**Effect of age on the pharmacokinetics of a single daily dose of gentamicin sulfate in healthy foals**

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**Summary**

**Reasons for performing study:** Therapeutic drug monitoring in a small number of foals of various ages indicates that the standard adult dose of 6.6 mg/kg bwt q. 24 h for gentamicin is too low and a dose of 12 mg/kg bwt has been proposed. The pharmacokinetics of this dosage in foals and the ages at which this higher dose should be used have not previously been investigated.

**Objective:** To determine the effect of age on the pharmacokinetics of a single 12 mg/kg bwt i.v. dose of gentamicin in foals.

**Methods:** Six healthy foals were given a single i.v. dose of gentamicin at 1–3 days, 2, 4, 8 and 12 weeks of age. Plasma concentrations were measured using LC-MS/MS.

**Results:** Elimination half-life (mean ± s.d.) was significantly longer in 1–3-day-old foals (8.2 ± 2.0 h) than in foals 4 weeks of age (3.7 ± 1.5 h) or older. Volume of distribution was significantly higher in 1–3-day-old foals (0.75 ± 0.20 l/kg bwt) than in 8 (0.27 ± 0.10 l/kg bwt) or 12-week-old foals (0.29 ± 0.11 l/kg bwt). Concentrations of gentamicin 1 h after administration were significantly lower in 1–3-day-old foals (20.52 ± 2.07 µg/ml) than in all other age groups (>42.16 ± 17.57 µg/ml). Concentrations of gentamicin 24 h after administration were significantly higher in the 1–3-day-old foals (1.97 ± 0.90 µg/ml) than in all the other age groups (<0.85 ± 0.46 µg/ml).

**Conclusions:** The pharmacokinetics of gentamicin change considerably in the first 2 weeks of life.

**Potential relevance:** Intravenous administration of gentamicin at a dose of 12 mg/kg bwt i.v. should be required in foals less than 2 weeks of age. In foals 2 weeks of age or older, a lower dose of 6.6 mg/kg bwt given q. 24 h was predicted to be adequate.

**Keywords:** horse; gentamicin sulfate; aminoglycoside; foal; pharmacokinetics

**Introduction**

Bacterial sepsis is the leading cause of morbidity and mortality in neonatal foals [1–3]. Gram-negative bacteria account for 70–95% of the microorganisms isolated from blood cultures, with *Escherichia coli* being the most common isolate [2–4]. Given that enteric Gram-negative microorganisms predominate, aminoglycosides such as gentamicin or amikacin are commonly used in conjunction with a β-lactam antimicrobial to provide coverage against Gram-positive bacteria. Amikacin has traditionally been considered the agent of choice for the treatment of sepsis in equine neonates with normal renal function because of a slightly broader spectrum against Enterobacteriaceae [2]. However, in a recent study, amikacin and gentamicin were both active in vitro against approximately 84% of 554 bacterial isolates from 423 bacteraemic foals [4]. Major advantages of gentamicin over amikacin include widespread availability and considerably lower cost.

Aminoglycosides exert concentration dependent bacterial killing characteristics. Their rate of killing increases as the drug concentration increases above the minimum inhibitory concentration (MIC) for a given pathogen, with optimal maximum serum concentration (Cmax) to MIC ratio of 8–10:1 [5,6]. Higher Cmax also results in a longer post antibiotic effect and reduces the selection of resistant bacterial mutants within a population [7,8]. Bacterial isolates from horses with a MIC ≥2 µg/ml are considered susceptible to gentamicin. As a result, target peak gentamicin concentrations should be around 16–20 µg/ml. By applying these principles, a dose of 6.6 mg/kg bwt i.v. q. 24 h has been recommended for gentamicin in adult horses [9,10]. Because aminoglycosides are water-soluble and thus highly distributed in extracellular fluid (ECF), their clinical pharmacokinetics are strongly influenced by variations in patient ECF volume due to disease state or age [11,12]. For example, compared to adults, human neonates require a higher dose of gentamicin to achieve therapeutic peak concentrations because of their greater percentage of body water, which leads to a significantly higher volume of distribution: 0.43–1.1 l/kg bwt for neonates vs. on average 0.25 l/kg bwt for adults [11,13].

