Lack of Vancomycin-associated Nephrotoxicity in Newborn Infants: A Case–Control Study

Varsha Bhatt-Mehta, PharmD*; Robert E. Schumacher, MD†; Roger G. Faix, MD‡; Michelle Leady, PharmD*; and Timothy Brenner, PharmD§

ABSTRACT. Objective. The purpose of this study was to compare the incidence of nephrotoxicity, defined as doubling of baseline serum creatinine concentration, in newborn infants with peak vancomycin serum concentrations ≥40 μg/mL at steady state to infants with peak vancomycin serum concentrations >40 μg/mL. A secondary objective was to correlate concomitant disease states and potentially nephrotoxic drug therapy with rises in serum creatinine in vancomycin recipients.

Methods. Newborn infants with culture-proven Staphylococcus aureus or coagulase-negative staphylococcal septicemia who received vancomycin therapy for >3 days between 1985 and 1995 were identified from an existing database and a review of medical record. All 69 patients included in the study had serial serum creatinine determinations, including a baseline value within 48 hours of starting treatment with vancomycin, and serum vancomycin concentrations determined after at least three doses, with peak and trough concentrations determined 1 hour after a 60-minute infusion and 15 to 30 minutes before a dose, respectively. Infants with congenital renal or cardiac anomalies were excluded. Demographic characteristics, vancomycin dosing regimen, serum vancomycin concentrations and sample times, concomitant drug therapy, and disease states were recorded. Patients were divided into group A (peak vancomycin concentration ≤40 μg/mL) and group B (peak vancomycin concentration >40 μg/mL). The change in serum creatinine concentration between the start and end of vancomycin therapy was determined. Nephrotoxicity was identified if serum creatinine doubled at any time from the start to the end of vancomycin therapy. Alternative definitions of nephrotoxicity (any rise in serum creatinine to >0.6 mg/dL or new abnormalities of urine sediment) were used in additional analyses.

Results. A total of 69 evaluable patients (gestational age, 28.9 ± 3 weeks; birth weight, 1219 ± 516 g) were identified, 61 in group A and 8 in group B. Six patients in group A underwent doubling of serum creatinine concentration during vancomycin therapy, whereas none in group B. Any increase in serum creatinine to >0.6 mg/dL was seen in 10 infants, 9 of whom were in group A. No confounding variable, including previous or concomitant underlying disease states associated with renal dysfunction or treatment with other potentially nephrotoxic agents, were associated with a significant rise in serum creatinine.

Conclusion. Vancomycin-associated nephrotoxicity is rare in neonates, even with serum peak concentrations >40 μg/mL. Pediatrics 1999;103(4). URL: http://www.pediatrics.org/cgi/content/full/103/4/e48; vancomycin, nephrotoxicity, newborn infants, NICU, Staphylococci, creatinine, renal, antibiotics.

Vancomycin is a bactericidal glycopeptide antibiotic that exerts its antimicrobial effect by inhibition of bacterial cell wall synthesis. Early pharmaceutical preparations of vancomycin were associated with considerable toxicity, including infusion-related phlebitis, anaphylaxis, eighth cranial nerve dysfunction, and nephrotoxicity. The introduction of the less toxic penicillinase-resistant penicillins led to a decline in the use of this agent. Resurgent interest in vancomycin therapy developed in the 1980s because of an increasing number of nosocomial infections caused by resistant strains of Staphylococcus aureus and coagulase-negative staphylococci. Newer formulations of vancomycin, with fewer contaminants and unwanted side effects, became available at approximately the same time and have become widely used in infants and children.

