Clinical Pharmacokinetics of Gentamicin

Estimation of Initial Dosing Parameters in Hospitalized Patients at Al-Amiri Hospital Kuwait

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Abstract

Objectives: The objectives of this study were to: (1) derive equations for estimating gentamicin clearance (Cl gent) and volume of distribution (Vd) based on the local population attending Al-Amiri Hospital, Kuwait; (2) independently evaluate these equations by comparison with other published methods in their predictive ability to estimate Cl gent and Vd.

Materials and Methods: Cl gent and Vd were calculated in 47 patients (group 1) using the Sawchuk-Zaske method. Regression analysis was used to derive a correlation between creatinine clearance (Cl cr) and Cl gent, Vd and actual body weight (ABW). Based on actual Cl gent and Vd values, the predictive ability of the estimated parameters from the regression equations was validated and compared with 4 published methods using mean error (ME), i.e. bias, and mean squared error (MSE) and root mean squared error (RMSE), i.e. precision. All equations were also evaluated in an independent second group (group 2) of 23 patients. Results: The mean ± SD values of Cl gent and Vd were 4.0 ± 1.8 l·h⁻¹ and 16.8 ± 6.7 liters, respectively. The derived equations were: Cl gent = (0.760) (Cl cr) + 1.117 (r = 0.701) and Vd = (0.165) (ABW) + 5.604 (r = 0.532). In comparison to the 4 published methods, the derived equations were less biased (ME = 0.00) and more precise (MSE = 1.68, RMSE = 1.02) in predicting Cl gent (p < 0.05), and less biased (ME = −0.01) with no difference in precision (MSE = 36.22, RMSE = 4.59) in predicting Vd (p > 0.05). This precision was confirmed in the second group of 23 patients, where the derived equations were less biased (ME = −0.1) and more precise (MSE = 3.22, RMSE = 1.48) in predicting Cl gent (p < 0.05), whilst no difference was found for prediction of Vd (p > 0.05).

Conclusion: The equations developed in this study provided a reliable estimation of Cl gent and Vd. It is planned to use them at Kuwait Hospitals to help provide more individualized patient dosing information to physicians.

Key Words

Gentamicin • Pharmacokinetics • Initial dosing parameters • Prediction error

Introduction

It is generally recognized that monitoring the serum concentration of certain drugs helps to improve clinical effectiveness by optimizing efficacy and minimizing toxicity. The aminoglycoside gentamicin, a potent antimicrobial against Gram-negative bacteria, is widely used in hospitalized patients. However, it has a narrow therapeutic index [1–3], which has prompted the development and wide use of initial dosing methods to achieve safe and effective blood levels. The goal of initial gentamicin dosing
is to compute the best dose for the patient according to the site and severity of the infection and any concurrent conditions which may influence gentamicin pharmacokinetics. Several kinetics equations are available for initial gentamicin dosing in patients to attain desired peak (5–10 mg l\(^{-1}\)) and trough (<2 mg l\(^{-1}\)) serum concentrations [4–7]. Such methods use defined population-based parameters, from which the gentamicin clearance (Cl\(_{\text{gent}}\)) and volume of distribution (V\(_d\)) are calculated prior to initial gentamicin dosing.

There have been 2 main approaches to aminoglycoside dosing in adults, the traditional multiple daily dosing and extended interval dosing (once daily). The rationale of once daily dosing is to achieve a high peak concentration which increases the postantibiotic effect and may also help minimize toxicity [8–10]. In Kuwait, gentamicin treatment in hospitalized patients is based on traditional multiple daily dosing (often 80 mg every 8 or 12 h). Substantial interpatient variability exists in Cl\(_{\text{gent}}\) and V\(_d\) [11–13], and there is a need for dosing methods based on local (Kuwaiti) population data [13].