Although there are multiple studies reporting the pharmacokinetics of low dose multiple daily administration of gentamicin in foals [14–17], there is little information on the pharmacokinetics of once daily gentamicin. Therapeutic drug monitoring in a small number of foals with various illnesses indicates that the standard adult dose of 6.6 mg/kg bwt q. 24 h for gentamicin is too low, and a dose of 10–14 mg/kg bwt has been proposed based upon these clinical observations [18,19]. However, the pharmacokinetics of higher single daily doses of gentamicin in foals and the ages at which these higher dosages should be used have not been investigated. The objective of the present study was to determine the effect of age on the pharmacokinetics of a single i.v. 12 mg/kg bwt dose of gentamicin in healthy foals.

**Materials and methods**

**Animals**

Three male and 3 female Quarter Horse foals considered healthy on the basis of a thorough physical examination, complete blood count, plasma biochemical profile and immunoglobulin G (IgG) concentrations were used. The foals ranged in weight from 45–63 kg at 1–3 days of age, 55–86 kg at 2 weeks of age, 76–143 kg at 4 weeks of age, 107–146 kg at 8 weeks of age and 133–177 kg at 12 weeks of age. The foals were kept with their dams in individual stalls during the experiment, with access to grass hay and water. The study was approved by the Institutional Animal Care and Use Committee of the University of Georgia.

**Experimental design and sample collection**

Gentamicin sulfate* was administered intravenously (i.v.) at a dose of 12 mg/kg bwt at 5 different ages. The first administration occurred when the foals were 1–3 days of age and was repeated on the same 6 foals at 2, 4, 8 and 12 weeks of age. Gentamicin sulfate was administered as a single i.v. bolus through a jugular vein catheter. Blood samples were obtained from a catheter placed in the opposite vein at 0 (prior to administration), 5, 10, 15, 20, 30, 45, 60 and 90 min as well as 2, 3, 4, 6, 8, 12, 16 and 24 h after administration of the drug. Samples were centrifuged at 1500 g, after which plasma was collected and stored frozen at -20°C until analysis.
Gentamicin in foals

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TABLE 1: Pharmacokinetic variables (mean ± s.d.) for gentamicin after i.v. administration of gentamicin sulfate at a dosage of 12 mg/kg bwt to 6 foals at 5 different ages (1–3 days, 2, 4, 8 and 12 weeks)

