Therapeutic Drug Monitoring of High-Dose Gentamicin in an Elderly Patient: A Case Report

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Abstract

Objective: To report the pharmacokinetics of gentamicin using traditional multiple daily doses and a high-dose regimen in an elderly patient. Clinical Presentation and Intervention: An 80-year-old male who presented with mild renal failure received two different gentamicin dosing regimens, 60 mg every 8 h for septicemia and a high dose of 400 mg with extended interval for suspected endocarditis. Based on population parameters of \( k_e \) (0.1030 h\(^{-1}\)) and \( V_d \) (18.1 liters), the initial gentamicin dosage regimen was calculated to be 80 mg every 12 h. The measured peak and trough concentrations were used to calculate the individual parameters of \( k_e \) (0.0749 h\(^{-1}\)) and \( V_d \) (30.9 liters). After a 5-mg·kg\(^{-1}\) gentamicin dose, the Hartford nomogram was used to estimate the extended dosage interval. Conclusion: The Hartford nomogram may be a valid tool for estimating the dosage interval after a 5-mg·kg\(^{-1}\) single dose of gentamicin.

Introduction

The aminoglycoside gentamicin is widely administered to treat serious gram-negative infections; however, its use is limited by concerns about toxicity \cite{1}. Conventional multiple daily dosing of gentamicin, in order to achieve peak concentrations of 5–10 mg·l\(^{-1}\) and trough concentrations of <2 mg·l\(^{-1}\), has been used for many years \cite{2}. However, more recent data support the use of an extended dosage interval for gentamicin in view of the potential for improved efficacy and reduced toxicity \cite{3}. By administering gentamicin as a single daily dose, a clinician can take advantage not only of the drug's concentration-dependent killing, but also its prolonged post-antibacterial effect \cite{4}. There are no clearly established ranges of peak and trough serum concentrations for monitoring the extended dosage interval administration of gentamicin. Recently, however, an extended dosage interval method (Hartford nomogram) has been used to calculate the dosage interval based on a 7-mg·kg\(^{-1}\) dose and single concentration measurement \cite{3}.

The pharmacokinetics of gentamicin are extremely variable \cite{5}. Changes in renal function can alter the rate and extent of aminoglycoside elimination with an increase in risk of toxicity. Since renal function tends to decline with increasing age, it is important to correct for this in establishing an individualized dosage regimen. The aminoglycosides currently in use in Al-Amiri Hospital are amikacin and gentamicin. Local resistance to these...
drugs is considered to be low and they are therefore used as empirical therapy. This case discusses the pharmacokinetics of gentamicin during both traditional multiple daily administration and extended interval dosing in one elderly patient with renal impairment admitted to Al-Amiri Hospital, Kuwait.

**Case Report**

An 80-year-old Kuwaiti male, weight 78 kg, height 177 cm, was admitted to the medical ward, Al-Amiri Hospital, Kuwait with severe headache and fever (temperature was 38.5°C). Past medical history included pulmonary edema, pneumonia, chronic obstructive pulmonary disease and mild renal impairment. Serum creatinine value on admission was 136 μmol·l⁻¹ (40–115, normal range).

Blood and urine samples were sent to bacteriology for identification and sensitivity test. The next day the patient collapsed and became critically ill and was transferred to the intensive care unit. Ampicillin 1 g every 6 h and gentamicin 60 mg every 8 h were prescribed.

**Calculation of the Appropriate Initial Dosage Regimen**

The ideal body weight, dosing weight, volume of distribution (V_d), creatinine clearance (Cl_cr), gentamicin clearance (Cl_gent), and elimination rate constant (k_e) were calculated, using standard population equations [6], as 68.4 kg, 72.2 kg, 18.1 liters, 37 ml·min⁻¹, 1.87 liters·h⁻¹, 0.103 h⁻¹, respectively. Subsequently, the predicted loading (8 mg·l⁻¹ as target level) and maintenance doses to achieve steady-state peak and trough concentrations within therapeutic range were calculated using the following equation: C_{ss} = (D/V_d) × e^{-k_e T} × (1/(1 - e^{-k_e T})), where C_{ss} is the steady-state concentration, t = time and T = dosage interval. The values for loading and maintenance doses were 145 mg and 80 mg/12 h, respectively, giving peak and trough levels of 5.6 and 1.8 mg·l⁻¹, respectively.