Therefore, the objectives of this study were to: (1) calculate gentamicin pharmacokinetic parameters for the local inpatient population; (2) develop dosing equations based on these parameters; (3) independently compare these equations with 4 published methods for their predictive ability in estimating Cl\(_{\text{gent}}\) and V\(_d\).

**Materials and Methods**

The study population comprised adult inpatients (medical/surgical) at Al-Amiri Hospital who were initiated on a gentamicin regimen, as decided by the responsible physician. The study did not alter clinically indicated therapy with gentamicin. Hospital inpatients who received intravenous gentamicin as part of their routine therapy were considered eligible for the study if: (1) they had gentamicin levels drawn at steady state (after 24–48 h of starting therapy); (2) levels were drawn appropriately, defined as a peak being drawn 1 h after a bolus injection and a trough immediately (or within 30 min) before the next dose; (3) blood sample times were correctly documented; (4) serum creatinine concentrations were determined 24 h before gentamicin dosing.

Patients were excluded from the study if: (1) demographic data, such as age, weight and height were not available; (2) they had experienced unstable renal function (defined as ≥0.3 mg dl\(^{-1}\) change in serum creatinine concentration); (3) received dialysis treatment; (4) previous gentamicin doses had not been given; (5) serum gentamicin concentration had been reported as below the sensitivity of assay (i.e. <0.1 mg l\(^{-1}\)).

The study comprised 2 groups; group 1: 47 patients who were randomly selected based on the chronological order of patients’ admissions to the medical/surgical wards between March 2003 and October 2005. This group was used to establish the relation-

<table>
<thead>
<tr>
<th>Method</th>
<th>Equation</th>
</tr>
</thead>
</table>
| Benjamyn [4] | \[ Cl_{\text{gent}} = 0.0438 \times Cl_{\text{cr}} + 0.0036 \times IBW \]
|              | \[ V_d = 0.25 \times (l\text{-kg}^{-1}) \times DW \]
|              | \[ DW = 0.4 \times (ABW - IBW) + IBW \]       |
| Benet et al. [5] | \[ Cl_{\text{gent}} = 0.82 \times Cl_{\text{cr}} + 0.11 \]
|              | \[ V_d = 0.31 \times (l\text{-kg}^{-1}) \times ABW \] |
| Dettli [6]   | \[ K_e = 0.0024 \times Cl_{\text{cr}} + 0.01 \]
|              | \[ V_d = 0.25 \times (l\text{-kg}^{-1}) \times IBW \]
|              | \[ Cl_{\text{gent}} = K_e \times V_d \]       |
| Bauer [7]    | \[ K_e = 0.00293 \times Cl_{\text{cr}} + 0.014 \]
|              | \[ V_d = 0.26 \times (l\text{-kg}^{-1}) \times (ABW^a) \]
|              | \[ V_d = 0.26 \times (IBW + 0.4 \times (ABW - IBW)) \]
|              | \[ Cl_{\text{gent}} = K_e \times V_d \]       |

\[ Cl_{\text{gent}} = \text{Gentamicin clearance (l h}^{-1}\text{)}; K_e = \text{elimination rate constant (h}^{-1}\text{)}; V_d = \text{volume of distribution (liters)}; Cl_{\text{cr}} = \text{creatinine clearance (ml min}^{-1}\text{)}; ABW = \text{actual body weight (kg)}; IBW = \text{ideal body weight (kg)}; DW = \text{dosing weight (kg)}.\]

\(^a\) Used for non-obese patients.

\(^b\) Used for obese patients (weight >30% of IBW).

**Gentamicin Dosage and Concentration**

All doses of gentamicin were determined by the patient’s attending physician and ranged from 2.5 to 3.5 mg kg\(^{-1}\) total body weight. All doses were diluted in 20 ml of 5% dextrose in water and administered by bolus intravenous injection over 1–3 min (with an average value of 1.5 min). Peak blood samples were obtained 1 h after the injection was completed, and trough samples within 30 min before the end of the dosing interval. The samples were assayed for gentamicin using the Cobas Integra System (Roche Diagnostics, Mannheim, Germany), utilizing fluorescence polarization. Precision for the assay (% coefficient of variation) was <5% for the concentration range 0.1–9.8 mg l\(^{-1}\).

