Sir,

Much of the gentamicin prescribed in the UK is given once daily and can be controlled by using the Hartford nomogram. Using the Hartford method gives time for assay of the blood sample before the next dose is due to be given, allowing appropriate dose modification to be made if necessary. This is not possible with control of therapy by ascertaining pre-dose levels. As clearly stated by its authors, this nomogram is designed only for 7 mg/kg/24 h.

Experience of interactions with other hospitals indicates that lower dosages are being used, some as low as 5 mg/kg/24 h and, anecdotally, the Hartford nomogram may still be used to adjust dosages. We describe here a study of the potential errors that could occur if dosages lower than 7 mg/kg are controlled by using this nomogram.

Blood level data for patients with normal renal function [estimated glomerular filtration rate (eGFR) >90 mL/min/1.73 m²] and receiving 7 mg/kg of gentamicin were abstracted from Figure 2 in a paper by the Hartford group. These showed that with normal renal function, the simulated blood level at 1 h (the end of the infusion) was 19.6 mg/L, the concentrations decreased linearly when plotted semi-logarithmically and the plasma $t_{1/2}$ was ~2.5 h. The corresponding 1 h concentrations for three lower doses (5, 4 and 3 mg/kg) were then calculated proportionally since the pharmacokinetics of aminoglycosides are linear in this dose range. The decision concentrations for altering the dosage interval were taken from the nomogram. These were ≥7.6 mg/L for a sample taken 6 h after the start of the infusion and ≥2.0 mg/L for a sample at 14 h. These values were plotted on a semi-logarithmic graph of concentration versus time, and blood concentration lines from the four 1 h values were taken through the 6 h and 14 h decision concentrations.

With doses lower than 7 mg/kg a sample at 6 h would not detect an increase in $t_{1/2}$ from that expected in a patient with normal function as reliably as one at 14 h. Taking a concentration of 7.6 mg/L at 6 h, the $t_{1/2}$ values for the four doses that would trigger a change in dosage using the nomogram, and the corresponding 24 h concentrations are shown in Figure 1.

The maximum $t_{1/2}$ of gentamicin detectable using the 6 h nomogram decision point and the likely concentration at 24 h were: 7 mg/kg, 3.7 h and 0.2 mg/L; 5 mg/kg, 5.7 h and 0.8 mg/L; 4 mg/kg, 8.9 h and 1.8 mg/L; and 3 mg/kg, 34.7 h and 5.2 mg/L. The corresponding values for the 14 h decision point were: 7 mg/kg, 3.9 h and 0.3 mg/L; 5 mg/kg, 4.6 h and 0.8 mg/L; 4 mg/kg, 8.9 h and 1.8 mg/L; and 3 mg/kg, 34.7 h and 5.2 mg/L.

Figure 1. Blood levels of gentamicin for doses of 7 to 3 mg/kg showing the concentration profiles that could be possibly present when using the 6 h decision point. ODA, once-daily aminoglycosides; gent, gentamicin; tobra, tobramycin; q, every.
Doses of 7 mg/kg are likely to produce misleading results if a sample is taken at 6 h and plotted on the Hartford nomogram. With increasingly smaller doses, the increase in $t_{1/2}$ and 24 h concentration that could occur before they would be detected, and therefore the dosage modified accordingly, rose exponentially. All lower doses were susceptible to producing misleading results of clinical significance, but doses of ≤4 mg/kg were particularly dangerous. If the Hartford nomogram is used for doses lower than 7 mg/kg, then samples should ideally be taken at 14 h after the start of the infusion. This may cause a problem in getting an assay done before the next dose. An alternative solution would be to adjust the observed concentration proportionally to the dose (e.g., the concentration following 5 mg/kg should be increased by 7/5) before plotting on the nomogram. The justification for these approaches lies in the suggestion by originators of the nomogram in using it for controlling amikacin therapy (15 mg/kg); although such methods have not been validated. A safer and more practical approach may be to use a nomogram that has been redrawn to reflect a 5 mg/kg dose, such as reported by Urban and Craig. However, irrespective of the control approach followed, it should be recognized that the Hartford nomogram fails to take into account volume of distribution changes, such as may occur in serious sepsis, which may serve to compound any difficulties in interpretation of gentamicin concentrations using it. Therefore, while superficially it might appear that lower doses are appropriate for patients with diminished renal function, the unmodified Hartford nomogram is unsuitable for controlling their treatment without adequate precautions.

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References