Antibiotic Pharmacodynamics in Surgical Prophylaxis: an Association between Intraoperative Antibiotic Concentrations and Efficacy

Sheryl A. Zelenitsky, 1,2,3,4* Robert E. Ariano, 1,2,3 Godfrey K. M. Harding, 2,4,5 and Richard E. Silverman 2,6

Received 24 September 2001/Returned for modification 25 March 2002/Accepted 18 June 2002

The objective of this study was to characterize the relationship between gentamicin concentrations during surgery and the development of wound infection following colorectal operations. Despite decades of research in surgical prophylaxis, the relationship between intraoperative antibiotic concentrations and postoperative infection and the concentrations required for effective prophylaxis have not been established. A pharmacodynamic analysis was conducted using data from a previous prospective, randomized, double-blind clinical study which compared two dosage regimens of gentamicin plus metronidazole for prophylaxis in connection with elective colorectal surgery. Univariate and multivariate analyses of risk factors for postoperative wound infection were conducted, and the relationship between intraoperative gentamicin concentrations and surgical outcome was characterized. The gentamicin concentration at the time of surgical closure was one of the strongest independent risk factors for infection (P = 0.02), along with the presence of diabetes mellitus (P = 0.02), stoma (P = 0.04), and advanced age (P = 0.05). Gentamicin concentrations at closure of less than 0.5 mg/liter were associated with an infection rate of 50% (representing 8 of 10 patients with concentrations below that level) (P = 0.003). Receiver operating characteristic curve analysis identified a critical closure concentration of 1.6 mg/liter for effective surgical prophylaxis (P = 0.002; sensitivity, 70.8%; specificity, 65.9%). This study provides new and important information on antibiotic pharmacodynamics in surgical prophylaxis. It demonstrates the critical effect of the antibiotic concentration at closure on wound infection and suggests a significant association between the concentration and other well-established risk factors, like the timing of preoperative antibiotic administration and surgery duration.

Surgical site infections, a significant postoperative complication, can lead to considerable patient morbidity and mortality (5, 14). Wound infections account for 38% of surgical infections and 17% of all nosocomial infections (14, 22). The benefits of preoperative antibiotics, which reduce bacterial contamination during clean-contaminated and contaminated operations, are well known (8, 14). However, the relationship between intraoperative antibiotic concentrations and postoperative infection and the concentrations required for effective prophylaxis have not been established. Over the past decade, pharmacodynamic research has advanced the treatment of infectious diseases by characterizing relationships between antibiotic concentrations and clinical response (7, 12, 20). Although the application of similar principles to surgical prophylaxis has been suggested, there is a notable lack of supportive study (1, 16, 18). It is probable that low antibiotic concentrations during surgery due to inappropriate timing of the preoperative antibiotic (3), prolonged surgery (9, 11, 21), and patient obesity (13, 17) contribute to the high infection rates associated with these factors. However, the direct effect of intraoperative antibiotic concentrations on surgical outcome has been largely overlooked by clinical studies, which have not included this variable in risk factor analyses. Pharmacodynamic data which characterize effective antibiotic concentrations during surgery could change the approach to surgical prophylaxis.

In a previous prospective, randomized, double-blind clinical study, regimens of single high doses of gentamicin (4.5 mg/kg of body weight preoperatively) and of multiple standard doses of gentamicin (1.5 mg/kg preoperatively and at 8, 16, and 24 h postoperatively), both in combination with metronidazole, were compared for prophylaxis in connection with colorectal surgery (24). Several observations suggested an association between low serum gentamicin concentrations during surgery and clinical failure. First, a trend towards fewer wound infections in the high-dose group suggested improved efficacy when higher antibiotic concentrations were achieved during surgery. Second, a strong association between prolonged surgery, which is a well-documented risk factor, and infection in the standard-dose but not in the high-dose group also supported an association between intraoperative antibiotic concentrations and clinical outcome. Our goal was to conduct a pharmacodynamic analysis of data from the original clinical study to characterize the relationship between intraoperative gentamicin concentrations and the development of wound infection following colorectal surgery. To our knowledge, this is the first such study in the area of surgical prophylaxis.