**Gentamicin Kinetics**

Gentamicin kinetic parameters were calculated from the measured serum gentamicin concentrations, using a modified two-point Sawchuk-Zaske method [14]. Although gentamicin is more accurately described by a multi-compartment model, a one-compartment model was used, as is frequently done in clinical practice [15]. The DataKinetics program (MDK), which is based on a
Table 2. Patient demographic characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 1 vs. group 2 p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>male (n = 34)</td>
<td>female (n = 13)</td>
<td>all (n = 47)</td>
</tr>
<tr>
<td>Age, years</td>
<td>50 ± 17 (21–89)</td>
<td>54 ± 16 (23–77)</td>
<td>51 ± 16</td>
</tr>
<tr>
<td>Height, inches</td>
<td>66 ± 4 (60–74)</td>
<td>63 ± 3 (60–71)</td>
<td>65 ± 4</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>73 ± 17 (42–110)</td>
<td>56 ± 11 (40–80)</td>
<td>68 ± 18</td>
</tr>
<tr>
<td>% of IBW</td>
<td>118 ± 22 (83–179)</td>
<td>110 ± 21 (68–140)</td>
<td>115 ± 22</td>
</tr>
<tr>
<td>S\text{cr}, mg/dL</td>
<td>0.9 ± 0.2 (0.6–1.6)</td>
<td>0.7 ± 0.2 (0.6–1.2)</td>
<td>0.9 ± 0.2</td>
</tr>
<tr>
<td>Cl\text{gent}, l/h</td>
<td>4.3 ± 1.4 (1.9–8)</td>
<td>2.3 ± 0.8 (1.3–4)</td>
<td>3.8 ± 1.6</td>
</tr>
</tbody>
</table>

Figures in parentheses are ranges. IBW = Ideal body weight; S\text{cr} = serum creatinine concentration; Cl\text{cr} = creatinine clearance.

* Actual body weight divided by ideal body weight × 100.

Table 3. Gentamicin pharmacokinetic parameters calculated from measured serum gentamicin concentration

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 1 vs. group 2 p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>male (n = 34)</td>
<td>female (n = 13)</td>
<td>all (n = 47)</td>
</tr>
<tr>
<td>Peak level, mg/l</td>
<td>4.3 ± 1.5 (1.6–8.7)</td>
<td>6.6 ± 4.1 (3.9–19.8)</td>
<td>4.9 ± 2.6</td>
</tr>
<tr>
<td>T_{1/2} (Kₑ) h</td>
<td>3.1 ± 1.2 (1.3–5.9)</td>
<td>3.4 ± 1.2 (2.1–6.6)</td>
<td>3.2 ± 1.2</td>
</tr>
<tr>
<td>V₆, liters</td>
<td>18.2 ± 7.1 (7.9–40.0)</td>
<td>13.5 ± 4.2 (8.5–25.6)</td>
<td>16.9 ± 6.7</td>
</tr>
<tr>
<td>Cl\text{gent}, l/h</td>
<td>4.4 ± 1.9 (1.6–10.3)</td>
<td>2.8 ± 0.8 (1.9–4.0)</td>
<td>4.0 ± 1.8</td>
</tr>
<tr>
<td>Cl\text{gent}/Cl\text{cr}</td>
<td>1.0 ± 0.3 (0.7–1.8)</td>
<td>1.3 ± 0.4 (0.7–2.0)</td>
<td>1.1 ± 0.4</td>
</tr>
</tbody>
</table>

Figures in parentheses are ranges. Peak levels were measured 1 h after the dose was completed and trough levels were taken within 30 min before the end of the dosing interval. Cl\text{gent}/Cl\text{cr} = Ratio of individual Cl\text{gent} and estimated Cl\text{cr}.

