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Comparative pharmacokinetics of amikacin following a single intramuscular or subcutaneous administration in goats (Capra hircus)

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Summary – The pharmacokinetics of amikacin sulfate was investigated following a single intramuscular (IM) or subcutaneous (SC) administration (10 mg/kg). The plasma concentration versus time data were analysed using the biexponential equation for first-order absorption and elimination phases for both the IM and SC routes. The absorption half-life values for the IM and SC routes were found to be 14.64 and 12.36 min, respectively. The biological half-life values of amikacin following IM and SC routes were found to be 84.46 and 93.96 min, respectively. The systemic availability of amikacin for both the IM (102.15 ± 5.08%) and SC (106.82 ± 12.95%) routes was found to be almost complete. Thus, based on the data of short absorption half life, almost complete systemic availability, slightly longer biological half life and ease of administration, we suggest that the SC route be preferred over the IM route for amikacin administration in goats. Amikacin at a dose level of 8 mg/kg body weight at 12 h intervals would result in a therapeutic peak plasma concentration (Cp max) of 32.30 µg/mL, which is not expected to produce any oto- or nephropathic effects.

amikacin / pharmacokinetics / bioavailability / goat

Résumé – Pharmacocinétique comparée de l’amikacine après administration unique intramusculaire ou sous-cutanée chez la chèvre (Capra hircus). La pharmacocinétique du sulfate d’amikacine a été étudiée chez des chèvres après une administration intramusculaire (IM) ou sous-cutanée (SC) unique (10 mg/kilo poids corporel). Les concentrations plasmatiques en fonction du temps ont été analysées à l’aide d’une équation bi-exponentielle, pour des phases d’absorption et d’élimination de premier ordre avec les deux modes d’administration, IM et SC. Les demi-vies d’absorption pour les administrations IM et SC ont été de 14.64 et 12.36 min, respectivement. Les demi-vies biologiques de l’amikacine après administration IM et SC ont été de 84.46 et 93.96 min, respectivement.

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La disponibilité systémique de l’amikacine après injections IM (102,15 ± 5,08 %) ou SC (106,82 ± 12,95 %) a été pratiquement totale. La rapidité d’absorption, une disponibilité systémique presque totale, une demi-vie biologique légèrement plus longue, et la facilité d’administration suggèrent que la voie SC peut être préférée à la voie IM pour l’amikacine chez la chèvre. L’amikacine, administrée à la dose de 8 mg/kg de poids corporel à intervalles de 12 h, résulterait en un pic de concentration plasmatique thérapeutique ($C_{P_{\text{max} \alpha}}$) de 32,30 μg/mL qui ne devrait pas entraîner d’effet oto- ou néphropathique.

amikacine / pharmacocinétique / biodisponibilité / chèvre

INTRODUCTION

Amikacin, a semisynthetic derivative of kanamycin, is an aminoglycoside antibiotic that is highly resistant to inactivating enzymes. It is primarily used for the treatment of infections caused by gentamicin- and tobramycin-resistant gram-negative (Chambers and Sande, 1996) and penicillinase-producing strains of gram-positive bacteria (Carli, 1985; Carbon et al, 1986). As with other aminoglycosides, amikacin has great potential to cause oto- and nephrotoxicity when the serum levels reach threshold concentrations over 35 μg/mL, thus limiting its use either by intramuscular or subcutaneous routes at recommended dosages (Carli, 1985).

Data on the disposition of amikacin have been generated following intravenous (IV), intramuscular (IM) and/or subcutaneous (SC) administration in dogs (Baggot et al, 1985), cats (Shille et al, 1985; Jernigan et al, 1988b), horses (Brown et al, 1984; Orsini et al, 1985), calves (Ziv, 1977; Carli et al, 1990), sheep (Carli et al, 1990) and goats (Uppal et al, 1992). However, pharmacokinetic data, with particular reference to bioavailability following IM or SC routes is lacking in goats. The purpose of the present study, therefore, was to determine the disposition kinetic data for IM or SC administration for amikacin (10 mg/kg body weight) in goats to determine its bioavailability after either the IM or SC routes, and to recommend the most suitable route and dosage regimen for amikacin administration in goats.

MATERIALS AND METHODS

Animals

Studies were conducted on six clinically healthy male goats (Beetal × Black Bengal) weighing 14–17 kg. Antibiotic-free diet and water were provided ad libitum throughout the experimental period. Animals were acclimatised for 10 days prior to the start of the experiment.

Drug treatment and sampling

Amikacin (Amicin; Biochem Pharmaceutical Industries, Mumbai, India) was administered intramuscularly or subcutaneously on the lateral side and ventrolateral side of the neck, respectively, of each animal at a dose level of 10 mg/kg. A washout period of 21 days was given between each route of administration. Blood samples were drawn (2 mL) by jugular vein puncture into heparinised tubes at 3, 6, 9, 15, 30 and 45 min and 1, 2, 3, 4, 6, 9, 12 and 24 h after drug administration by either route. Plasma was separated and stored at –20 °C until assayed for amikacin.