Although dosage regimens and therapeutic drug ranges for vancomycin have been established in adult patients over the last 2 decades, controversy still exists about the ideal dosing regimen and desired serum concentration for vancomycin in premature and full-term newborn infants and children. Recently, the effect of a commonly accepted dosing regimen for vancomycin on renal function in very low birth weight infants was evaluated and reported to be safe in their population. No data on the achieved plasma vancomycin concentrations or concomitant drug therapy were included. There are a few reports of nephrotoxicity with simultaneous administration of an aminoglycoside and vancomycin, although one study found the combination to be safe. No reports have addressed the role of other concomitant potentially nephrotoxic drugs or underlying disease states on vancomycin nephrotoxicity in neonates.

The primary purpose of this study was to determine and compare the incidence of nephrotoxicity, defined as a doubling of serum creatinine from a baseline value obtained within 48 hours of starting vancomycin therapy in newborn infants with peak serum vancomycin concentrations <40 μg/mL to
that in a group with a peak ≥40 μg/mL at steady state. A secondary objective was to correlate concomitant disease states and potentially nephrotoxic drug therapy with rises in serum creatinine.

METHODS

This study was conducted as a retrospective chart review. All newborn infants in the neonatal intensive care unit at our institution who were treated with vancomycin for culture-proven sepsis caused by resistant staphylococci for a 10-year period beginning January 1985 were identified using a computerized database. Infants were included in the present study if they had received vancomycin for at least 3 days, had appropriate serum vancomycin concentrations (peak serum concentrations 1 hour after a 1-hour infusion and trough concentrations just before a dose) determined after at least three doses, and had serum creatinine measured within 48 hours of starting vancomycin treatment and longitudinally thereafter. Infants who had serum vancomycin concentrations obtained >5 minutes from the indicated times for peak and trough determinations were excluded. Infants with congenital renal or cardiovascular anomalies were excluded.

Data collection included patient demographics and identification of additional preexisting or concurrent diseases (paput ductus arteriosus, respiratory distress syndrome, or urine output <0.5 mL/kg per hour) that may influence renal function. Serum chemistries; microscopic and dipstick urinalyses; and concomitant potentially nephrotoxic drug therapy (loop or thiazide diuretics, aminoglycosides, or indomethacin) were recorded from 1 week before the start of vancomycin therapy until 2 weeks after the conclusion of treatment. Data collected relating to vancomycin therapy included the dose and frequency of administration, the time and length of dose infusion, time and values for peak and trough plasma concentrations, and duration of therapy. The appropriateness of the dosing regimen was assessed according to guidelines contained in the manual for neonatal intensive care issued to all our house officers at the time. From 1985 to 1991, the recommended doses were 10 mg/kg every 8 hours for infants ≤40 weeks and every 6 hours for infants >40 weeks’ postconceptional age. From 1992 through the end of the study period and to the present, dosing guidelines include 15 mg/kg at intervals of 36, 24, 22, and 18, and 12 hours for infants whose postconceptional ages were <27, 27 to 30, 31 to 34, and >34 weeks, respectively.

Nephrotoxicity was evaluated based on changes in serum creatinine concentration from a baseline value obtained within 48 hours of starting vancomycin treatment. The principal definition was a doubling of serum creatinine from the start any time through the end of vancomycin therapy. Alternative definitions that were analyzed included doubling of serum creatinine to >0.6 mg/dL (previously published population mean value6); any rise in serum creatinine to >0.6 mg/dL; and the new onset of hematuria, glycosuria, or proteinuria.

Discrete variables were analyzed by χ² or Fisher’s exact test, depending on cell size. Continuous data were compared using the Student’s t test if normally distributed and the Wilcoxon rank-sum test if not normally distributed. The effects of concomitant drug therapy and disease states were to be evaluated using simple and multiple regression analysis.

RESULTS

Of 174 patients with blood cultures positive for S aureus or coagulase-negative staphylococci who were identified in the database, 69 met inclusion criteria. Among the 105 who were excluded, 39 had organisms with susceptibility patterns that did not require vancomycin therapy and 66 lacked requisite data (14 with inappropriately timed or absent vancomycin serum concentrations, 10 without the necessary longitudinal serum creatinine determinations, and 42 with deficiencies in both categories). Of the 69 infants who met inclusion criteria, peak serum vancomycin concentration was ≤40 μg/mL in 61 infants (88%, group A) and >40 μg/mL in 8 (12%, group B). No significant differences were found between the two groups for birth weight, gestational age, postconceptional age, or postnatal age at treatment (Table 1).

