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PHARMACOKINETICS OF GENTAMICIN FOLLOWING SINGLE-DOSE PARENTERAL ADMINISTRATION TO GOATS

S. K. GARG*, S. P. VERMA† and R. P. UPPAL†

*Department of Pharmacology and Toxicology, College of Veterinary and Animal Sciences, H.P. Agricultural University, Palampur-176062, *College of Veterinary Science and Animal Husbandry, Mathura-281001 and †Haryana Agricultural University, Hisar-125004, India*

SUMMARY

The disposition kinetics of parenterally administered gentamicin (5 mg kg^{-1}) has been studied in Gaddi goats. The serum concentration–time profile was described by bi-exponential and mono-exponential equations following intravenous (i.v.), intramuscular (i.m.) and subcutaneous (s.c.) administration with elimination half-life values of 0.96 ± 0.09, 2.37 ± 0.47 and 3.56 ± 0.39 h, respectively. The apparent volume of distribution following i.v. administration (Vd_{area}: 0.26 ± 0.04 l kg^{-1}) reflected limited extracellular distribution of the drug. The bioavailability was higher following i.m. administration (96.3%) compared to s.c. (76.9%). In view of the significantly longer biological half-life and larger area under the curve values, the s.c. route may be preferred. It is concluded that a suitable and practical dosage recommendation for gentamicin in goats would be 3.35 mg kg^{-1} body weight given s.c. at 12 h intervals.

KEYWORDS: Pharmacokinetics; disposition kinetics; gentamicin; goats; dosage regimen.

INTRODUCTION

Gentamicin is effective against majority of the Gram-negative aerobic pathogens isolated from dogs, cats, horses and cattle (Bachmann *et al.*, 1975). At a plasma concentration of 4 μg ml^{-1}, it inhibits most of the sensitive pathogenic organisms regardless of host animal species (Black *et al.*, 1963). Although the pharmacokinetics of gentamicin has been studied in several species including dogs (Riviere & Coppoc, 1981; Riviere *et al.*, 1981; Wilson *et al.*, 1989), cats (Jernigan *et al.*, 1988), pigs (Riond & Riviere, 1988), sheep (Brown *et al.*, 1985, 1986; Garg *et al.*, 1990), cattle (Clarke *et al.*, 1985; Haddad *et al.*, 1986; Burrows *et al.*, 1987) and

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buffaloes (Garg & Garg, 1989; Garg *et al.*, 1991a, b), no data are apparently available for goats.

MATERIALS AND METHODS

Five healthy female Gaddi goats weighing 12–16.5 kg were acclimatized for 10 days prior to the start of the experiment. Animals were maintained on locally available forage, concentrates and minerals, and water was available *ad lib.*

Gentamicin sulphate (Hindustan Antibiotics Ltd, India) was administered at a dose of 5 mg kg^{-1} body weight by the intravenous (i.v.) and intramuscular (i.m.) route in the neck region and subcutaneous (s.c.) route in the caudo lateral aspect of the thigh region. An intervening wash-out period of 21 days was allowed between different routes of drug administration. Jugular blood samples were collected at 2.5, 5, 10, 20 and 40 min and at 1, 1.5, 2, 4, 6, 8, 12 and 24 h following i.v. administration but after i.m. and s.c. administration, the 2.5 min sample was omitted. Serum was separated and stored at −20°C until assayed.

Concentration of gentamicin in serum was measured using the ^{125}I-labelled solid phase Coat-A-Count radioimmunoassay kits (Diagnostic Products Corporation). Sensitivity of the assay was 0.10 μg ml^{-1}.

The serum gentamicin concentrations as a function of time in individual goats were analysed with the aid of curve stripping (to determine whether data can best be described by a mono-, bi- or tri-exponential equation) and by non-linear least squares regression (SASNONLIN) computer programs. Relevant pharmacokinetic parameters were calculated using standard equations (Gibaldi & Perrier, 1975; Baggot, 1977). Data were analysed statistically using Student's *t*-test. Based on the disposition kinetic data, the dosage regimens were computed (Notari, 1980).