MATERIALS AND METHODS

Previous clinical study. Data were obtained from a previous prospective, randomized, double-blind clinical study (number of patients, 146) of antibiotic prophylaxis for elective colorectal surgery (24). Study treatments consisted of either single high doses of gentamicin (4.5 mg/kg) plus metronidazole (500 mg)
preoperatively or multiple standard doses of gentamicin (1.5 mg/kg) plus metronidazole (500 mg) preoperatively and at 8, 16, and 24 h postoperatively. Only those patients with serum creatinine levels of less than 150 μmol/liter were enrolled in the clinical study. Gentamicin doses were based on actual body weight or on dosing weight for subjects weighing more than 120% of their ideal body weight. Dosing weights were calculated according to the formula [0.40 × (actual body weight − ideal body weight)] + ideal body weight. The ideal body weight was defined as 50 kg plus 2.3 kg for each inch of height over 5 ft for males and 45.5 kg plus 2.3 kg for each inch of height over 5 ft for females. Metronidazole and gentamicin were infused over 30 min and administered sequentially.

Twelve of the clinical study participants were excluded because the timing of the preoperative antibiotic was not documented. Therefore, 134 subjects, of which 68 received the high-dose regimen and 66 received the standard-dose regimen, were included in the pharmacodynamic study. As shown in Table 1, there were no significant differences in characteristics between the high-dose and standard-dose regimens.

Twelve of the clinical study participants were excluded because the timing of the preoperative antibiotic was not documented. Therefore, 134 subjects, of which 68 received the high-dose regimen and 66 received the standard-dose regimen, were included in the pharmacodynamic study. As shown in Table 1, there were no significant differences in characteristics between the high-dose and standard-dose regimens.

**Pharmacokinetics.** Two blood samples were collected from the first 35 participants after the administration of the preoperative gentamicin dose. The first sample was drawn at least 30 min after the infusion, and the second sample was collected in the recovery room. Concentrations of gentamicin in serum were measured by fluorescence immunoassay (TDx; Abbott, Chicago, Ill.). The limit of detection was 0.2 μg/liter, and the coefficients of variation were 10.8% at 2.2 μg/liter and 6.5% at 13.4 μg/liter. The gentamicin assay results were concealed from the model was then used to predict the probability of infection as follows:

\[
1/(1 + \exp(-(\beta_1 \times 1) + (\beta_2 \times 2) + ... (\beta_n \times n)))
\]

Receiver operating characteristic (ROC) curves were used to further analyze significant gentamicin concentration parameters. All statistical analyses were performed with SPSS for Windows, release 10 (SPSS Inc., Chicago, Ill.).

**RESULTS**

Twelve of the clinical study participants were excluded because the timing of the preoperative antibiotic was not documented. Therefore, 134 subjects, of which 68 received the high-dose regimen and 66 received the standard-dose regimen, were included in the pharmacodynamic study. As shown in Table 1, there were no significant differences in characteristics between the high-dose and standard-dose regimens.

**Pharmacokinetics.** The reference group \((n = 16)\), the mean \(k_{el} = 0.34 \text{ hr}^{-1}\) (95% confidence interval [CI] 0.29 to 0.39 hr\(^{-1}\)), which corresponds to a mean harmonic half-life of 2 h, and the mean \(V = 0.23 \text{ liter/kg} (\text{CI}_{0.05} 0.19 \text{ to } 0.26 \text{ liter/kg})\). The pharmacokinetic model was described by the following equations:

\[
k_{el} (\text{h}^{-1}) = 0.0031 \times \text{CI}_{\text{cr}} (\text{ml/min}/\text{1.73m}^2) + 0.082
\]

\[V (\text{liters}) = 0.22 \times \text{weight (kg)}
\]

In the validation analysis (Fig. 2), the pharmacokinetic model showed excellent correlations between predicted and measured serum gentamicin concentrations \((r^2 = 0.85)\), with good measures of precision (0.92 mg/liter) and bias (0.031 mg/liter). The gentamicin concentration parameters measured for the reference group and predicted for all other subjects are provided in Table 2.