All 8 infants in group B had serum creatinine >0.6 mg/dL at the start of treatment (mean, 1.3; range, 0.8 to 2.2). None underwent doubling of serum creatinine during therapy (Table 2). Only 1 patient had any increase in serum creatinine (from 1.2 to 1.3 mg/dL), whereas 6 decreased and 1 remained unchanged. Six of the infants had abnormal urinalyses (hematuria, proteinuria, or glycosuria) at the start of treatment; 3 of these had normal findings by the end of therapy. One infant developed a new abnormal urinalysis.

### Table 1. Demographic Features of Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Birth Weight (g)</th>
<th>Gestational Age (wk)</th>
<th>Weeks Postconception</th>
<th>Weeks Postnatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (N = 69)</td>
<td>1060 (854–1465)</td>
<td>28.9 ± 3.0</td>
<td>32.4 ± 4.0</td>
<td>2.7</td>
</tr>
<tr>
<td>Peak ≤40 μg/mL (n = 61)</td>
<td>1120 (854–1580)</td>
<td>29.1 ± 3.0</td>
<td>32.6 ± 4.0</td>
<td>2.7</td>
</tr>
<tr>
<td>Peak &gt;40 μg/mL (n = 8)</td>
<td>980 (930–1040)</td>
<td>27.3 ± 2.1</td>
<td>33.0 ± 7.6</td>
<td>2.6</td>
</tr>
</tbody>
</table>

### Table 2. Characteristics of Infants With Peak Serum Vancomycin Concentration >40 μg/mL

<table>
<thead>
<tr>
<th>Patient</th>
<th>Serum Cr (mg/dL)</th>
<th>Vanc Peak (μg/mL)</th>
<th>Vanc Trough (μg/mL)</th>
<th>Dose (mg/kg)</th>
<th>Interval (h)</th>
<th>Start Weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.8</td>
<td>49.7</td>
<td>18.0</td>
<td>24</td>
<td>12</td>
<td>1001</td>
</tr>
<tr>
<td>2</td>
<td>1.2</td>
<td>47.5</td>
<td>39.4</td>
<td>9.6</td>
<td>8</td>
<td>1040</td>
</tr>
<tr>
<td>3</td>
<td>1.3</td>
<td>45.0</td>
<td>22.5</td>
<td>15.1</td>
<td>24</td>
<td>930</td>
</tr>
<tr>
<td>4</td>
<td>0.9</td>
<td>42.7</td>
<td>15.7</td>
<td>15</td>
<td>8</td>
<td>1220</td>
</tr>
<tr>
<td>5</td>
<td>1.8</td>
<td>40.9</td>
<td>31.0</td>
<td>16</td>
<td>8</td>
<td>1020</td>
</tr>
<tr>
<td>6</td>
<td>2.2</td>
<td>40.5</td>
<td>20.4</td>
<td>15</td>
<td>24</td>
<td>1005</td>
</tr>
<tr>
<td>7</td>
<td>1.0</td>
<td>40.4</td>
<td>26.1</td>
<td>9.3</td>
<td>8</td>
<td>700</td>
</tr>
<tr>
<td>8</td>
<td>1.1</td>
<td>40.2</td>
<td>20.2</td>
<td>15</td>
<td>8</td>
<td>1300</td>
</tr>
</tbody>
</table>

Cr indicates creatinine; Vanc, vancomycin; B, creatinine concentration at beginning of vancomycin therapy; E, creatinine concentration at end of vancomycin therapy.
during treatment, but had a concurrent fall in serum creatinine. Although appropriate for then-existent dosing guidelines, dosing intervals were inappropriately short for 5 infants based on current postconceptual age guidelines. Two of these 5 also received individual doses >15 mg/kg. Three infants had appropriate doses and intervals. All 8 infants had a trough serum vancomycin concentration >10 μg/mL.

