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PHARMACOKINETICS AND BIOAVAILABILITY OF GENTAMICIN AFTER A SINGLE INTRAVENOUS AND INTRAMUSCULAR ADMINISTRATION IN CAMELS (*Camelus dromedarius*)

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ABSTRACT

The pharmacokinetics and bioavailability of gentamicin sulphate (3 mg/kg body weight) were studied in 5 healthy male camels *(Camelus dromedarius)* after a single intravenous (IV) and intramuscular (IM) administration according to a cross-over randomised design. Gentamicin concentrations were determined using a microbiological assay and *Bacillus subtillis* (ATCC 6633) as a test organism. The disposition curves were analysed using non-compartmental methods based on statistical moment theory. Following single IV administration, the elimination half-life ($t_{1//2}b$), mean residence time (MRT), volume of distribution at steady state (Vd_{ss}), volume of distribution (Vd_{area}) and the total body clearance (Cl_B) were 5.98±0.42 h, 6.73±0.37 h, 0.28±0.02 l/kg, 0.36±0.02 l/kg and 0.71±0.02 ml/min/kg, respectively. After a single IM administration, the maximum plasma concentrations (C_{max}) was 6.26±0.36 mg/ml achieved at (t_{max}) 2h post-injection time. The $t_{1//2}b$, MRT, Vd_{area}, Cl_B and the absolute bioavailability (F) were 5.24±0.31 h, 7.87±0.35 h, 0.42±0.03 l/kg, 0.95±0.05 ml/min/kg and 75.56±4.92%, respectively. Based on these kinetics parameters, a dosage of 3 mg/kg by IM and IV administration every 24 h can be recommended for the treatment of bacterial infections in camels with MIC_{90} ³ 0.75 and 3.75 mg/ml, respectively.

Key words: *Bacillus subtilis*, bioavailability, camels, gentamicin, microbiological assay, pharmacokinetics

Gentamicin, a well-known aminoglycoside antibiotic, is widely used to treat serious bacterial infections in different species of animals including camels. It has broad-spectrum of activity against aerobic Gram-negative microorganisms such as *E. coli, Klebsiella* spp., *Pseudomonas aeruginosa, Salmonella* spp. and some Gram-positive bacterial species (Houdeshell *et al*, 1982; Gilbert, 1991). Gentamicin like other aminoglycosides displays a concentration-dependent bactericidal activity (Drusano, 2004). The peak drug concentration (C_{max}) to minimum inhibitory concentration (MIC) ratio (C_{max}:MIC) has been shown to be the most useful pharmacokinetics/ pharmacodynamics (PK/PD) parameters for predicting clinical efficacy of aminoglycosides (Mckellar *et al*, 2004). Gentamicin concentration of not less than 8-10 fold of *in vitro* MIC is associated with effective bacterial killing (Gunderson *et al*, 2001; Albarellos *et al*, 2004). Gentamicin has narrow range between toxic and therapeutic dose, therefore careful monitoring of plasma gentamicin levels is indicated (Ladislav, 1999). Gentamicin is not absorbed from gastrointestinal tract; nevertheless it is rapidly absorbed after intramuscular (IM) and subcutaneous (SC) administration that revealed 70-100% bioavailability (Brown and Riviere, 1991; Riviere and Spoo, 1995).

Several pharmacokinetics data have been previously reported in different animal species including cattle (Ziv *et al*, 1982; Clarke *et al*, 1985), buffalo calves (Garg *et al*, 1991a, 1991b), sheep (Wilson *et al*, 1981; Brown *et al*, 1986), goats (Garg *et al*, 1995), horses (Pedersoli *et al*, 1980), dogs (Riviere and Coppoc, 1981), cats (Jernigan *et al*, 1988) and avian species (Haritova *et al*, 2004). Most of the drugs used in camels depends on PK/PD obtained from other species of animals. This due to lack of information about drug dosage regimens in the camels (Ali *et al*, 1996). The aim of the current study was to determine plasma concentrations and disposition kinetics of gentamicin in camels after a single IV and IM administration and to recommend a rational dosage schedule in camels.