<table>
<thead>
<tr>
<th>Variable</th>
<th>1–3 days</th>
<th>2 weeks</th>
<th>4 weeks</th>
<th>8 weeks</th>
<th>12 weeks</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A [µg/ml]</td>
<td>34.97 ± 15.09a</td>
<td>94.64 ± 14.19a</td>
<td>90.50 ± 44.83a</td>
<td>89.37 ± 16.01a</td>
<td>261.40 ± 235.79a</td>
<td>0.0003</td>
</tr>
<tr>
<td>α (h⁻¹)</td>
<td>1.32 ± 0.50</td>
<td>1.19 ± 0.36</td>
<td>1.76 ± 0.98</td>
<td>0.97 ± 0.35</td>
<td>1.51 ± 0.85</td>
<td>0.0029</td>
</tr>
<tr>
<td>t₁/₂β (h)</td>
<td>0.6 ± 0.3</td>
<td>0.7 ± 0.3</td>
<td>0.5 ± 0.2</td>
<td>0.8 ± 0.3</td>
<td>0.5 ± 0.2</td>
<td>0.3407</td>
</tr>
<tr>
<td>B [µg/ml]</td>
<td>13.36 ± 3.54</td>
<td>15.59 ± 4.67</td>
<td>38.57 ± 24.93</td>
<td>33.91 ± 13.17</td>
<td>22.50 ± 8.08</td>
<td>0.0168</td>
</tr>
<tr>
<td>β (h⁻¹)</td>
<td>0.09 ± 0.03</td>
<td>0.12 ± 0.03</td>
<td>0.23 ± 0.11</td>
<td>0.18 ± 0.058</td>
<td>0.16 ± 0.032</td>
<td>0.0028</td>
</tr>
<tr>
<td>t₁/₂β (h)</td>
<td>8.2 ± 2.0</td>
<td>5.8 ± 1.6</td>
<td>3.7 ± 1.5</td>
<td>4.0 ± 1.0</td>
<td>4.4 ± 0.8</td>
<td>0.0010</td>
</tr>
<tr>
<td>Vdmean (litres/kg bwt)</td>
<td>0.75 ± 0.21</td>
<td>0.76 ± 0.58</td>
<td>0.37 ± 0.29</td>
<td>0.26 ± 0.10</td>
<td>0.28 ± 0.10b</td>
<td>0.0060</td>
</tr>
<tr>
<td>CL (ml/h/kg bwt)</td>
<td>64.3 ± 10.4</td>
<td>63.7 ± 23.9</td>
<td>65.5 ± 34.8</td>
<td>44.9 ± 12.7</td>
<td>44.4 ± 11.8</td>
<td>0.0020</td>
</tr>
<tr>
<td>AUCmean (µg • h/ml)</td>
<td>191.5 ± 28.2</td>
<td>206.1 ± 59.5</td>
<td>210.8 ± 70.3</td>
<td>273.9 ± 66.2</td>
<td>283.5 ± 82.0</td>
<td>0.0049</td>
</tr>
<tr>
<td>AUCM/C (µg • h/ml)</td>
<td>1972.1 ± 706.2</td>
<td>1049.3 ± 315.9</td>
<td>819.7 ± 376.0</td>
<td>1215.6 ± 518.8</td>
<td>946.7 ± 132.6</td>
<td>0.0013</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>10.5 ± 3.3</td>
<td>5.28 ± 0.83</td>
<td>4.03 ± 1.67</td>
<td>4.15 ± 1.08</td>
<td>3.4 ± 1.20</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>C₁₂h (µg/ml)</td>
<td>30.37 ± 9.45c</td>
<td>64.16 ± 12.63</td>
<td>71.22 ± 33.86</td>
<td>75.45 ± 26.22</td>
<td>96.08 ± 26.38</td>
<td>0.0010</td>
</tr>
<tr>
<td>C₁₀h (µg/ml)</td>
<td>20.52 ± 2.07</td>
<td>48.95 ± 15.07</td>
<td>42.16 ± 17.57</td>
<td>67.77 ± 12.28</td>
<td>65.05 ± 22.81</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>C₀h (µg/ml)</td>
<td>1.97 ± 0.90</td>
<td>0.86 ± 0.46</td>
<td>0.37 ± 0.35bc</td>
<td>0.71 ± 0.61b</td>
<td>0.67 ± 0.25b</td>
<td>0.0036</td>
</tr>
</tbody>
</table>

A and α — Intercept and slope, respectively, of the distribution phase. t₁/₂β — Distribution half-life. B and β — Intercept and slope, respectively, of the elimination phase. t₁/₂β — Elimination half-life. Vdmean — Volume of distribution based on AUC. CL — Clearance. AUCmean — Area under the plasma concentration vs. time curve extrapolated to infinity. AUCM/C — Area under the first moment of the concentration-time curve vs. time curve extrapolated to infinity. MRT — Mean residence time. C₁₀h — Plasma concentrations of gentamicin 30 min after administration of a single i.v. dose. C₁₂h — Plasma concentrations of gentamicin 1 h after administration of a single i.v. dose. C₁₀ — Plasma concentrations of gentamicin 24 h after administration of a single i.v. dose. a,b,c — Different letters within a given variable indicate a statistically significant difference between age groups (P<0.05).

To monitor renal function, plasma creatinine was measured on heparinised blood samples collected before and 24 h after each dose of gentamicin sulfate.