Analytical method

Plasma amikacin concentrations were determined using the commercially available solid phase 125I-labelled Coat-A-Count radioimmunoassay kit (Diagnostic Products Corporation, Los Angeles, USA). The radio-activity was measured by an automatic gamma counter (KLB 1271,
RIAGAMMA, USA). The sensitivity of the assay was 0.1 µg/mL.

**Pharmacokinetic analysis**

The pharmacokinetic analysis of amikacin plasma concentration–time data for each goat was performed with the aid of a nonlinear iterative curve fitting computer programme (Statis, Version 3, M/s Clydesoft, Glasgow, UK). Values for the pharmacokinetic constants and exponents (A’, B, Ka, β) generated by the computer programme, were used in conjunction with the administered dose of amikacin to calculate the values for other pharmacokinetic parameters (Baggot, 1977).

The values of systemic availability (F; %) of amikacin following administration by extravascular (IM or SC) routes were determined by using the equation:

\[ F = \frac{\text{AUC (IM/SC)}}{\text{AUC (IV)}} \]

where the values of AUC for the IV route of administration reported earlier in goats (4807.8 ± 444.9 µg.min/mL) (Uppal et al, 1992) were used.

The data following IM and SC administration were compared statistically using Student’s t-test.

Using the pharmacokinetic data generated in the present study, we were able to predict the achievable steady-state peak (Cpmax) plasma amikacin concentration for the SC route by applying the following equation:

\[ Cp_{\text{max}} = \frac{D}{V_{\text{d(area)}}} \left( 1 - e^{-\beta t} \right) \]

where D is the dose, Vd(area) is the apparent volume of distribution, β is the elimination rate constant, t is the dosing interval and e is the base to the natural logarithm (Baggot, 1977). Calculations were based on 12-h dosing intervals at a dose level of 8 mg/kg body weight.

**RESULTS**

The mean (± SEM) plasma amikacin concentrations at different time intervals following IM or SC routes of administration (10 mg/kg) are shown in figure 1. The peak plasma concentrations of amikacin were observed to be 27.63 ± 1.61 and 38.93 ± 3.06 µg/mL following IM and SC routes, respectively. These occurred at 45 and 30 min following administration by the IM or SC routes, respectively (fig 1). Amikacin concentrations of more than 2 µg/mL were maintained for up to 6 h after drug administration by both the routes. However, beginning at 9 h and continuing thereafter, no further trace of drug could be detected in the plasma.

The plasma concentration–time data in the present study were fitted to a biexponential equation describing the first-order absorption and elimination phases following IM and SC routes (r = 0.97 ± 0.006 and 0.94 ± 0.02 for IM and SC routes, respectively). The weighting mode for fitting the plasma concentration–time curve was kept at zero.

Disposition kinetic parameters describing the absorption and elimination characteristics of amikacin following both the extravascular routes are presented in table I. Comparison of the pharmacokinetic determinants of amikacin following the IM or SC routes did not reveal any appreciable or significant differences between the two routes. Systemic availability (F) of amikacin was almost complete following either route of administration as the values of F were found to be 102.15 ± 5.08 and 106.82 ± 12.95 percent following drug administration by IM or SC routes, respectively.

**DISCUSSION**

Figure 1 revealed that following amikacin administration by extravascular routes in goats, plasma concentrations of more than 2 µg/mL were achieved within 3 min, and maintained for up to 6 h by either of the two administration routes. Amikacin was rapidly absorbed into the goat’s blood stream as reflected by the early blood level values and absorption half-life values of 14.64 and
12.36 min after IM and SC route, respectively. The observed peak plasma concentration ($C_{max}$) in goats was higher for the SC route ($38.93 \pm 3.06 \mu g/mL$) compared to that after IM administration ($27.63 \pm 1.61 \mu g/mL$). In addition, the time taken to achieve peak plasma concentration ($t_{max}$) was shorter for the SC route (30 min) compared to the IM route (45 min). Absorption from the SC route may be faster and better than that from the IM site because the drug can disperse in the subcutaneous region, leading to contact with a greater surface area of blood vessels, thus promoting faster absorption. Following the IM route, $t_{max}$ for goat was very similar to that reported for cats (Jernigan et al., 1988b) and calves (Carli et al., 1990); however, it was faster than that reported for sheep (Carli et al., 1990). Data on $t_{max}$ and $C_{max}$ values following SC administration in domestic animals, particularly ruminants, are lacking; therefore, it is difficult to comment on the comparative absorption characteristics in goats. It does seem, however, to have been faster than that in cats (Jernigan et al., 1988b).

Following IM and SC injections of amikacin, the respective plasma elimination half lives of 84.46 and 93.96 min in goats were very similar to those previously reported in sheep and calves following IM administration (Carli et al., 1990) and after IM and SC administration in cats (Jernigan et al., 1988b).

The value of the apparent volume of distribution for amikacin following administration by either route (0.25–0.27 L/kg) in goats was almost equal to the extracellular fluid volume value and similar to that

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**Fig 1.** Plasma amikacin concentrations (mean ± SE) profile following a single intramuscular or subcutaneous dose (10 mg/kg) in goats.
reported for other species (Brown and Riviere, 1991). This suggests that amikacin is adequately distributed to the extra cellular fluids in the body.