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Materials and Methods

Animals

Five healthy male camels *(Camelus dromedarius)*, 5-15 years old and weighing 450-700 kg, were used in this study. These were reared in a free-range in the eastern desert of Jordan. The animals were fed hay and had free access to water.

Drugs

For IV and IM administration a commercially injectable gentamicin sulphate 4% (GENTAYET, SYVA Laboratories, SPAIN) was used. Working standard powder of gentamicin sulphate was obtained from Veterinary and Agricultural Products Manufacturing Co. Ltd, (VAPCO), Amman, Jordan and was used to prepare standard curves.

Experimental design

Camels were given gentamicin sulphate in a cross-over randomised design with 21 days washout period to ensure complete clearance of the drug. Gentamicin was administrated in a single dose of 3 mg/kg body weight (bw). The drug was intravenously injected into the jugular vein and intramuscularly into the lower 3rd region of the neck.

Collection of samples

Blood samples (5 ml) were collected from the right jugular vein into heparinised tubes just before drug administration (pretreatment) and at 5, 10, 15, 30 minutes and at 1, 2, 3, 5, 8, 12, 18, 24 and 48 h after IV and at 0 (pretreatment), 10, 20, 30 minutes and 1, 1.5, 2, 3, 5, 8, 12, 18, 24 and 48 h after IM administration. Blood samples were centrifuged (1000g, 10 min, 4°C) and plasma stored at –20°C until assayed.

Analytical procedure

Camel plasma samples were assayed for determination of gentamicin concentrations by microbiological assay using Mueller-Hinton agar (Difco Laboratories, Detroit, MI, USA) and *Bacillus subtilis* (ATCC 6633) as test organism as previously described (Tsai and Kondo, 2001). Prior to analysis Mueller-Hinton broth culture containing cell density 10^8 cfu/ml that match 0.5 Mcfarland standard was prepared. The assay agar medium was prepared to contain cell density 10^6 cfu/ml (1ml broth culture per 99 ml melted agar medium). The solutions for the standard curve were prepared by dissolving gentamicin sulphate in distilled water, in a measuring flask to obtain a concentration of 1000 µg/ml. Then double fold serial dilution was done in untreated camel plasma to cover a range from 0.01 to 100 µg/ml. Five wells, 8 mm in diameter, were made in standard petri dishes (120 mm) containing inoculated 25 ml agar. Wells were filled with either plasma samples or gentamicin standard solutions in duplicate manner. Zones of inhibition were measured after 18 h of incubation at 37°C and the concentrations of gentamicin were calculated from the standard curve. The standard curve in camel plasma was linear from 0.2 to 100 µg/ml (R^2 =0.99). The limit of quantification was 0.2 µg/ml.

Pharmacokinetics and Statistical Analysis

The pharmacokinetics analysis of the data was performed using non-compartmental analysis based on statistical moment theory according to the method described by Gibaldi and Perrier (1982), with the help of computerised Topfit® programme (Tanswell and Koup, 1993). The calculated parameters were area under plasma concentration-time curve (AUC) using linear trapezoid method; area under the first moment curve (AUMC); mean residence time (MRT), where MRT= AUMC/AUC; volume of distribution (Vd_{area}), where Vd_{area} = (dose/AUC) b; total body clearance (Cl_B), where Cl_B = dose/AUC; apparent volume of distribution at steady state (V_{ss}), where V_{ss} = MRT x Cl_B; elimination rate (k_{el}) was determined by least-square regression analysis of terminal log-linear portions of the plasma concentration-time profile (k_{el} = 2.303 × slop); elimination half-life ($t_{1/2b}$), where $t_{1/2b} = 0.639/k_{el}$; the maximum concentration (C_{max}) and the corresponding peak time (t_{max}) were determined by the inspection of the individual drug plasma concentration-time profiles. The absolute bioavailability (F) was calculated as ($AUC_{non\text{-}IV}$ / AUC_{IV}) x100. All data are expressed as mean ± SE.