Drug analysis in plasma and body fluids by liquid chromatography tandem mass spectrometry (LC-MS/MS)

The concentration of gentamicin sulfate in foal plasma was measured using liquid chromatography tandem mass spectrometry (LC-MS/MS), adapted from previously described techniques [20]. Briefly, gentamicin was extracted from plasma (500 µl) using protein precipitation with an equal volume of ice-cold 90:10 acetone/0.2% formic acid (v/v). Extracted samples were centrifuged (2°C, 10,000 g for 10 min) and the resultant supernatants transferred to glass vials and capped. Calibration standards were prepared in drug-free foal plasma and extracted as described above. A concentration range of 0.09–200 µg/ml gentamicin sulfate was used to construct standard curves. The lower limit of quantification (LLOQ) was 0.09 µg/ml. The interassay coefficient of variation was <10% at concentrations 200–6.25 µg/ml and ±15% at concentrations 6.25–0.09 µg/ml. The analytes were separated on an Agilent Eclipse XDB C18 column (100 x 4.6 mm i.d., 3.5 µm) equipped with a Phenomenex Security Guard C18 guard column (4.0 x 3.0 mm). Analytes were eluted from the column using isocratic mobile phase consisting of 0.2% formic acid and acetonitrile (1:1, v/v). LC-MS/MS measurement of gentamicin was performed on an Agilent 1100 HPLC system coupled to an Agilent XCT Ultra Plus ion-trap mass spectrometer. Samples were introduced into the MS with a flow rate of 0.25 ml/min using an Electrospray ionisation (ESI) source. Injection volume was 20 µl with a total run-time of 5 min. Nitrogen gas was used as desolvation gas (flow of 8 l/min at 350°C) and as nebuliser gas (30 ps) and helium used as a collision gas. Capillary voltage was set at 3500 V, skimmer at 40 V and cap exit at 158.5 V. Mass spectra were acquired in positive-ion mode and mass transitions monitored using multiple-reaction monitoring (MRM). The MRM transition from m/z 478 → 322 was used for gentamicin quantification.

Pharmacokinetic analysis

For each foal, 1-, 2- and 3-compartment models were fitted to the plasma concentration vs. time data by use of a computer software package (WinNonlin Professional v 5.1). A linear 2-compartment model with weighting by the inverse of the model predicted drug concentrations (1/y) was most appropriate, based upon computer-assisted examination of residual plots, goodness of fit the Akaike’s information criterion and the sum of squares: C = A e⁻ᵃ • t + B e⁻ᵇ • t; where C is the serum drug concentration at time t; e is the base of the Napierian logarithm; A and a are the intercept and slope, respectively, of the distribution phase; B and b are the intercept and slope, respectively, of the elimination phase. Elimination half-life (t₁/₂β) was calculated as the natural logarithm of 2 divided by β. The area under the concentration-time curve (AUC) and area under the first moment of the concentration-time curve (AUCM/C) were calculated using the trapezoidal rule, with extrapolation to infinity using C₀h/β, where C₀h is the plasma gentamicin concentration at the last quantifiable time point. Mean residence time (MRT) was calculated as AUCM/C/AUC. Apparent volume of distribution based on the AUC (Vdmean) was calculated as dose/AUC and systemic clearance (CL) was calculated from dose/AUC. Based on the model fit for the single dose data, the individual model parameters for each foal were fixed and used to simulate steady state gentamicin concentration vs. time plots at various dosages (6.6, 9, 12, 15 and 18 mg/kg bwt) and dosing intervals (24, 36 and 48 h) for each age group (WinNonlin Professional v 5.1).

Data analysis

Normality and equality of variance of the data were assessed using the Shapiro-Wilk and Levene tests, respectively. Data that were not normally distributed were log transformed. A one-way ANOVA for repeated measures was used to determine the effect of age group (1–3 days, 2, 4, 8 or 12 weeks) on each measured and calculated pharmacokinetic variable. When appropriate, multiple pairwise comparisons were done using the Holm-Sidak test. For each day of gentamicin administration, plasma creatinine concentrations prior to administration of gentamicin were compared to plasma gentamicin concentrations 24 h after gentamicin administration using a paired t test. For all analyses, significance was set at P<0.05.

