

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