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Statistical Analysis

The predicted Cl\text{gent} and V₆ derived from this study and the 4 published methods were compared with actual Cl\text{gent} and V₆ determined from the measured gentamicin peak and trough concentrations. The predictive performance of these methods compared to the study equations was determined using the Sheiner and Beal method [17]. The absolute and relative bias (the tendency of methods to either over- or underpredict actual gentamicin parameters) of each method was calculated by determination of the mean prediction error (ME) and the mean error squared (MSE). The absolute and relative precision of each method was determined from the mean squared prediction error (MSE), root mean squared error (RMSE) and the change in mean square error ($\Delta$MSE).

Prediction error (PE) = predicted parameter – actual parameter; ME = $\Sigma$PE/n; MSE = $\Sigma$PE²/n; RMSE = $\sqrt{\text{MSE}}$; $\Delta$ME = ME1 – ME2; $\Delta$MSE = MSE1 – MSE2; where n is the sample size, ME1 and ME2 are the mean errors for 2 different prediction methods, and MSE1 and MSE2 are the MSEs for the 2 methods.

Differences between predicted and measured gentamicin parameters for each method were compared using paired t tests. Statistical significance was accepted at p < 0.05, and 95% CI were considered to be significantly different if the 95% CI did not include zero. SPSS version 13.0 was used for statistical analysis.

Results

Seventy patients (forming 2 independent groups: 1 and 2) met the inclusion criteria. Patients in group 1 were used to derive the equations for the estimation of Cl\text{gent} and V₆. The predictive ability of the derived equations was then compared with those of the published methods.
Group 2 was used for an independent comparison of the study equations with the published methods. The demographic characteristics of both patient groups are presented in table 2. The age range of all patients was between 21 and 89 years, with 52% of the patients aged 50 years or older. The mean actual body weight (ABW) and ideal body weight (IBW) were 68 and 58 kg, respectively. Thirty percent of the patients had an ABW of ≥130% of the IBW, whereas only 2% had an ABW of ≤70%. The mean values for Cl\textsubscript{gent}, V\textsubscript{d} (determined from measured gentamicin concentrations) and T\textsubscript{1/2} (half-life) for both patient groups are shown in table 3. For both groups, peak gentamicin concentrations were subtherapeutic, with mean values of 4.9 and 4.7, due to inadequate initial dosing by physicians.

Figure 1 shows the relationship between Cl\textsubscript{cr} and Cl\textsubscript{gent} for group 1, described by the equation Cl\textsubscript{gent} (l·h\textsuperscript{-1}) = (0.760) × (Cl\textsubscript{cr}) + 1.117. The equation describing the relationship between body weight and V\textsubscript{d} was V\textsubscript{d} (liters) = 0.165 × (ABW) + 5.604. Figure 2.

**Absolute Predictive Performance**

The prediction error and performance values (bias and precision) of the methods used to estimate Cl\textsubscript{gent} and V\textsubscript{d} are shown in tables 4 and 5 for groups 1 and 2, respectively. A smaller ME indicates a less biased method (absolute bias), whereas a smaller RMSE indicates a more precise method (absolute precision). A graphical illustration of the predictive performance of the methods used to estimate Cl\textsubscript{gent} and V\textsubscript{d} is shown in figure 3.

For both patient groups, it was found that ME confidence intervals for the derived study equations included zero for both Cl\textsubscript{gent} and V\textsubscript{d} indicating a low bias.

The other studies [4, 5, 6, 7] only showed good predictive performance in estimating V\textsubscript{d} (95% CI included zero). All of the published methods were biased in predicting Cl\textsubscript{gent} (95% CI did not include zero), whilst 1 method [5] was biased in predicting both Cl\textsubscript{gent} and V\textsubscript{d}. Overall, the derived equations from the present study showed the smallest value of RMSE in almost all predictions, indicating better precision in predicting Cl\textsubscript{gent} and V\textsubscript{d}.

