Disposition kinetics of gentamicin following repeated parenteral administration in buffalo calves (*Bubalus bubalis*)

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GARG (SATISH K.), GARG (B.D.). Cinétique d'absorption et d'élimination de la gentamicine chez le bufflon (*Bubalus bubalis)* après administration parentérale répétée. *Revue Élev. Méd. vét. Pays trop.*, 1992, **45** (3-4) : 315-317

La cinétique d'absorption et d'élimination de la gentamicine a été déterminée chez des bufflons après administration parentérale répétée de 5 mg/kg de poids vif. Les demi-vie d'absorption ($t_{1/2Ka}$) et d'élimination ($t_{1/2}\beta$) ont été respectivement de 0,40 ± 0,12 et 4,33 ± 0,39 h. La comparaison statistique des valeurs des déterminants pharmacocinétiques établis dans la présente étude, avec les valeurs correspondantes obtenues après une seule injection intramusculaire de la même dose que dans une étude antérieure de GARG et GARG (1990), a révélé que l'administration répétée de gentamicine influence son profil pharmacocinétique, la demi-vie d'élimination étant statistiquement plus longue (P < 0,05). La valeur constante du taux d'élimination étant diminuée, les doses ultérieures doivent être réduites, en particulier en cas d'insuffisance rénale. Dans le cas contraire, les doses de gentamicine à administrer n'ont pas lieu d'être modifiées.
Mots clés : Buffle - *Bubalus bubalis* - Pharmacocinétique - Gentamicine - Dosage biologique - Inde.

INTRODUCTION

Gentamicin, a bacterial aminoglycoside antibiotic has gained widespread acceptance in veterinay medicine against several Gram-negative aerobic and some of the Gram-positive microbes. The high potential for oto-, hepato-, nephro- and immunotoxicosis (1, 2, 3, 6, 11) warrants the generation of a detailed pharmacokinetic profile for its judicious and safe use in animals. Data on the pharmacokinetics of gentamicin in buffalo calves following a single intramuscular (IM) or intravenous (IV) administration have been reported previously (5, 7). Gentamicin has the tendency to accumulate in higher concentrations in kidneys (4, 8). Tissue binding of this drug may not be influencing the pharmacokinetic behaviour of the drug. Therefore, the present study was undertaken to investigate the disposition kinetics of gentamicin following two consecutive doses *i.e.* first intravenous followed by intramuscular 9 h after the first injection.

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MATERIALS AND METHODS

Animals and treatment

The study was conducted in four clinically healthy male Murrah buffalo calves 8 to 10 months old and weighing between 60-75 kg. Animals were maintained on greed fodder and wheat straw. Water was provided *ad libitum.* Animals were acclimatised for 8-10 days prior to start of the experiment.

Gentamicin sulfate* was administered intravenously at the dose rate of 5 mg/kg body weight. Seven days after the first IV injection, blood samples were collected and the same dose of gentamicin given again by the intraveneous route ; 9 h after the latter dose, blood samples were collected and the same dose of gentamicin administered intramuscularly in the neck region.

Collection of blood samples and assay

Blood samples were collected by jugular venipuncture 5, 10, 15, 30 and 45 min and 1, 1.5, 2, 3, 4, 6, 9, 12 and 24 h after the first intravenous injection and at the same time intervals after IM injection. Plasma was separated and stored at -20 ° C until assayed for gentamicin concentration within 15 days after the collection of blood samples. Plasma concentration of gentamicin was determined using the solid phase ^{125}I labelled coat-A-count radio-immunoassay kits** by the procedure described by GARG and GARG (1990). The sensitivity of the assay was 0.1 µg/ml.

Pharmacokinetic analysis

Plasma gentamicin levels following the first intravenous injection @ 5 mg/kg (7), second intravenous injection (only one point *i.e.* 9 h) and the third intramuscular dose 9 h after the second IV dose were fitted simultaneously to derive the absorption and elimination rate constants following the IM dose taking into consideration the bioavailability factor (calculated by the non-compartmental approach)

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using a computer program for the non-linear regression analysis adaptated from Multi (14). The peak plasma drug concentration (C_{max}) and the time for achieving this maxima (t_{max}) were read directly from the plasma concentration versus time profile.

The data generated in the present study were compared statistically (13) with the data of single IM administration of gentamicin (5 mg/kg) in buffalo calves reported earlier (5). Values in the text are reported as mean ± SE.

RESULTS AND DISCUSSION

Mean plasma gentamicin concentrations at different time intervals following IM injection (5 mg/kg body) 9 h after the preceeding IV administration (same dose) are given in table I. Immediately before the administration of the IM dose, plasma drug concentration was 1.76 ± 0.19 µg/ml (9 h after the IV injection), and peaked (C_{max} : 10.48 ± 1.53 µg/ml) at 45 min (t_{max}). The drug could be detected in the plasma until 24 h post-injection (1.17 µg/ml).