**Calculation of Individual Pharmacokinetic Parameters**

After the third dose, the measured peak (1 h) and the trough (6.75 h) concentrations were 4 and 2.6 mg·l⁻¹, respectively. Gentamicin levels were measured on the COBAS INTEGRA systems using a fluorescent principle of fluorescence polarization immunoassay. Pharmacokinetic parameters (k_e, V_d and Cl_gent) calculated using a modified two-point Sawchuk-Zaske method [7] were 0.0749 h⁻¹, 30.9 liters and 2.31 liters·h⁻¹ for k_e, V_d and Cl_gent, respectively.

Using the Hartford Nomogram for High-Dose Gentamicin

On day 4 of admission, the patient became severely ill and his condition was critical. Endocarditis was suspected. Therefore, the dosage regimen was changed from 60 mg every 8 h to 400 mg (5.1 mg·kg⁻¹) as a single dose. The dose of 400 mg was administered in the morning and blood samples were taken at 7, 21, 24 and 48 h later for determination of gentamicin levels (table 1).

The Hartford nomogram uses a dose of 7 mg·kg⁻¹ [3] and the initial dosage interval is estimated according to the patient’s Cl_cr. The dosage frequency is determined by using a single monitored random serum gentamicin concentration drawn between 6 and 14 h after the start of the initial intravenous dose. Dosage intervals for patients are then adjusted to every 24, 36 or 48 h [3]. Assuming linear pharmacokinetics, clinicians have begun to use the Hartford nomogram for doses other than 7 mg·kg⁻¹ (in this case clinicians used 5 mg·kg⁻¹), but this approach has not been formally evaluated [8].

In the present case, the S_{cr} on 12/5/03 was 196 μmol·l⁻¹ and the subsequent estimated Cl_cr was 26 ml·min⁻¹. Based on the estimated Cl_cr, the initial dosage interval was estimated as 48 h. Gentami-

<table>
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<th>Day</th>
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<th>Mode of administration</th>
<th>Dose mg</th>
<th>Sample time h</th>
<th>Measured concentration mg·l⁻¹</th>
<th>Predicted concentration mg·l⁻¹</th>
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<tr>
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<tr>
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<tr>
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* Revised parameter of k_e (0.0530 h⁻¹) was used to predict gentamicin levels.

### Table 1. Gentamicin dosage regimen in an elderly patient associated with mild renal impairment
gentamicin dose adjustment based on an individualized $V_d$. After 32 h from starting the first dose (60 mg), the $S_{cr}$ level had risen from 136 to 196 µmol·l$^{-1}$ (on 12/05/03), indicating a deterioration in renal function. A trough gentamicin level of 2.6 µg·l$^{-1}$, obtained a few hours later, was above the predicted levels, reflecting the reduced renal function. When a single dose of 400 mg gentamicin started on day 4 after admission, no further reduction in renal function occurred as indicated by the stable $S_{cr}$ level over the next 3 days (table 1).

Based on an individualized $Cl_{gent}$ of 2.31 liters·h$^{-1}$ the predicted gentamicin level (8.6 µg·l$^{-1}$) 7 h following the 400-mg dose was lower than the measured level (10 µg·l$^{-1}$). Therefore, $Cl_{gent}$ was recalculated (based on 10 mg·l$^{-1}$) and found to be 1.64 liters·h$^{-1}$. Using this value and the principle of superposition, all predicted gentamicin concentrations were very close to the measured levels. In addition, the observed trough level of 1.5 µg·l$^{-1}$ suggested that the use of the Hartford nomogram was applicable in this patient at a dose of 5 mg·kg$^{-1}$. The validity of this nomogram at this dose was confirmed by the predicted concentration at 48 h (1.2 µg·l$^{-1}$, which is very close to the observed level of 1.5 µg·l$^{-1}$). Furthermore, the nomogram indicated a dosage interval of just over 48 h in this patient. This was validated separately using a standard non-steady-state equation, which indicated that a target gentamicin trough concentration of 1 µg·l$^{-1}$ would be reached 48.4 h following a 5-mg·kg$^{-1}$ dose. This report, in a patient with nonstable renal function, emphasizes the importance of therapeutic drug monitoring when gentamicin is administered, in order to individualize a safe and effective dosage regimen.

## Conclusion

Our data show that the Hartford nomogram might be used to estimate dosing interval when doses other than 7 µg·kg$^{-1}$ gentamicin are administered.

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### References