**Relative Predictive Performance**

The ΔME, indicating relative bias, and ΔMSE, indicating relative precision, are shown in tables 4 and 5. With the exception of all but 1 comparison, the power to detect a difference between derived equations and published methods was 90% or greater at the significance level p < 0.05.

**Group 1**

The study equations (having the smallest ME) were significantly less biased (p < 0.05) in predicting Cl\textsubscript{gent} and V\textsubscript{d} compared to the published methods (95% CI for ΔME did not include zero), with the exception of 2 methods [4, 6] for prediction of V\textsubscript{d} (95% CI for ΔME included zero).
With respect to prediction of Cl\textsubscript{gent}, the study equation (having the smallest RMSE) was significantly more precise ($p < 0.05$) than the other methods (95% CI for $\Delta$MSE did not include zero), with the exception of 1 method [7]. With respect to $V_d$ prediction, the study equation was significantly more precise ($p < 0.05$), with the exception of 2 methods [5, 7].

**Group 2**

The study equations (having the smallest ME) were significantly less biased ($p < 0.05$) in predicting Cl\textsubscript{gent} and $V_d$ compared to the other methods, with the exception of 1 method [6] in predicting $V_d$. There was no significant difference in precision among any of the methods when predicting Cl\textsubscript{gent} and $V_d$, with the exception of 1 method [5], which showed poorer precision in predicting $V_d$ ($p < 0.05$; 95% CI for $\Delta$ME did not include zero).

**Discussion**

Gentamicin is a first line antibiotic treatment for serious Gram-negative infections. At Al-Amiri Hospital, Kuwait, traditional multiple daily dosing based on the manufacturer’s recommended dose (often 80 mg every 8 or 12 h) is used routinely when patients are first prescribed gentamicin. However, this practice has not been found to be uniformly reliable and measured plasma gentamicin concentrations are often outside target goals [13].

Patients in group 1 were those used to derive the study equations. Therefore, as expected, the derived study equations were uniformly non-biased in absolute predictive performance for both Cl\textsubscript{gent} and $V_d$ and performed either similarly or better than the 4 published methods in terms of relative predictive performance.

To offset the problem of bias in favor of the derived study equations, their performance was evaluated independently using a new set of data (group 2, comprising 23 patients). In this group, patient demographics and gentamicin pharmacokinetic parameters were not significantly different ($p > 0.05$) from those of group 1, suggesting minimal sampling error despite the relatively small sample size. In terms of both absolute predictive performance and relative predictive performance, similar results (with minor variations) to those described for group 1 were again obtained. When we compared the study equations with the 4 published methods, the conclusion from this comparison indicated that the study equation was less biased ($p < 0.05$) and equally precise ($p > 0.05$) than other methods with regard to predicting Cl\textsubscript{gent}. Also, the
Table 4. Absolute and relative predictive performance of study equation and 4 published methods: estimated $Cl_{g,nt}$ and $V_d$ in group 1 (n = 47)