Pharmakokinetic determinants describing the absorption and elimination of gentamicin are presented in table II. Following the second IM injection, absorption of the drug into the blood stream was slower ($t_{1/2Ka}$: 0.40 ± 0.12 h) compared to the single IM data ($t_{1/2Ka}$: 9.03 min), but non significant. The elimination half life in this study was found to be significantly ($P < 0.05$) longer (4.33 ± 0.39 h) than the corresponding value following single IM administration (3.32 h) reported earlier (5). Our observations suggest that a repeated administration of gentamicin in buffalo calves alters the disposition kinetics of the drug. The affinity of gentamicin to accumulate in the renal tissues may be due to the longer biological half-life of the drug. Similar observations have been reported for cats (9), rats (10), human beings (12) and cows (8).

Extended biological half-life of gentamicin suggests that the dosage or the frequency of administration may be decreased and duration of treatment may also be adjusted particularly in animals which seem be at risk for nephrotoxicosis. However, in animals with acceptable renal functions, dosage regimen does not need to be altered (8).

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***TABLE I** Plasma concentrations of gentamicin at 9h after the intravenous administration (5 mg/kg) and at various time intervals following the intramuscular administration at same dose level in buffalo calves 9h after the intravenous injection.*

Time interval (min)	Mean ± SE
540 (I.V.)	1.76 ± 0.19
5 (I.M.)	5.71 ± 1.21
10	7.12 ± 1.19
15	8.40 ± 0.98
30	9.14 ± 0.85
45	10.48 ± 1.53
60	9.12 ± 0.84
90	7.54 ± 0.80
120	6.54 ± 0.57
180	4.96 ± 0.55
360	3.30 ± 0.39
540	2.22 ± 0.16
720	1.55 ± 0.22

Data are Mean ± SE of four animals.

***TABLE II** Pharmacokinetic parameters after an administration of gentamicin (biexponential model, simultaneous fit of the 2 I.V. and I.M. administrations).*

Parameter	Mean ± SE
Ka (h^{-1})	2.299 ± 0.70
$t_{1/2Ka}$ (h)	0.40 ± 0.117
β (h^{-1})	0.16 ± 0.015
$t_{1/2\beta}$ (h)	4.33 ± 0.39
Vc ($l.kg^{-1}$)	0.07 ± 0.009
t_{max} (h)	0.45 ± 0.000
c_{max} (µg/ml)	10.48 ± 1.53

Data are Mean ± SE of four animals.
Ka : rate constant of absorption ; $t_{1/2Ka}$: absorption half life ; β : rate constant of elimination ; $t_{1/2\beta}$: elimination half life ; Vc : volume of central compartment ; t_{max} : time to achieve the peak plasma concentration ; C_{max}: peak plasma concentration.

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Disposition kinetics of gentamicin was determined in buffalo calves following repeated parenteral administration of 5 mg/kg body weight. The absorption ($t_{1/2\ Ka}$) and elimination half-life ($t_{1/2\ \beta}$) were found to be 0.40 ± 0.12 and 4.33 ± 0.39 h, respectively. Statistical comparison of the values of pharmacokinetic determinants generated in this study with the corresponding values following single intramuscular injection at the same dose level as reported earlier by GARG and GARG, 1990, revealed that the consecutive administration of drug influenced the pharmacokinetics profile of gentamicin. Elimination half-life was significantly longer (P < 0.05). Since elimination rate constant value was significantly reduced, the subsequent dosage will have to be reduced particularly if kidney functions are not normal. Otherwise, dosage regimen need not be changed. *Key words* : Buffalo - *Bubalus bubalis* - Pharmacokinetics - Gentamicin - Dose level - India.

GARG (SATISH K.), GARG (B.D.). Cinética de disposición de la gentamicina como resultado de la administración parenteral repetida en terneros de búfalo (*Bubalus bubalis). Revue Élev. Méd. vét. Pays trop.*, 1992, **45** (3-4) : 315-317

Se determinó la cinética de disposición de la gentamicina en terneros de búfalo como resultado de una administración parenteral repetida de 5 mg/kg peso vivo. La absorción ($t_{1/2\ Ka}$) y la vida media de eliminación ($t_{1/2\ \beta}$) fueron de 0,40 ± 0,12 y 4,33 ± 0,39 h respectivamente. La comparación estadística de los valores de los determinantes farmacocinéticos generados en este trabajo, en relacion con los valores correspondientes después de una sola inyección intramuscular de la misma dosis (tal y como lo reportaron con anterioridad GARG y GARG (1990)), reveló que la administración continua de la droga influencia el perfil farmacocinético de la gentamicina. La vida media de eliminación fue significativamente más larga (P < 0,05). En vista de que el valor constante de la tasa de eliminación se redujo significativamente, las dosis subsiguientes deben disminuirse, particularmente en caso de función renal anormal. En todos los otros casos, no es necesario un cambio en la dosificación. *Palabras claves* : Búfalo - *Bubalus bubalis* - Farmacocinética - Gentamicina - Nivel de dosificación - India.

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