Systemic availability of amikacin following administration by the IM and SC routes was almost complete in goats (table I) and comparable to that in cats after the IM and SC routes (Jernigan et al, 1988b) and horses (Orsini et al, 1985) and calves (Carli et al, 1990) after IM administration. It was slightly higher than that of 87.0±20.0 per cent in sheep (Carli et al, 1990) after IM injection.

The comparative pharmacokinetic data of amikacin generated in goats following the IM and SC routes convincingly suggested that the SC route be preferred over the IM route as it attained similar and even slightly higher blood levels of drug more quickly (table I). Following amikacin administration by either the IM or SC routes, similarity in elimination half life, apparent volume of distribution, area under the curve and systemic availability values and above all, the ease of administration without signs of any pain suggested the obvious merit of using the SC route. The SC route of administration has also been preferably recommended over IM for amikacin and gentamicin in cats (Jernigan et al, 1988a, b) and gentamicin in dogs (Wilson et al, 1989) and goats (Garg et al, 1995).

The minimum inhibitory concentration (MIC<sub>90</sub>) of amikacin for a variety of clinical isolates from several species has been reported to be 1–2 μg/mL except for Serratia spp where it is 8 μg/mL (Wiedmann and Atkinson, 1991). However, the clinical

### Table I. Pharmacokinetic parameters of amikacin in goats (n = 6) following a single intramuscular (IM) or subcutaneous (SC) injection (10 mg/kg body weight).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Unit</th>
<th>IM</th>
<th>SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>A&lt;sup&gt;+&lt;/sup&gt;</td>
<td>μg/mL</td>
<td>49.60 ± 6.00</td>
<td>47.20 ± 4.30</td>
</tr>
<tr>
<td>Ka</td>
<td>min&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>0.05 ± 0.009</td>
<td>0.07 ± 0.004</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2Ka&lt;/sub&gt;</td>
<td>min</td>
<td>14.64&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12.36&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>B</td>
<td>min&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>0.0065 ± 0.001</td>
<td>0.0067 ± 0.001</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2B&lt;/sub&gt;</td>
<td>min</td>
<td>84.46&lt;sup&gt;a&lt;/sup&gt;</td>
<td>93.96&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt;</td>
<td>μg.min/mL</td>
<td>4945.30 ± 575.80</td>
<td>4948.40 ± 356.00</td>
</tr>
<tr>
<td>C&lt;sub&gt;B&lt;/sub&gt;</td>
<td>mL/min.kg</td>
<td>2.16 ± 0.25</td>
<td>2.11 ± 0.14</td>
</tr>
<tr>
<td>V&lt;sub&gt;d(area)&lt;/sub&gt;</td>
<td>L/kg</td>
<td>0.27 ± 0.02</td>
<td>0.25 ± 0.014</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;</td>
<td>min</td>
<td>45.00</td>
<td>30.00</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>μg/mL</td>
<td>27.63 ± 1.61</td>
<td>38.93 ± 3.06b</td>
</tr>
<tr>
<td>F</td>
<td>%</td>
<td>102.15 ± 5.08</td>
<td>106.82 ± 12.95</td>
</tr>
</tbody>
</table>

<sup>a</sup> Values expressed are the harmonic mean; <sup>b</sup> P < 0.05 compared to that of the IM route. A<sup>+</sup>, Ka, t<sub>1/2Ka</sub>: intercept, rate constant and half life of absorption phase, respectively; B, t<sub>1/2B</sub>: rate constant and half life of elimination phase, respectively; AUC<sub>0-∞</sub>: total area under plasma drug concentration curve; C<sub>B</sub>: total body clearance; V<sub>d(area)</sub>: apparent volume of distribution; T<sub>max</sub>: observed time for peak plasma concentration; C<sub>max</sub>: observed maximal plasma concentration; F: systemic availability of the drug.
outcome of treatment of susceptible infections with aminoglycosides appears to be more strongly influenced by the peak plasma concentration of the drug and the AUC (Koritz and Bevill, 1991). The aminoglycosides concentrations can be allowed to fall below the MIC of infecting bacteria during the dosage intervals because these exert a long inhibitory post-antibiotic effect on susceptible bacteria (Koritz and Bevill, 1991). It is important that the maximal peak plasma amikacin concentrations not be allowed to exceed 35 μg/mL, as above this level it has been reported to cause oto- and nephrotoxicity (Carli, 1985).

Amikacin at a dose level of 8 mg/kg body weight by the SC route in goats at 12-h intervals is expected to provide a peak plasma concentration ($C_{p_{max}}$) of 32.30 μg/mL, which is well within the safety limits of less than 35 μg/mL (Carli, 1985). A dosage level of 10 mg/kg at 12-h intervals would result in the $C_{p_{max}}$ of 40.30 μg/mL, which is not desirable. Therefore, amikacin at a dose level of 8 mg/kg at 12-h intervals is recommended for goats.

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