Gentamicin dosage intervals in neonates: Longer dosage interval—less toxicity

MW DAVIES and DW CARTWRIGHT
Grantley Stable Neonatal Unit, Royal Women's Hospital, Bowen Bridge Road, Herston, Brisbane, Queensland, Australia

Objectives: The aim of this study was to determine the incidence of toxic trough serum gentamicin levels in neonates in the first week of life, with different dosage intervals.

Methods: This was a retrospective study of neonates born between 01.07.95 and 31.12.95, who received gentamicin. Data were collected on birth weight, gestation, gentamicin dose, the trough level of gentamicin, serum creatinine and urine output. A trough serum gentamicin level of $\geq 1.5$ mg/L was considered toxic.

Results: One hundred and seventy infants met the study criteria. All 21 infants in group one (24–29 weeks) received gentamicin with a dosage interval of 24 h. Sixteen (76%) infants had toxic trough serum gentamicin levels. In group two (30–34 weeks) 8 infants had gentamicin q12hly and all (100%) had toxic trough serum gentamicin levels. Fourteen infants had gentamicin every 18 h and 13 (93%) had toxic trough serum gentamicin levels. Sixty-one infants had gentamicin q24hly and 25 (41%) had toxic trough serum gentamicin levels. The differences in proportions with toxic levels were statistically significant. In group three ($\geq 35$ weeks) 29 infants had gentamicin q12hly and 25 (86%) had toxic trough serum gentamicin levels. Six infants had gentamicin every 18 h and 2 (33%) had toxic trough serum gentamicin levels. Thirteen infants had gentamicin q48hly and 4 (31%) had toxic trough serum gentamicin levels. The differences in proportions comparing infants having gentamicin q12hly with those having it q48hly were statistically significant.

Conclusions: A starting gentamicin dosage interval of 12 h in infants of any gestational age, or a starting dosage interval of 24 h for infants of less than 30 weeks gestational age, leads to most having toxic trough serum gentamicin levels. In infants of 30 weeks gestational age or greater, most have safe non-toxic trough serum gentamicin levels if started on a dosage interval of 24 h.

Key words: drug administration schedule; drug monitoring; drug toxicity; gentamicins; infant, newborn.
RESULTS

One hundred and seventy infants met the study criteria. The infants were divided into three groups for analysis. Group one, infants from 24 to 29 completed weeks gestation (n = 21). Group two, infants from 30 to 34 completed weeks gestation (n = 83). Group three, infants of ≥35 weeks gestation (n = 66). Birthweights, gestational ages and gentamicin doses are summarised in Table 1.

All 21 infants in group one received gentamicin q24hly. Sixteen (76%) infants had toxic trough serum gentamicin levels. In group two, 6 infants had gentamicin q12hly and all (100%) had toxic trough serum gentamicin levels. These infants were significantly larger and more mature than the infants receiving gentamicin q24hly. Fourteen infants had gentamicin every 18 h (q18hly) and 13 (93%) had toxic trough serum gentamicin levels. These infants were significantly larger than the infants receiving gentamicin q24hly. Sixty-one infants had gentamicin q24hly and 25 (41%) had toxic trough serum gentamicin levels. The differences in proportions with toxic levels were statistically significant (Table 2). That is gentamicin given every 12 or 18 h was more likely to lead to toxic trough serum gentamicin levels compared with gentamicin given q24hly.

In group three, 29 infants had gentamicin q12hly and 25 (86%) had toxic trough serum gentamicin levels. These infants were significantly larger than the infants receiving gentamicin q24hly. Six infants had gentamicin q18hly and 2 (33%) had toxic trough serum gentamicin levels. Thirty-one infants had gentamicin q24hly and 4 (13%) had toxic trough serum gentamicin levels. The differences in proportions comparing infants having gentamicin q12hly with those having it q24hly were statistically significant (Table 2). That is gentamicin given q12hly was more likely to lead to toxic trough serum gentamicin levels than was gentamicin given q24hly.

DISCUSSION

In our unit, in 1995, infants were commenced on different dosing regimens of gentamicin. This gave us an opportunity to ascertain how many of our infants had toxic trough serum gentamicin levels and to see if the incidence of toxicity varied with the dosage interval. Any evidence of renal impairment would significantly influence the prescribed dosage interval and gentamicin clearance, so we excluded these infants from our analysis. Our results confirm our impression that the shorter the dosage interval of gentamicin the greater the likelihood of high trough levels.