Results

There were no identifiable reaction post gentamicin administration. The mean plasma concentration-time profiles of gentamicin (3 mg/kg bwt) after a single IV and IM administration are shown in Fig 1. Gentamicin was not detected at 24 h post drug administration for both routes in all tested camels plasma. Pharmacokinetics parameters of gentamicin (3 mg/kg bwt) obtained after single IV and IM administration are given in Table 1. After IV injection, the plasma gentamicin concentration was 30.12 µg/ml at 5 min post-injection. The elimination half-life ($t_{1/2b}$), mean residence time (MRT), volume of distribution at steady state (Vd_{ss}), volume of distribution (Vd_{area}) and the total body clearance (Cl_B) were 5.98±0.42 h, 6.73±0.37 h, 0.28±0.02 l/kg, 0.36±0.02 l/kg and 0.71±0.02 ml/min/kg, respectively.

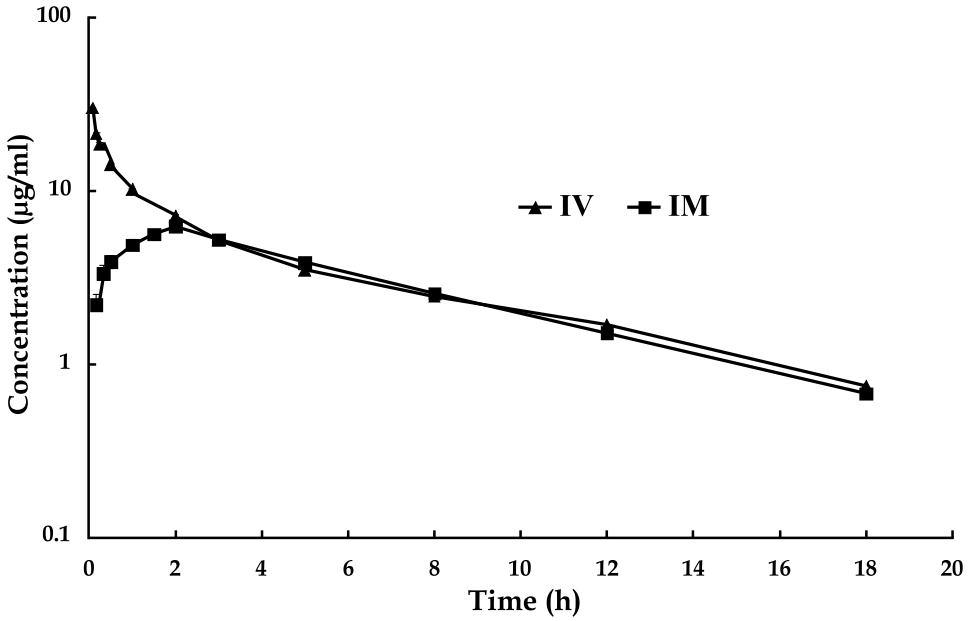

Fig 1. Plasma concentration-time profile (mean ± SE) of gentamicin after IV and IM administration of 3 mg/kg body weight. (n = 5)

Table 1. Pharmacokinetics parameters (mean ± SE) of gentamicin (3 mg/kg bwt) in camels after a single IV and IM administration. (n=5).

Parameters	Units	IV	IM
$t_{1/2b}$	h	5.98±0.42	5.24±0.31
MRT	h	**6.73±0.37**	**7.87±0.53**
Vd_{area}	l/kg	0.36±0.02	0.42±0.03
V_{ss}	l/kg	0.28±0.02	-
CL_B	ml/min/kg	0.71±0.02	0.95±0.05
C_{max}	µg/ml	30.12±0.00	6.26±0.36
t_{max}	h	0.08±0.00	2.00±0.00
AUC_{0-18}	µg.h/ml	64.59±1.51	48.34±2.57
AUC_{0-8}	µg.h/ml	70.92±1.81	53.42±3.17
F	%	-	75.56±4.92

After a single IM administration of gentamicin (3 mg/kg bwt), the drug reached a peak plasma concentration of 6.26±0.36 µg/ml at (t_{max}) 2 h. The $t_{1/2b}$, MRT, Vd_{area}, Cl_B and the absolute bioavailability (F) were 5.24±0.31 h, 7.87±0.35 h, 0.42±0.03 l/kg, 0.95±0.05 ml/min/kg and 75.56±4.92%, respectively.