Results

Measured gentamicin concentrations at selected time points and calculated pharmacokinetic variables for the different age groups are presented in Table 1. Increasing age resulted in a significant decrease
Based on modelling of the data, in foals 2 weeks of age or older a dose of administration of gentamicin at a dose of 12 mg/kg bwt q. 24 h were 2.08 h horses has moved away from low doses (2.2–3.3 mg/kg bwt) every 6–12 h, pharmacodynamics of aminoglycosides [5,6], dosing of gentamicin in adult Over the past 30 years, in line with improved understanding of the Discussion

![Graph](image)

**Fig 1:** Mean (± s.d.) plasma concentrations of gentamicin after i.v. administration of gentamicin sulfate at a dosage of 12 mg/kg bwt to 6 foals at 5 different ages (1–3 days, 2, 4, 8 and 12 weeks).

in t₁/₂p, Vd, clearance, AUMC, MRT and concentration 24 h after administration (C₀→∞) and a significant increase in Cₗ, C₀ₗ, and intercepts of the distribution and elimination phases (Table 1). Elimination half-life was significantly longer in 1–3-day-old foals than in foals 4 weeks of age or older (Fig 1). Volume of distribution was significantly higher in 1–3-day-old foals (0.75 ± 0.20 l/kg bwt) than in 8– (0.27 ± 0.10 l/kg bwt) or 12– (0.29 ± 0.11 l/kg bwt)-week-old foals. Concentrations of gentamicin 1 h after administration were significantly lower in 1–3-day-old foals (20.52 ± 2.07 μg/ml) than in all other age groups. Concentrations of gentamicin 24 h after administration were significantly higher in the 1–3-day-old foals (1.97 ± 0.90 μg/ml) than in all other age groups.

Predicted minimum plasma concentrations at steady state after administration of gentamicin at a dose of 12 mg/kg bwt q. 24 h were 2.08 ± 0.91 μg/ml for the 1–3-day-old foals and <1 μg/ml for all other age groups (Table 2). Increasing the dosing interval to q. 36 h in 1–3-day-old foals was predicted to reduce trough concentrations to 0.72 ± 0.34 μg/ml (Table 2). Based on modelling of the data, in foals 2 weeks of age or older a dose of 6.6 mg/kg bwt q. 24 h was predicted to maintain mean concentrations of gentamicin 1 h after administration >20 μg/ml (Table 2).

None of the foals experienced any adverse effects during the course of the study. Plasma creatinine concentrations remained within the reference interval throughout the study. There was a significant decrease in plasma creatinine concentrations 24 h after administration of gentamicin in 1–3-day-old (from 128 ± 38.0 to 102 ± 19.4 μmol/l) and in 4-week-old (from 125 ± 25.6 to 113 ± 22.1 μmol/l) foals. Creatinine concentrations before and after administration of gentamicin were not significantly different at 2, 8 and 12 weeks of age.

**Table 2:** Predicted steady state peak (1 h after administration) and trough plasma concentrations of gentamicin (mean ± s.d.) at different ages after i.v. administration of various dosages of gentamicin q. 24, 36 or 48 h

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose (mg/kg bwt)</th>
<th>Dose interval (h)</th>
<th>Peak (μg/ml)</th>
<th>Trough (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–3 days</td>
<td>12</td>
<td>24</td>
<td>25.23 ± 5.91</td>
<td>2.08 ± 0.91</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>24</td>
<td>23.98 ± 6.40</td>
<td>0.72 ± 0.34</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>24</td>
<td>23.56 ± 6.57</td>
<td>0.27 ± 0.14</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>24</td>
<td>31.53 ± 7.40</td>
<td>2.60 ± 1.13</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>24</td>
<td>29.97 ± 7.99</td>
<td>0.90 ± 0.43</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>24</td>
<td>29.45 ± 8.22</td>
<td>0.34 ± 0.17</td>
</tr>
<tr>
<td>2 weeks</td>
<td>18</td>
<td>24</td>
<td>37.85 ± 8.87</td>
<td>3.15 ± 1.36</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>24</td>
<td>35.96 ± 9.60</td>
<td>1.08 ± 0.51</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>24</td>
<td>35.34 ± 9.86</td>
<td>0.41 ± 0.21</td>
</tr>
<tr>
<td>4 weeks</td>
<td>2 weeks 6.6</td>
<td>24</td>
<td>24.64 ± 6.72</td>
<td>0.44 ± 0.15</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>24</td>
<td>33.51 ± 9.00</td>
<td>0.60 ± 0.19</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>24</td>
<td>44.68 ± 11.99</td>
<td>0.80 ± 0.26</td>
</tr>
<tr>
<td>8 weeks</td>
<td>4 weeks 6.6</td>
<td>24</td>
<td>25.27 ± 9.52</td>
<td>0.20 ± 0.22</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>24</td>
<td>34.46 ± 12.98</td>
<td>0.27 ± 0.29</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>24</td>
<td>45.95 ± 17.31</td>
<td>0.36 ± 0.39</td>
</tr>
<tr>
<td>12 weeks</td>
<td>8 weeks 6.6</td>
<td>24</td>
<td>34.55 ± 8.80</td>
<td>0.33 ± 0.25</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>24</td>
<td>47.11 ± 12.00</td>
<td>0.44 ± 0.34</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>24</td>
<td>62.81 ± 15.91</td>
<td>0.59 ± 0.46</td>
</tr>
<tr>
<td></td>
<td>12 weeks 6.6</td>
<td>24</td>
<td>34.52 ± 14.11</td>
<td>0.26 ± 0.11</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>24</td>
<td>47.07 ± 19.24</td>
<td>0.36 ± 0.15</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>24</td>
<td>62.75 ± 25.65</td>
<td>0.48 ± 0.20</td>
</tr>
</tbody>
</table>