<table>
<thead>
<tr>
<th>Method</th>
<th>$Cl_{g,nt}$</th>
<th>$V_d$</th>
<th>$Cl_{g,nt}$</th>
<th>$V_d$</th>
<th>$Cl_{g,nt}$</th>
<th>$V_d$</th>
<th>$Cl_{g,nt}$</th>
<th>$V_d$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Measures of absolute performances</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bias</td>
<td>ME</td>
<td>–0.01</td>
<td>–1.02a</td>
<td>–1.19</td>
<td>–0.89a</td>
<td>4.29a</td>
<td>–1.10a</td>
<td>0.21</td>
</tr>
<tr>
<td>95% CI</td>
<td>–0.30 to 0.38</td>
<td>–1.79 to 1.78</td>
<td>–1.40 to –0.63</td>
<td>–2.99 to 0.61</td>
<td>–1.27 to –0.50</td>
<td>2.36 to 6.22</td>
<td>–1.49 to –0.70</td>
<td>–1.62 to 2.05</td>
</tr>
<tr>
<td>Precision</td>
<td>MSE</td>
<td>36.22</td>
<td>2.72</td>
<td>38.07</td>
<td>2.48</td>
<td>60.88</td>
<td>2.97</td>
<td>38.35</td>
</tr>
<tr>
<td>95% CI</td>
<td>18.85 to 53.59</td>
<td>17.89 to 58.25</td>
<td>1.04 to 3.91</td>
<td>34.22 to 87.53</td>
<td>1.79 to 4.14</td>
<td>21.51 to 55.19</td>
<td>1.23 to 3.38</td>
<td>18.16 to 55.82</td>
</tr>
<tr>
<td>RMSE</td>
<td>1.02</td>
<td>4.59</td>
<td>1.18</td>
<td>4.59</td>
<td>1.15</td>
<td>6.12</td>
<td>1.38</td>
<td>4.61</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.78 to 1.25</td>
<td>3.46 to 5.71</td>
<td>0.85 to 1.52</td>
<td>3.39 to 5.78</td>
<td>0.84 to 1.46</td>
<td>4.72 to 7.52</td>
<td>1.08 to 1.68</td>
<td>3.41 to 5.80</td>
</tr>
<tr>
<td><strong>Measures of relative performances</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bias</td>
<td>ΔME (vs. study equation)</td>
<td>1.02</td>
<td>1.18</td>
<td>0.88</td>
<td>–4.30</td>
<td>1.09</td>
<td>–0.22</td>
<td>0.60</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.01 to 1.03b</td>
<td>0.87 to 1.51</td>
<td>0.86 to 0.91b</td>
<td>–5.04 to –3.55b</td>
<td>0.87 to 1.31b</td>
<td>–0.66 to 0.21</td>
<td>0.39 to 0.82b</td>
<td>0.24 to 0.88b</td>
</tr>
<tr>
<td>Precision</td>
<td>ΔMSE (vs. study equation)</td>
<td>–1.04</td>
<td>–1.85</td>
<td>–0.79</td>
<td>–24.66</td>
<td>–1.29</td>
<td>–2.13</td>
<td>–0.62</td>
</tr>
<tr>
<td>95% CI</td>
<td>–1.84 to –0.24b</td>
<td>–7.43 to 3.74</td>
<td>–1.43 to –0.16b</td>
<td>–50.51 to 1.19</td>
<td>–2.12 to –0.43b</td>
<td>–9.67 to 5.43</td>
<td>–1.36 to 0.12b</td>
<td>–4.85 to 3.31</td>
</tr>
</tbody>
</table>

*a p < 0.05 vs. zero (biased); b p < 0.05, significant difference in predictive performance (i.e. 95% CI excludes zero). All comparisons have power ≥90%, except those italicized (68%).
### Table 5. Absolute and relative predictive performance of study equation and 4 published methods: estimated Cl\textsubscript{gent} and V\textsubscript{d} in group 2 (n = 23)