**Pharmacodynamics.** In univariate analyses, several risk factors for infection were identified in the standard-dose group but none were observed in the high-dose group. In the standard-dose group, the gentamicin concentration at the time of closure \((P = 0.001)\), the concentration at incision \((P = 0.001)\), and
the surgery duration \( (P = 0.001) \), the presence of diabetes mellitus \( (P = 0.003) \), the presence of stoma \( (P = 0.03) \), and the timing of the preoperative antibiotic \( (P = 0.03) \) were associated with infection. As detailed in Table 3, however, only the gentamicin concentration at closure \( (P = 0.02) \) and the presence of diabetes mellitus \( (P = 0.02; \text{odds ratio}, 18.2; \text{CI } 95, 1.7 \text{ to } 193.8) \), stoma \( (P = 0.04; \text{odds ratio}, 4.3; \text{CI } 95, 1.1 \text{ to } 17.3) \), and advanced age \( (P = 0.05) \) were independent risk factors for infection. A concentration at closure of less than 0.5 mg/liter in 10 participants was associated with an 80\% infection rate \( (P = 0.003; \text{odds ratio}, 2.8) \). The overall probability of infection is described by the following equation:

\[
1/(1 + \exp \left[-3.28 + (\text{diabetes})(2.90) + (\text{stoma})(1.45) - (\log \text{ concentration at closure})(2.66) + (\text{age in years})(0.038)\right])
\]

where the values for diabetes and stoma were equal to 1 if present and 0 if absent. Figure 3 simulates the effect of the gentamicin concentration at closure on the probability of surgical site infection in a representative 57-year-old patient population. ROC curve analysis identified a critical value for the gentamicin concentration at closure of 1.6 mg/liter for effective surgical prophylaxis \( (P = 0.002, \text{sensitivity } 70.8\%, \text{speciﬁcity } 65.9\%) \).

**DISCUSSION**

Although the goal of surgical prophylaxis is to maintain adequate antibiotic exposure during surgery, research establishing effective intraoperative concentrations has not been conducted (1, 16, 18). This study provides new and important information on antibiotic pharmacodynamics in surgical prophylaxis. In the standard-dose group, the risk of wound infection was dependent on the gentamicin concentration at closure

---

**TABLE 1.** Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value(^a) for group</th>
<th>Standard dose ((n = 66))</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High dose ((n = 68))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>56.6 ± 18.9(^b)</td>
<td>56.8 ± 17.7</td>
<td>1.0</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>37 (54.4)</td>
<td>39 (59.1)</td>
<td>0.6</td>
</tr>
<tr>
<td>Normalized wt (actual/ideal wt)</td>
<td>1.16 ± 0.18</td>
<td>1.17 ± 0.24</td>
<td>0.8</td>
</tr>
<tr>
<td>CL(_{\text{CR}}) (ml/min/1.72 m(^2))</td>
<td>102 ± 25</td>
<td>104 ± 22</td>
<td>1.0</td>
</tr>
<tr>
<td>Presence of:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>25 (36.8)</td>
<td>15 (22.7)</td>
<td>0.09</td>
</tr>
<tr>
<td>Malignancy</td>
<td>35 (51.5)</td>
<td>42 (63.6)</td>
<td>0.2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (7.4)</td>
<td>8 (12.3)</td>
<td>0.5</td>
</tr>
<tr>
<td>Chronic corticosteroid use</td>
<td>11 (16.2)</td>
<td>10 (15.2)</td>
<td>0.9</td>
</tr>
<tr>
<td>Right colon operation</td>
<td>18 (26.5)</td>
<td>19 (28.8)</td>
<td>0.9</td>
</tr>
<tr>
<td>Stoma</td>
<td>33 (48.5)</td>
<td>22 (33.3)</td>
<td>0.09</td>
</tr>
<tr>
<td>Intraoperative core temp (°C)</td>
<td>35.6 ± 0.8</td>
<td>35.3 ± 0.7</td>
<td>0.10</td>
</tr>
<tr>
<td>Timing of preoperative antibiotic (min)</td>
<td>71 ± 33</td>
<td>67 ± 35</td>
<td>0.5</td>
</tr>
<tr>
<td>Surgery duration (min)</td>
<td>196 ± 81</td>
<td>186 ± 65</td>
<td>0.5</td>
</tr>
<tr>
<td>Surgical site infections (total)</td>
<td>19 (27.9)</td>
<td>24 (36.4)</td>
<td>0.27</td>
</tr>
<tr>
<td>Deep</td>
<td>6 (8.8)</td>
<td>4 (6.1)</td>
<td></td>
</tr>
<tr>
<td>Superficial</td>
<td>13 (19.1)</td>
<td>20 (30.3)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Except where otherwise indicated, values are given in number (percent) of patients.

\(^b\) Values expressed as means ± standard deviations.