Disscussion

Gentamicin was introduced in 1960 and still considered to be the drug of choice for treatment of serious aerobic Gram-negative infections in different animal species including camels (Ali, 1988). The economic importance of the camels obliged the researchers to target it in their pharmacological research. To our knowledge, there are few pharmacokinetics studies that describe the disposition kinetics of gentamicin in camels after different route of administration. Therefore, the dosage of gentamicin used in camels was derived empirically from PK/PD data obtained from other species of animals mainly cattle (Ali *et al*, 1996). This procedure may lead to undesirable effect associated with toxicity (Ali and Hassan, 1986), decrease effectiveness of the drug (Oukessou, 1994) and problems related to public health (e.g. antibiotic residue). Accordingly, the important pharmacokinetics parameters have been calculated at a single dose of 3 mg/kg bwt in camels. The concentrations of gentamicin in camels plasma was determined using a microbiological assay. This method did not distinguish between different gentamicin components. Nevertheless, it measures the total bactericidal activity, which is useful in pharmacodynamic evaluation. The disposition curves of gentamicin (3 mg/kg bwt) after a single IV and IM administration in camels were best described by a non-compartmental model, based on statistical moment theory that permits an accurate calculation of the major pharmacokinetics parameters, avoiding problems encountered in curve fitting.

After a single IV administration of gentamicin (3 mg/kg bwt), the $t_{1/2b}$, (5.98 h) was similar to those reported in buffalo calves (Garg *et al*, 1991a) and different from those found in camels (Ziv *et al*, 1991), higher of lower cattle (Ziv *et al*, 1982; Clarke *et al*, 1985), sheep (Wilson *et al*, 1981; Brown *et al*, 1986), goats (Garg *et al*, 1995) and horses (Pedersoli *et al*, 1980).

The prolonged $t_{1/2b}$ reported in the present study and study conducted by Garg *et al* (1991a) indicate that the drug tends to stay (MRT=6.73) for along time in camels and buffalo calves tissues. Whereas, the differences in $t_{1/2b}$ may be due to drug formulation, dosage and interspecies variation. The value of V_{ss} (0.28) indicates a good extravascular distribution of the drug. This value was parallel to the respective values reported in horses (Pedersoli *et al*, 1980) and pigs (Riond and Riviere, 1988), and moderately higher than those reported in cattle (Clarke *et al*, 1985) and lower than those for sheep (Brown *et al*, 1986).

The Vd_{area} (0.36 l/kg) indicates the low distribution of gentamicin in the body. This small volume of distribution is parallel to those reported in camels (Ziv *et al*, 1991), buffalo calves (Garg *et al*, 1991a), cattle (Clarke *et al*, 1985), sheep (Wilson *et al*, 1981), pigs (Riond and Riviere, 1988) and horses (Pedersoli *et al*, 1980), and lower than those reported in 4-5 weeks old cattle (Ziv *et al*, 1982). Gentamicin was slowly cleared out of the body (Cl_B=0.71 ml/min/kg). The reduction in total body clearance in camels may result from the low volume of distribution of gentamicin in the current study. However, these results are in agreement to those reported in sheep (Brown *et al*, 1986) and horses (Bowman *et al*, 1986) and slightly different from those reported in camels (Ziv *et al*, 1991) and cattle (Ziv *et al*, 1982; Clarke *et al*, 1985). The anatomical, biochemical and physiological features that differentiate the camel from other animal species may affect the disposition kinetics of the drugs in the body (Kadir *et al*, 1997). Camels urine is acidic (pH 6.3-7.2) with glomerular filtration rate (GFR) and urine flow of 0.55-0.65 ml/kg/min and 0.70-2.2 l/day, respectively. The nephron in camels is twice as long as that in cows and goats. Subsequently, a lot of water that filtered through the glomerulus will be reabsorbed and thus significantly reduce urine flow (Kumar *et al*, 1998). Moreover, GFR in camels is lower than recorded for other ruminant species (Benlamlih and Depomyers, 1989). In addition, camels have developed a special adaptation with a respect to water metabolism (Etzion and Yagil, 1986).