Similar to that reported in adult horses (0.14 ± 0.06 to 0.21 ± 0.05 μg/kg bwt) administered i.v. gentamicin at 6.6 mg/kg bwt [9,10]. The decrease in Vₘ within the first few weeks of life is well documented in human patients [13]. In addition, wide variations in the Vₘ of aminoglycosides have been reported in human neonates of similar actual and gestational ages, with premature infants usually requiring a higher dose owing to an increased Vₘ [24]. Differences in Vₘ for a given age and weight are especially likely in conditions where there is significant third-spacing, such as diseases causing oedema or cavity effusions, which would result in an increased Vₘ [11].

Pharmacodynamic data gathered over recent decades show that administration of aminoglycoside by an extended dosing interval scheme maximises efficacy, with the goal of achieving a peak plasma drug concentration (Cₘₚₚ) to MIC ratio of 8:10. Based on the current guidelines from the Clinical and Laboratory Standards Institute (CLSI) bacterial isolates from horses with an MIC ≥2 μg/ml are considered susceptible to gentamicin. As a result, target peak gentamicin concentrations should be around 16–20 μg/ml. The Cₘₚₚ should be collected after the distribution phase to be representative of maximal tissue concentrations [11]. Unfortunately, the optimal time after i.v. gentamicin administration at which to sample for Cₘₚₚ in horses has been the source of considerable debate, with most authors recommending either 0.5 or 1 h after bolus administration [18,19]. Correct timing of peak sample collection is important because aminoglycosides have a short but important distribution phase. Drawing a peak sample prematurely during the distribution phase would result in unrepresentatively high concentrations and lead to underdosing. Based on the results of the present study, 0.5 h after administration was still well within the distribution phase in all foals, regardless of age, thus sampling for peak concentration 1 h after bolus administration would be more appropriate. Selection of a 1 h peak sampling time is also supported by the fact that peak synovial and allantoic fluid concentrations occur 1 h after i.v. bolus administration of gentamicin to adult horses [25,26].

In the present study, peak gentamicin concentrations 1 h after administration (Cₘₚₚ) to 1–3-day-old foals were right at the target concentration of 16–20 μg/ml (20.52 ± 2.07 μg/ml; range 18.1–23.24 μg/ml). Corresponding with the higher Vₘ, peak plasma

**Discussion**

Over the past 30 years, in line with improved understanding of the pharmacodynamics of aminoglycosides [5,6], dosing of gentamicin in adult horses has moved away from low doses (2.2–3.3 mg/kg bwt) every 6–12 h, to an extended dosing interval of 6.6 mg/kg bwt q. 24 h [9,21]. This study demonstrates that age has a profound effect on the pharmacokinetics of gentamicin, particularly in foals <4 weeks of age. Therefore, extrapolation of the 6.6 mg/kg bwt q. 24 h dose to neonatal foals would not be appropriate.