---

**TABLE 2.** Gentamicin concentration parameters

<table>
<thead>
<tr>
<th>Dosage group</th>
<th>Concentration (mg/liter)(^a) at time of:</th>
<th>(\text{AUC}_{\text{Surg}}) (mg h/liter)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose</td>
<td>Incision 14.5 ± 3.8 4.7 ± 2.6 26.1 ± 8.9</td>
<td></td>
</tr>
<tr>
<td>Standard dose</td>
<td>Incision 5.2 ± 1.3 1.8 ± 1.0 8.8 ± 2.5</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Values are given as means ± standard deviations. \(P\) values for all concentrations were <0.0001.
and on the presence of diabetes mellitus, stoma, and, to a lesser degree, advanced age. Other well-established risk factors, including the timing of preoperative antibiotic and surgery duration, were identified in univariate tests but were not independently associated with infection. The identification of the gentamicin concentration at closure as an independent variable suggests that a low antibiotic concentration was the predominant risk associated with inappropriate timing of the preoperative antibiotic and with prolonged surgery. Notably, no risk factors for infection were identified in the otherwise-matched, high-dose group. This result could represent a gentamicin dose (i.e., 4.5 mg/kg) that produced adequate concentrations at closure for surgical prophylaxis and which therefore did not characterize the relationship between low antibiotic concentrations and clinical failure. Furthermore, neither timing of preoperative antibiotic nor surgery duration was significantly associated with infection in the high-dose group. This could also indicate that the gentamicin dose achieved sufficient intraoperative concentrations even in cases where the timing of the preoperative antibiotic administration was too early or the surgery duration was prolonged.

In the treatment of infectious diseases, antibiotic concentrations are usually related to the pathogen and its susceptibility, as indicated by the MIC. Pharmacodynamic indices such as the peak concentration-to-MIC ratio, time above MIC, and AUC divided by MIC are analyzed to identify those which best correlate with the eradication of microbes or with clinical cure. The application of such principles to the prevention of infection is uncertain (1, 16, 18). However, this study shows the importance of gentamicin concentrations at surgical closure and identifies a critical value of 1.6 mg/liter for effective prophylaxis. This suggests that standard gentamicin doses, as used in our clinical study, may be suboptimal for colorectal operations. For example, a 1.5-mg/kg preoperative gentamicin dose would require a second dose in 3.8 h to maintain concentrations above 1.6 mg/liter (assuming a patient weighing 70 kg, a $\bar{\kappa}_{d}$ of 0.35 h$^{-1}$, and a $V$ of 0.25 liter/kg). A 4.5-mg/kg dose would extend the coverage to 6.9 h, which may be more appropriate for operations with a mean duration exceeding 3 h. The critical gentamicin concentration of 1.6 mg/liter must be interpreted with some caution. First, the value was determined for a specific antibiotic and patient population and may not apply to other operations, for example. Second, it was derived from a retrospective analysis of clinical study data and therefore may have been influenced by the range of intraoperative concentrations available. Although a prospective investigation of preselected and targeted antibiotic concentrations would provide the most complete pharmacodynamic characterization, it would also require the deliberate administration of low, presumably ineffective, doses resulting in clinical failure. This method of study has obvious ethical barriers.

One limitation of this study was the application of pharmacokinetic data from a reference group to all other subjects. However, the pharmacokinetic model produced pharmacokinetic parameters that were within expected ranges and that demonstrated excellent predictive performance in the validation analysis (6, 23). The model described a relatively homogenous population of participants with normal renal function who were admitted for elective surgery.

This study was based on the assumption that bacterial wound infections are located in interstitial spaces and that concentrations in serum reflect those in interstitial fluids. First, clean incisional sites and other uninfected tissues are represented by high ratios of surface area to volume and by rapid equilibration of antibiotic levels between serum and wound fluid (2, 15, 19). The use of gentamicin, with low protein binding and rapid distribution into extracellular fluid, further justifies the use of concentrations in serum to approximate intraoperative levels in tissue.

This study demonstrates the critical effect of antibiotic concentration at closure on wound infection following colorectal surgery. The results also suggest a significant association between low concentrations and high infection rates found with other well-established risk factors. Finally, this study shows the value of pharmacodynamic research in surgical prophylaxis and the need for investigations of other antibiotics for colorectal and other operations.

**ACKNOWLEDGMENT**

We acknowledge the contributions of Mary Cheang, Department of Community Health Sciences, Department of Medicine, University of Manitoba, for biostatistical consultation.

**REFERENCES**