RESULTS

Results are presented as mean ± SEM. The peak serum concentrations of gentamicin were 53.51 ± 8.66 μg ml^{-1} 2.5 min after i.v. administration and 33.97 ± 4.37 and 27.97 ± 3.84 μg ml^{-1} at 40 min following i.m. or s.c. administration, respectively (Table I). A concentration ≥2 μg ml^{-1} was maintained for 2, 6 and 8 h after administration by all the routes.

The pharmacokinetic parameters following different routes of drug administration are presented in Table II. Following i.v. administration, the serum drug concentration declined rapidly during the initial disposition phase, with a very short distribution half-life of 0.04 ± 0.01 h; the elimination half-life was 0.96 ± 0.09 h. Gentamicin had an apparent volume of distribution of 0.26 ± 0.04 l kg^{-1} and the total body clearance was 3.10 ± 0.27 ml kg^{-1} min^{-1}. Following i.m. or s.c. administration, gentamicin achieved high serum concentration within 5 min suggesting rapid absorption. The biological half-life with s.c. administration (3.56 ± 0.39 h) was significantly longer ($P<0.05$) than following i.m. administration (2.37 ± 0.47 h). The bioavailability following administration by i.m. and s.c. routes was 96.27 and 76.88%, respectively.

Table I

Serum concentrations (μg ml^{-1}) of gentamicin in goats following a single intravenous (i.v), intramuscular (i.m.) and subcutaneous (s.c.) dose of 5 mg kg^{-1} body weight

Time after administration	*Route of administration*		
	i.v.	*i.m.*	*s.c.*
2.5 min	53.51 ± 8.66	—	—
5.0 min	27.71 ± 5.24	16.60 ± 4.48	15.09 ± 3.58
10.0 min	20.35 ± 4.45	18.83 ± 3.90	18.17 ± 4.17
20.0 min	15.53 ± 1.80	23.39 ± 4.10	20.25 ± 5.09
40.0 min	10.42 ± 1.19	33.97 ± 4.37	27.97 ± 3.84
1.0 h	8.53 ± 1.06	19.70 ± 2.69	18.14 ± 4.19
1.5 h	6.90 ± 1.03	15.00 ± 2.50	14.53 ± 4.04
2.0 h	4.09 ± 0.32	11.30 ± 2.23	14.45 ± 3.32
4.0 h	1.54 ± 0.24	4.80 ± 1.96	7.98 ± 3.04
6.0 h	0.19 ± 0.08	2.54 ± 1.33	5.16 ± 1.15
8.0 h	0.14 ± 0.02	1.73 ± 0.92	2.85 ± 0.61
12.0 h	ND	0.61 ± 0.58	1.90 ± 0.54

Data presented are mean ± SE of five animals.
ND, not detected.

Table II

Pharmacokinetic parameters of gentamicin in goats after a single intravenous (i.v.) intramuscular (i.m.) and subcutaneous (s.c.) dose of 5 mg kg^{-1} body weight

Pharmacokinetic parameters	*Route of administration*		
	i.v.	*i.m.*	*s.c.*
C^0_p (μg ml^{-1})	235.36 ± 95.89	—	—
A (μg ml^{-1})	217.68 ± 97.41	—	—
α (h^{-1})	39.37 ± 13.02	—	—
$t_{\frac{1}{2}\alpha}$ (h)	0.04 ± 0.01	—	—
B (μg ml^{-1})	17.68 ± 1.75	20.00 ± 6.23	17.10 ± 2.66
β (h^{-1})	0.75 ± 0.06	0.36 ± 0.08	0.21 ± 0.02
$t_{\frac{1}{2}\beta}$ (h)	0.96 ± 0.09	2.37 ± 0.47	*3.56 ± 0.39
AUC (μg min^{-1} ml^{-1})	1659.70 ± 144.9	3328.80 ± 936.4	4556.0 ± 1028.3
Vd_{area} (l kg^{-1})	0.26 ± 0.037	—	—
CL_B (ml kg^{-1} min^{-1})	3.10 ± 0.27	—	—
C_{max} (μg ml^{-1})	—	33.97 ± 4.37	27.97 ± 3.84
t_{max} (h)	—	0.66 ± 0.00	0.66 ± 0.00
F (%)	—	96.27	76.88

Data are mean ± SE of five animals.
*$P<0.05$.