As expected based upon the declining proportion of body water and extracellular fluid with increasing age, mean Vₘ decreased with age, being at its highest in 1–3-day-old foals (0.75 ± 0.20 l/kg bwt). This value was higher than those previously reported for foals of the same age receiving lower doses of gentamicin (0.31 ± 0.03 l/kg bwt), but comparable to that reported in healthy foals (0.588 ± 11.9 l/kg bwt to 0.862 l/kg bwt) receiving the aminoglycoside amikacin at 21–25 mg/kg bwt i.v [17,22,23]. By 8 weeks of age, the Vₘ of the foals in the present study (0.26 ± 0.1 l/kg bwt) was
concentrations were signiﬁcantly lower in 1–3-day-old foals than in older foals. By 2 weeks of age, Cmin was considerably above the target of 20 μg/ml in 5 of 6 foals (48.95 ± 15.07 μg/ml; range 19.71–60.71 μg/ml). Based on these results and modelling of the data, administration of a lower dose of 6.6 mg/kg bwt, as recommended for adult horses, would be more appropriate in foals 2 weeks of age or older. However, owing to the considerable interindividual variation, predicted doses for particular age ranges should be taken as a starting point from which to tailor daily dose on a patient-by-patient basis to maintain target peak concentrations.

Elimination half-life was longer at 1–3 days of age and decreased significantly during the ﬁrst month of life, which is consistent with maturation of renal function [27]. Although 1–3-day-old foals had the lowest peak concentrations, they also had the highest trough concentrations (1.97 ± 0.90 μg/ml). Because renal cellular uptake of gentamicin is saturable, nephrotoxicity is associated with insufﬁciently low trough levels, rather than excessively high peaks [28]. The maximal trough concentration to minimise the risk of nephrotoxicity is unknown in horses. In human patients, trough gentamicin concentrations >2 μg/ml have been associated with nephrotoxicity and troughs >4 μg/ml for over 10 days with ototoxicity [11,29,30]. The optimal trough concentration for minimising nephrotoxicity after administration of gentamicin to human patients is controversial, with recommendations ranging from maintaining a trough <2 μg/ml to maintaining a period of <0.5 μg/ml for at least 4 h [13,31,32]. Maintaining a low trough concentration is not only important for reducing toxicity but also to avoid the development of adaptive resistance. Adaptive resistance is a reversible downregulation of the active transport of aminoglycoside into Gram-negative bacteria [33]. This resistance phenomenon is induced rapidly after a dose of aminoglycosides but is reversible during drug free intervals. As a result, prolongation of the dose interval may enable time for the return of bacterial susceptibility before the subsequent dose [33,34]. Based on the aforementioned ﬁndings and on the fact that 5 of 6 foals in the 1–3-day-old age group had trough concentrations >2 μg/ml (range 0.24–2.78 μg/ml), a prolonged dosing interval of q. 36 h or 48 h would be recommended for foals less than 2 weeks of age. Large clinical data sets in children and neonates indicate that extending dosing intervals to q. 36 h or 48 h minimises cost, simpliﬁes administration and results in more favourable peak and trough concentrations [13,32]. In addition, any disease resulting in renal insufﬁciency would also necessitate an increased dosing interval or use of an alternative antimicrobial.

Based on the present study, i.e. administration of gentamicin at a dose of 12 mg/kg bwt, q. 36 h would be required to achieve adequate peak concentrations (≥20 μg/ml) and to maintain trough concentrations <2 μg/ml in healthy foals less than 2 weeks of age. In foals 2 weeks of age or older, a dose of 12 mg/kg bwt was excessive and a dose of 6.6 mg/kg bwt given q. 24 h was predicted to be sufﬁcient. Additional studies will be necessary to conﬁrm this lower dosage. The effects of age on the pharmacokinetics of gentamicin in foals are probably complicated by the inﬂuence of disease, prematurity and concurrent administration of other medications. Therefore, therapeutic drug monitoring is recommended to ensure that desired peak and trough concentrations are being achieved, especially because of the inherent interindividual variation in the pharmacokinetic parameters of gentamicin, even in healthy foals.

Authors’ declaration of interests

No competing interests have been declared.

Source of funding

Supported by the Grayson Jockey Club Research Foundation, the Marguerite T. Hodgson Equine Research Endowment, and the Steve Lee Memorial Scholarship for Equine Research.

Acknowledgements

We thank Londa J. Berghaus for technical assistance.

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References