Non-toxic or safe trough gentamicin levels are set arbitrarily and there is no good evidence that any particular trough level to aim for is correct—threshold levels between 0.5 and 2.0 mg/L have been recommended. The threshold level we use for trough gentamicin levels is 1.5 mg/L. Our gentamicin assays are carried out at the Department of Microbiology, Royal Brisbane Hospital. They recommend that gentamicin dosage intervals be increased if levels are ≥1.5 mg/L. This level was initially introduced years ago before the use of TDX technology with its speed of turnaround time of 1–2 h. The recommended level has been retained “because it has an inbuilt sense of ‘safety’ in case of delays in action by clinical staff or if there is a loss of test sensitivity/reproducibility, and because staff are familiar with and understand what it means”.[19]

Toxicity of aminoglycosides is related to accumulation of the drug if it is given too often. Harmful effects on the kidney and middle ear can lead to renal failure and deafness.[20] Renal toxicity results from accumulation of gentamicin in lysosomes of cells in the proximal tubule. This leads to disordered reabsorption and decreased glomerular filtration rate.[15] Auditory brain stem evoked responses in neonates demonstrate a clear effect from gentamicin (even in the absence of any trough toxic gentamicin levels of ≥2.0 mg/L) and animal studies demonstrate anatomical damage to the cochlea with electron microscopy.[5] However, sensorineural hearing loss is common in graduates of neonatal intensive care and the contribution of gentamicin is largely unknown.[5]

Once the decision has been made to start a baby on gentamicin the clinician must then decide how much of the drug to give (the dose) and how often to give it (the dosage interval). For term neonates, the recommended dosage regimen up until the early 1990s has been 2.5 mg/kg/dose given q12hly.[4] Neonates have a longer half life for gentamicin than adults[1] and in the very preterm infant it may be prolonged to 14 h.[10] Therefore neonates require a longer dosage interval compared with older children and adults, and preterm neonates require even longer dosage intervals. Preterm neonates also have a larger volume of distribution for gentamicin than more mature infants and may require larger doses of gentamicin to achieve adequate peak gentamicin levels.[20][21]

There are many compelling reasons for giving gentamicin less often, apart from the decreased incidence of high trough levels found in this study. These include savings related to drug costs and staff time, and a reduction in the incidence of toxic trough gentamicin levels. However, if treatment is required, it is often for only a few days and a more concentrated dosing regimen may be appropriate in these circumstances.
Table 2  Birthweight, gestation and gentamicin dose data by dosage interval

<table>
<thead>
<tr>
<th>Dosage Interval</th>
<th>12 h</th>
<th>18 h</th>
<th>24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>14</td>
<td>6</td>
<td>33</td>
</tr>
<tr>
<td>sGent&lt;1.5 mg/L</td>
<td>8</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>sGent&gt;1.5 mg/L</td>
<td>6</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Birthweight (kg)</td>
<td>3.40</td>
<td>3.04</td>
<td>3.06</td>
</tr>
<tr>
<td>Gestation (weeks)</td>
<td>38.7</td>
<td>38.6</td>
<td>39.4</td>
</tr>
</tbody>
</table>

Conclusion

A starting gentamicin dosage interval of 12 h in infants of any gestational age leads to most having toxic trough serum gentamicin levels. The same can be said for infants of less than 30 weeks gestational age with a starting dosage interval of 24 h. In infants of 30 weeks or more, most have safe non-toxic trough serum gentamicin levels if started on a dosage interval of 24 h. In our unit, as a result of the above data, we recommend that gentamicin is commenced at a dose of 2.5 mg/kg at a dosage interval of 24 h. The effect has been demonstrated in vitro for that gentamicin is commenced at a dose of 2.5 mg/kg at a dosage interval of 36 h for infants less than 30 weeks gestation and a dosage interval of 24 h for infants of 30 weeks or more.

References

4 Shann F, Duncan A. Drug doses in paediatrics, 7th edn. Royal Children’s Hospital, Melbourne, 1992.