Key to the pharmacokinetic parameters: C^0_p, serum drug concentration immediately following i.v. injection of single dose; A, zero-time serum drug concentration, intercept of regression line of distribution phase; α, overall distribution rate constant; $t_{\frac{1}{2}\alpha}$, distribution half-life; B, zero-time serum drug concentration, intercept of regression line of elimination phase; β, overall elimination rate constant; $t_{\frac{1}{2}\beta}$, elimination half-life; AUC, area under the curve; total area under the serum drug concentration-time curve; Vd_{area}, volume of distribution; Cl_B, the total body clearance of drug; C_{max}, peak serum concentration of the drug; t_{max}, time at which the peak concentration was achieved; F, bioavailability.

DISCUSSION

Evaluation of the disposition kinetic data revealed that bi-exponential and mono-exponential equations were best suited to describe the serum disposition of gentamicin following i.v. and i.m./s.c. routes of administration, respectively. The elimination half-life following i.v. administration (0.96 h) in goats was similar to that reported for dogs (Riviere & Coppoc, 1981; Riviere *et al.*, 1981), but shorter than for cattle (Haddad *et al.*, 1986; Burrows *et al.*, 1987), sheep (Brown *et al.*, 1985, 1986; Garg *et al.*, 1990), pigs (Riond & Riviere, 1988), buffaloes (Garg & Garg, 1989; Garg *et al.*, 1991a, b) and cats (Jernigan *et al.*, 1988).

Following i.m. and s.c. injection, the apparent plasma elimination half-lives of gentamicin were 2.37 ± 0.47 and 3.56 ± 0.39 h, respectively. Thus, the biological half-life of gentamicin in goats varied with the route of administration. Such differences were not seen in cats (Jernigan *et al.*, 1988).

The value of apparent volume of distribution (Vd_{area}) of gentamicin following i.v. administration ranged between 0.18 to 0.38 l kg^{-1} (mean 0.26 ± 0.04 l kg^{-1}) which indicated that distribution may be limited to the extracellular space. These values are comparable to those reported for other species (Brown *et al.*, 1985; Clarke *et al.*, 1985; Jernigan *et al.*, 1988; Riond & Riviere, 1988; Wilson *et al.*, 1989). Better distribution of gentamicin in the extracellular compartment has been reported in buffaloes (Garg *et al.*, 1991a, b) and sheep (Brown *et al.*, 1986; Garg *et al.*, 1990).

A minimum peak serum concentration of 4 μg ml^{-1} gentamicin has been recommended for treatment of infections caused by most of the sensitive pathogenic organisms (Black *et al.*, 1963). However, gentamicin continues to suppress bacterial growth after the serum concentrations decrease below the minimal inhibitory concentration (MIC), a phenomenon termed the post-antibiotic effect (Bundtzen *et al.*, 1984). Serum drug concentrations may thus be allowed to fall below the MIC between peak levels achieved by repeated administration and the dosage interval of gentamicin can be suitably adjusted under clinical conditions. With a trough concentration of >2 μg ml^{-1} and a maximal peak concentration of ≤12–15 μg ml^{-1} (Conzelman, 1980) and a therapeutic window of 4–16 μg ml^{-1} (Baggott, 1977), the dosage regimen for the s.c. route of administration to goats has been suggested as 3.63 and 3.34 mg kg^{-1} body weight as the loading and maintenance doses, respectively, to be repeated at 12 h intervals. In clinical practice, gentamicin may be administered at a dose rate of 3.35 mg kg^{-1} s.c. repeated at 12 h intervals.

The comparative pharmacokinetic data generated on goats following i.v., i.m. or s.c. routes suggests that the s.c. route may be preferred because it gives almost comparable blood serum levels of the drug (Table I), significantly longer elimination half-life and high bioavailability values than other routes. The s.c. route has also been recommended for cats (Jernigan *et al.*, 1988) and dogs (Wilson *et al.*, 1989).

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