In group A, 6 (10%) of 61 patients underwent doubling of baseline serum creatinine during vancomycin therapy (Table 3). The serum creatinine values in 3 of these, however, still were ≤0.6 mg/dL. Serum creatinine >0.6 mg/mL at the start of treatment was noted in 17 infants (27.9%). Nine of the 61 infants had an increase in serum creatinine to >0.6 mg/mL. Four infants developed newly abnormal urinary sediment during treatment, but all 4 had concomitant declines in serum creatinine. Sixteen of those in group A (26.2%) received starting doses of vancomycin >15 mg/kg/dose or had inappropriate dosing intervals based on current postconceptual age guidelines; 8 of these 16 had serum creatinine >0.6 mg/mL at the start of treatment.

Of the 61 infants in group A, 21 (34.4%) had vancomycin trough plasma concentrations >10 μg/mL. Thirteen of these 21 had serum creatinine >0.6 mg/dL at the start of treatment; 2 of these 13 also underwent doubling of serum creatinine. Three of the 21 had inappropriately short dosing intervals per current guidelines. For the remaining 5 children, no reason could be found for the elevated serum trough concentrations.

In the combined study population of 69 infants, the mean serum creatinine fell significantly from the beginning to the end of vancomycin therapy (Table 4). Although serum creatinine was not significantly different between the two study groups at the start or the end of therapy, infants in group B had a significantly greater drop in serum creatinine at the end of treatment than those in group A.

The effects of potential confounding variables (preexisting diseases or concurrent drug therapy with such nephrotoxic agents as aminoglycosides, indomethacin, and loop or thiazide diuretics) on changes in serum creatinine during vancomycin therapy were assessed using univariate analysis. No disease or drug was statistically associated with a rise in serum creatinine. Multiple regression analysis therefore was unwarranted. Concurrent gentamicin was received during all or part of vancomycin therapy by 49 infants, 38 of whom received such treatment for >3 days and also had serum gentamicin concentrations assessed. Eight of these 38 (21.0%) had a trough serum gentamicin concentration >2 μg/mL; 3 of these 8 also had an elevated trough vancomycin concentration. All 8 had serum creatinine ≥0.6 mg/dL at the start of treatment. No infant had a peak serum gentamicin concentration ≥9 μg/mL.

**TABLE 3.** Characteristics of Infants Who Doubled Serum Creatinine Concentration During Vancomycin Therapy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Serum Cr (mg/dL) B</th>
<th>Serum Cr (mg/dL) E</th>
<th>Vanc P/T (μg/mL)</th>
<th>Days on Vanc</th>
<th>Disease State</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.2</td>
<td>0.5</td>
<td>21.1/3.0</td>
<td>5</td>
<td>BPD</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>1.0</td>
<td>1.9</td>
<td>30.4/10.7</td>
<td>20</td>
<td>PDA, RDS, oliguria</td>
<td>Indo, Lasix</td>
</tr>
<tr>
<td>3</td>
<td>1.6</td>
<td>2.9</td>
<td>24.8/10.9</td>
<td>8</td>
<td>PDA, RDS</td>
<td>Indo, Lasix</td>
</tr>
<tr>
<td>4</td>
<td>0.2</td>
<td>0.7</td>
<td>39.7/19.7</td>
<td>20</td>
<td>RDS</td>
<td>Gent, Lasix</td>
</tr>
<tr>
<td>5</td>
<td>0.2</td>
<td>0.4</td>
<td>26.4/19.9</td>
<td>14</td>
<td>BPD</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>0.2</td>
<td>0.4</td>
<td>24.2/5.5</td>
<td>15</td>
<td>BPD</td>
<td>Lasix</td>
</tr>
</tbody>
</table>

Cr indicates creatinine; B, at beginning of vancomycin therapy; E, at end of vancomycin therapy; Vanc, vancomycin; P/T, peak/trough serum concentrations; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome; BPD, bronchopulmonary dysplasia requiring mechanical ventilation; Gent, gentamicin; Indo, indomethacin.