<table>
<thead>
<tr>
<th>Method</th>
<th>Cl\textsubscript{gent}</th>
<th>V\textsubscript{d}</th>
</tr>
</thead>
<tbody>
<tr>
<td>study equation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cl\textsubscript{gent}</td>
<td>3.22</td>
<td>14.07</td>
</tr>
<tr>
<td>V\textsubscript{d}</td>
<td>1.73 to 4.72</td>
<td>5.50 to 2.59</td>
</tr>
<tr>
<td>Benjamyn [4]</td>
<td>−0.10</td>
<td>0.09</td>
</tr>
<tr>
<td>Cl\textsubscript{gent}</td>
<td>−1.13\textsuperscript{a}</td>
<td>−1.48</td>
</tr>
<tr>
<td>V\textsubscript{d}</td>
<td>−1.90 to −0.35</td>
<td>−3.09 to 0.14</td>
</tr>
<tr>
<td>Benet et al. [5]</td>
<td>−0.97\textsuperscript{a}</td>
<td>4.53\textsuperscript{a}</td>
</tr>
<tr>
<td>Cl\textsubscript{gent}</td>
<td>−1.79 to −0.15</td>
<td>2.55 to 6.54</td>
</tr>
<tr>
<td>V\textsubscript{d}</td>
<td>−1.30\textsuperscript{a}</td>
<td>0.40</td>
</tr>
<tr>
<td>Dettli [6]</td>
<td>−2.02 to −0.59</td>
<td>−1.41 to 2.21</td>
</tr>
<tr>
<td>Cl\textsubscript{gent}</td>
<td>4.31</td>
<td>16.88</td>
</tr>
<tr>
<td>V\textsubscript{d}</td>
<td>2.24 to 6.37</td>
<td>8.82 to 24.95</td>
</tr>
<tr>
<td>Bauer [7]</td>
<td>−1.65 to −0.03</td>
<td>−2.50 to 0.77</td>
</tr>
<tr>
<td>Cl\textsubscript{gent}</td>
<td>4.10</td>
<td>14.42</td>
</tr>
<tr>
<td>V\textsubscript{d}</td>
<td>2.29 to 5.91</td>
<td>5.92 to 22.91</td>
</tr>
</tbody>
</table>

### Measures of absolute performances

**Bias**

| ME   | 1.03 |
| 95% CI | 1.02 to 1.04\textsuperscript{b} |

**Precision**

| MSE  | 1.57 |
| 95% CI | 1.15 to 1.99\textsuperscript{b} |

### Measures of relative performances

**Bias**

| ΔME (vs. study equation) | 0.88 |
| 95% CI | 0.84 to 0.91\textsuperscript{b} |

**Precision**

| ΔMSE (vs. study equation) | −4.45 |
| 95% CI | −5.23 to −3.66\textsuperscript{b} |

\textsuperscript{a}p < 0.05 vs. zero (biased); \textsuperscript{b}p < 0.05, significant difference in predictive performance (i.e. 95% CI excludes zero).

All comparisons have power ≥90%.
study method was less biased than other methods (p < 0.05), with one exception [6] for predicting V_d (p > 0.05), and equally precise as other methods, with one exception [5] for predicting V_d.

Individualized dosing, based on measurement of serum gentamicin concentration, has been shown to be the most accurate method for adjusting gentamicin doses in order to maintain serum levels within the therapeutic range [18, 19]. However, initiating a suitable dosing regimen is reliant on a ‘best guess’ approach based on standard doses recommended by the manufacturer or by standardized dosing nomograms. Since there have been reports of differences in gentamicin pharmacokinetics in different genetic populations [20–22], the latter method may not be ideal. Dosing equations based on a particular institution's own patient population may be a more appropriate approach for formulating an individualized initial dosing regimen. This, hopefully, would result in a more reliable and rapid attainment of therapeutic serum concentrations, while avoiding the danger of either sub-therapeutic or supratherapeutic serum levels. Software programs based on Bayesian kinetics are an accurate and precise technique for estimation of Cl_{gent} and V_d [23]; however, in this study, the Sawchuk-Zaske method was used to determine Cl_{gent} and V_d. The equations then derived by simple regression analysis have been shown to provide a satisfactory estimation of the initial gentamicin dosing parameters required to achieve therapeutic peak and trough levels, which can be easily applied by practicing pharmacists or physicians at ward level.

### Conclusion

The dosing equations developed in this study provided a reliable estimation of Cl_{gent} and V_d. It is planned to use these equations in Kuwait Hospitals to help provide more individualized patient dosing information to physicians.

### References