LETTER TO THE EDITOR

Improving gentamicin dosing: A suggested approach to a simplified once-daily dosing schedule

To the Editor,

Traditionally, gentamicin has been administered at a dosage of 3–5 mg/kg daily in divided doses, typically every 8 h. However, therapeutic drug monitoring has shown that multiple daily dosing rarely achieves adequate peaks and often produces high trough levels [1]. During the last two decades, there has been a move toward single daily dosing. Randomized controlled trials have indicated that once-daily aminoglycoside administration is as efficacious as the traditional multiple-dose method; may lower, but not eliminate, the risk of drug-induced nephrotoxicity and ototoxicity; and is simpler, less time-consuming and more cost-effective than multiple-dose regimens [2–4]. The aims of once-daily dosing are as follows: (1) to achieve high peak serum levels [10 times the minimum inhibitory concentration (MIC)] for maximum bacterial kill, as efficacy relates to the ratio by which post-dose levels exceed MIC; and (2) to achieve a short period of low drug concentration to minimize toxicity (approximately 4 h).

Data from Table 1 clearly show that most patients treated with gentamicin at our institution over a period of six months were given multiple daily doses, and 97.3% (72/74) of gentamicin prescriptions were for less than 5 mg/kg. When the single small dose prescriptions, which were most likely given for prophylaxis, were excluded, multiple daily dosing was found to account for 89.2% (74/83) of the prescriptions compared to 10.8% (9/83) for the once-daily dosing. When the once-daily dosing regimen was used, only one patient (1/9) received an optimal dose of 5 mg/kg. In contrast, 25.7% (19/74) of the patients treated with multiple divided doses were given suboptimal doses of less than 3 mg/kg. Most prescriptions (89%) were given by surgeons and gynecologists, suggesting that this useful antimicrobial agent may be underprescribed by internal medicine physicians.

Aminoglycosides show concentration-dependent activity. The duration of the post-antibiotic effect (PAE) of aminoglycosides increases with their peak concentration. Once-daily dosing results in a high peak serum concentration (10 times the MIC), and the serum concentration can fall below the MIC for a short period before the next dose without loss of efficacy. Moreover, a high peak serum level reduces concern about the adaptive resistance phenomenon, which may arise due to the emergence of a resistant subgroup or the downregulation of aminoglycoside uptake following the initial exposure of the organism to the drug (known as the first exposure effect) [5]. In cases with renal impairment, extension of the dosage intervals is favored over the reduction of the dose with once-daily administration, because extended dosage intervals achieve higher peak levels with enhanced bactericidal activity. Until further evidence is available, once-daily dosing should not be used in the following groups of patients: (1) those with severe renal impairment, i.e., CrCl < 20 mL/min and/or patients on dialysis; (2) those with infective endocarditis; (3) those with ascites; (4) those with major burns (>20%); (5) those with exacerbated cystic fibrosis; and (6) pregnant patients.

The recommended once-daily gentamicin dose is 5–7 mg/kg per day. A higher dose has a clear advantage in patients with an increased volume of drug distribution, e.g., those with congestive heart failure or “leaky” capillaries as a result of bacteremia. No controlled studies have compared 5 versus 7 mg/kg of gentamicin, but clinical experience with the 7 mg/kg dosage is substantial [6]. The ‘Hartford Hospital Nomogram’ uses a constant dose of gentamicin of 7 mg/kg for all eligible patients [6]. A gentamicin level measured anytime between 6 and 14 h after the start of the first gentamicin infusion is used to establish the dosing interval from the nomogram. For example, if the serum level falls in the area designated q24hr, q36hr or q48hr in the nomogram, the new dosing interval becomes every
Table 1  Gentamicin dosing in adults at Qatif Central Hospital over a period of six months (January–June, 2012).a

<table>
<thead>
<tr>
<th>Dose cohortb</th>
<th>No. of patients</th>
<th>Daily dose (mg/kg)c</th>
<th>Service</th>
<th>Durationd</th>
<th>Agee</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;3</td>
<td>3–4</td>
<td>≥5</td>
<td>MD</td>
</tr>
<tr>
<td>SD</td>
<td>8</td>
<td>8</td>
<td>—</td>
<td>—</td>
<td>6</td>
</tr>
<tr>
<td>OD</td>
<td>9</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>MD</td>
<td>74</td>
<td>19</td>
<td>53</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>91</td>
<td>33</td>
<td>55</td>
<td>3</td>
<td>10</td>
</tr>
</tbody>
</table>

a Exclusions include the following patients/conditions: pediatric patients, renal impairment, burns, endocarditis, pregnancy, cystic fibrosis and patients with ascites.
b SD, single dose; OD, once-daily regimen; MD, multiple-dose regimen.
c Doses were calculated based on ideal body weight but the actual body weight was used if it was less than the ideal body weight.
d Values are modes (ranges).
e Values are means (ranges).

24 h, 36 h or 48 h, respectively; however, the initial dose remains the same. Similarly, if a once-daily dose of 5 mg/kg is used, the 'Urban-Craig Nomogram' can be applied to monitor and interpret the gentamicin levels [5]. In contrast to the Hartford nomogram, there is the option to decrease the dosing interval to every 12 h for patients with unusually low drug levels after dosage. Alternatively, pre-dose levels can be monitored to target a serum level of less than 1 mg/L before the administration of the next dose.

References


Funding

No funding sources.

Competing interests

None declared.

Ethical approval

Not required.

Arif Al-Hamad *  
Division of Clinical Microbiology, Pathology and Laboratory Medicine, Qatif Central Hospital, Qatif 31911, Saudi Arabia  
* Tel.: +966 (0)13 8361000.  
E-mail address: arifhamad@doctors.org.uk

4 March 2013