**TABLE 4.** Serum Creatinine Concentration During Vancomycin Therapy*

<table>
<thead>
<tr>
<th>Group</th>
<th>Start (mg/dL)</th>
<th>End (mg/dL)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (N = 69)</td>
<td>0.8 ± 0.4</td>
<td>0.7 ± 0.4</td>
<td>.026</td>
</tr>
<tr>
<td>(0.2–2.2)</td>
<td>(0.3–2.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak ≤40 μg/dL (n = 61)</td>
<td>0.7 ± 0.4</td>
<td>0.6 ± 0.4</td>
<td>.45</td>
</tr>
<tr>
<td>(0.2–1.7)</td>
<td>(0.2–1.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak &gt;40 μg/dL (n = 8)</td>
<td>1.3 ± 0.4‡</td>
<td>1.0 ± 0.4‡</td>
<td>.02</td>
</tr>
<tr>
<td>(0.8–2.2)</td>
<td>(0.5–1.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Data are mean ± standard deviation; figures in parentheses are ranges.
† Difference in mean serum creatinine at beginning of vancomycin therapy between groups with peak vancomycin concentration >40 μg/dL and ≤40 μg/dL was significant at P < .01.
‡ Difference in mean serum creatinine at end of vancomycin therapy between groups with peak vancomycin >40 μg/dL and ≤40 μg/dL was significant (P = .30).

**DISCUSSION**

Our findings do not support the hypothesis that peak serum vancomycin concentration >40 μg/mL is associated with nephrotoxicity, defined as doubling of baseline serum creatinine. Plausible explanations include that contemporary formulations of vancomycin are not truly nephrotoxic at this peak value, that the definition of nephrotoxicity used was too restrictive, that vancomycin is only toxic at higher concentrations, or combinations of the above. Because alternative definitions of nephrotoxicity explored in this report also resulted in more frequent abnormalities among infants with peak vancomycin concentration ≤40 μg/mL, the first explanation seems most plausible. Despite dosing regimens in several infants that are considered inappropriate according to current guidelines, peak serum vancomycin concentrations >40 μg/mL were seen only in infants with baseline serum creatinine >0.6 mg/dL. These data suggest that although peak serum vancomycin concentration >40 μg/mL may not predict renal dysfunction, the converse may be true.

Several studies have evaluated the safety of van-
Vancomycin used concurrently with gentamicin.23–25 To the best of our knowledge, however, this report is the first to evaluate the effect of multiple potentially nephrotoxic drugs and underlying disease states that may contribute to renal dysfunction. Linder and associates25 reported an 8.6% incidence of nephrotoxicity (defined as an increase in serum creatinine of ≥0.5 mg/dL from baseline) in a study of 35 patients with peak vancomycin concentration >30 μg/mL. We did not detect clinically important nephrotoxicity when gentamicin was administered with vancomycin. Similar observations were made when more than one potentially nephrotoxic agent was used concurrently with vancomycin.

CONCLUSION

Vancomycin-associated nephrotoxicity is rare in neonates requiring intensive care, even in the presence of other potentially nephrotoxic drugs and disease states associated with renal dysfunction. Although peak serum vancomycin concentration >40 μg/mL was not associated with nephrotoxicity, monitoring serum concentration still seems appropriate in this critically ill group of patients because the safety of higher concentrations (eg, >60 μg/mL) is unknown and to ensure that an effective antimicrobial concentration has been attained. Although the current dosing regimen makes plasma concentrations >60 μg/mL highly unlikely, vigilance appears warranted when serum creatinine is ≥0.6 mg/dL at the start of treatment.

REFERENCES

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