The curves obtained following single IM administration indicate a slow absorption rate of gentamicin, with a maximum plasma concentration (C_{max}) of 6.26 µg/ml achieved at 2 h (t_{max}). These results are in agreement with those reported in camels (Ziv *et al*, 1991) and pony foals (Gronwall *et al*, 1988) and lower than those reported in buffalo calves (Garg *et al*, 1991b), cows (El-Sayed *et al*, 1989), goats (Garg *et al*, 1995), mares (Swan *et al*, 1995). The $t_{1/2b}$ (5.24 h) was higher than those reported in buffalo calves (Garg *et al*, 1991b), cows (El-Sayed *et al*, 1989), goats (Garg *et al*, 1995), mares (Swan *et al*, 1995), and pony mares (Haddad *et al*, 1985). Gentamicin had a low volume of distribution (Vd_{area}=0.42 l/kg) and slow body clearance (Cl_B=0.71 ml/min/kg). These finding are in agreement with those reported in buffalo calves (Garg *et al*, 1991b) and different from those reported in pony mares (Haddad *et al*, 1985) and goats (Garg *et al*, 1995). Gentamicin clearance decreases as the body weight increases and therefore the dose must be reduced to avoid renal dysfunction (Riviere and Spoo, 1995). The bioavailability (F) of gentamicin after IM administration (75.56%) was within the expected range (70-100%) for aminoglycosides antibiotic. However, the calculated F gained in the current study was lower than those reported in camels (135%) (Ziv *et al*, 1991), goats (96%) (Garg *et al*, 1995), lactating cows (92%) (Haddad *et al*, 1986) and pony mares (87%) (Haddad *et al*, 1985) and higher than those reported in dehydrated camels (54%) (Ziv *et al*, 1991) and cows (70%) (El-Sayed *et al*, 1989). Site of injection and regional blood flow may slow or accelerate the absorption of the drug and subsequently may interfere with the C_{max} and t_{max} that lead eventually to significant variation in the AUC that affect the rate and bioavailability (F) of the drug in the body.

The success of antimicrobial therapy in veterinary as well as in human medicine is greatly determined by the integration between pharmacokinetics and pharmacodynamics (PK/PD) parameters. The PK/PD parameters that have been investigated and correlated with high drug efficacy for the concentration-dependent drugs are the AUC0-24:MIC and C_{max}:MIC of ratios $\geq$ 100 and $\geq$ 8, respectively. Whereas, drug plasma concentration must exceed MIC by 1-5 for > 70% of the inter-dosing interval for the time-dependent agents (Mckellar *et al*, 2004). Gentamicin is a concentration-dependent, whereby the antimicrobial drugs kill bacteria to a greater extent at increasing exposure concentration (C_{max}:MIC $\geq$ 8) (Gunderson *et al*, 2001; Albarellos *et al*, 2004). The minimum inhibitory concentrations (MICs) of microorganisms isolates from camels that are susceptible to gentamicin have not been determined. Recently, we isolated different pathogens from pneumonic lungs of camels with MIC range 0.5-4, 0.25-4, 0.5-8 and 0.25-0.5 µg/ml for *E. coli , Klebsiella* spp., *Pseudomonas aeruginosa* and *Staphylococcus aureus* isolates, respectively (Al-Tarazi and Elsheikh, submitted). The MIC value of 0.75 µg/ml was used along with the C_{max} (6.26 and 30.12 µg/ml for IM and IV, respectively) obtained in

this study for the purpose of calculation of surrogate marker. Accordingly, the C_{max}:MIC of 8.35 and 40.16 are obtained for gentamicin after IM and IV administration, respectively. Based on these kinetics parameters, a dosage of 3 mg/kg by IM and IV administration every 24 h can be recommended for the treatment of bacterial infection in camels with MIC_{90} £ 0.75 and 3.75 µg/ml, respectively.

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