Vancomycin Pharmacokinetics in Burn Patients and Intravenous Drug Abusers

MICHAEL J. RYBAK,1,2* LISA M. ALBRECHT,1† JULIE R. BERMAN,2 LAWRENCE H. WARBASSE,3,4 AND CRAIG K. SVENSSON1

College of Pharmacy and Allied Health Professions1* and School of Medicine,3 Wayne State University, Detroit, Michigan 48202, and Departments of Pharmacy Services2 and Internal Medicine,4 Detroit Receiving Hospital and University Health Center, Detroit, Michigan 48201

Received 6 September 1989/Accepted 15 February 1990

The pharmacokinetics of vancomycin were evaluated in 34 patients (10 burn patients, 14 intravenous drug abusers [IVDA], and 10 controls). Multiple serum samples were drawn following a 1-h vancomycin infusion at steady state over an 8- to 12-h dosing interval. Pharmacokinetic parameters were derived by noncompartmental analysis. There were no significant differences among the groups with respect to age, weight, serum creatinine, volume of distribution, or protein binding. Burn patients had a significantly higher creatinine clearance than did IVDA or controls. Vancomycin clearances averaged 142.8, 98.0, and 67.7 ml/min in burn patients, IVDA, and controls, respectively. The renal clearance of vancomycin was also higher in burn patients than in the other groups. IVDA tended to have a higher vancomycin clearance (31% higher) than did controls, but the difference was not statistically significant. Vancomycin clearance was much higher in burn patients requiring dosage individualization and close monitoring. A considerable amount of vancomycin was eliminated through renal tubular secretion, making dosage predictions based on creatinine clearance more difficult. Further work with IVDA will be needed to determine if they represent a group requiring aggressive vancomycin dosages.

Renewed interest in vancomycin, resulting from the increase in methicillin-resistant Staphylococcus aureus and Staphylococcus epidermidis, has prompted new investigations regarding the pharmacokinetics, potential for toxicity, and dosage adjustment guidelines of vancomycin (8, 9, 11, 16, 17, 21). Altered pharmacokinetics of vancomycin resulting in increased dosage requirements have been investigated in burn patients. Although there is clinical evidence for increased vancomycin dosage requirements in this patient population, data supporting these observations have been inconclusive (3, 6). A similar phenomenon has been documented to occur with aminoglycoside administration in burn patients. The mechanism for enhanced aminoglycoside elimination that results in increased dosage requirements for burn patients appears to be related to an increased glomerular filtration rate (12, 23–25). Intravenous drug abusers (IVDA) have also been reported to eliminate aminoglycosides at a rate which necessitates more aggressive aminoglycoside dosage regimens (10). This observation has not been reported with vancomycin administration in this patient population. In this investigation, we compared the steady-state pharmacokinetics of vancomycin in burn patients, IVDA, and a control population.

MATERIALS AND METHODS

A total of 34 patients participated in this study. Ages ranged from 18 to 64 years (mean ± standard deviation, 37 ± 10.9 years). Ten burn patients (5 males) and 14 IVDA (9 males) made up the treatment study groups. The inpatient control group (nonburn, non-IVDA) consisted of 10 patients (8 males).

Informed consent was obtained from all patients prior to participation in the study. Patients who were admitted to our hospital and who were started on vancomycin by their physicians for presumed or documented gram-positive infections were evaluated for the study. Patients were eligible for the burn group if they presented with >10% total body surface area burn injury and for the IVDA group if they had a history of recently injecting intravenous drugs; all other patients were eligible for the control group. Exclusion criteria consisted of significant liver or renal disease (liver transaminase values greater than three times the normal range or serum creatinine of >2.0 mg/dl), recent surgery or infection of the upper urinary tract, concurrent exposure to drugs which may affect the renal elimination of vancomycin (dopamine, dobutamine, loop diuretics, etc.), or inability to provide informed consent.

The dosages of vancomycin ranged from 2,000 to 6,000 mg/day (28.9 to 42.7 mg/kg of actual body weight). All vancomycin doses were administered by intravenous infusion over a 1-h period. The pharmacokinetic evaluation was carried out a minimum of 48 h after the initiation of vancomycin therapy. Sampling for vancomycin occurred over the prescribed dosing interval of 8 or 12 h.

Blood samples were serially collected from a central line catheter or a heparin lock placed in the forearm opposite the infusion site. Samples were obtained before infusion, at the end of infusion, and at 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, and 7 h postinfusion for patients on an 8-h dosing interval. Additional samples were obtained at 8 and 11 h for patients receiving vancomycin on a 12-h dosing interval. Specimens were allowed to clot for approximately 45 min before centrifugation. Urine was collected from the start of the vancomycin infusion to the end of the dosing interval for the determination of creatinine clearance (CLcr) and vancomycin renal clearance (CLv).

Burn patients were catheterized, assuring accurate urine collection. Nonburn patients were asked to void prior to dose administration. Urine was
collected over the dosing interval by spontaneous voiding. One of the investigators was present in the subject’s room for the majority of the collection period. Serum and urine samples were stored at −20°C until analysis. Samples were assayed for vancomycin content within 1 week from the time of collection by a fluorescence polarization immunoassay (TDx; Diagnostic Division, Abbott Laboratories, Irving, Tex.). Our intra- and interrun coefficients of variation were less than 6% in the concentration range of 0.6 to 100 µg/ml. The coefficients of variation for the control standards that were run with each group of subject specimens averaged 4.7% for the high control (75 µg/ml), 1.8% for the medium control (35 µg/ml), and 3.5% for the low control (7.0 µg/ml).

Vancomycin serum protein binding was determined by ultrafiltration of the 1-, 6-, and 11-h serum samples. Total vancomycin and unbound vancomycin concentrations were determined in serum with a micropartition system (MPS-1; Amicon Corp., Danvers, Mass.). The free fraction (f_u) of vancomycin was expressed as the ratio of the vancomycin concentration in the ultrafiltrate to that in serum multiplied by 100. Minimum vancomycin absorption (mean ± SD recovery, 97.2% ± 0.8%) was observed when an ultrafiltrate of serum was spiked (24 µg/ml) with vancomycin (five replicates). This observation is consistent with those in previous reports using this method for the determination of vancomycin serum protein binding (1, 16).

The serum concentration-versus-time data were fit to polynomial functions with a nonlinear least-squares regression program (4). The minimum number of exponents needed to describe the curve was determined with a modified Akaike Information Criteria test with a weighting factor of 1/τ² (4). The area under the serum concentration-versus-time curve over the dosing interval (AUCss-r) was calculated by the linear trapezoidal rule with the LAGRAN program (15). Total body clearance (CL) was calculated as follows:

\[ CL = \frac{\text{dose} \cdot \text{AUMCi}_{v,0-\infty}}{(\text{AUCsso-\tau}^2 + 2 \cdot \text{AUCss-\tau}^2)} \]

where AUMCi_{v,0-\infty} is the area under the first non-normalized moment curve after single-dose administration from zero time to infinity and t is the duration of infusion. AUMCi_{v,0-\infty} was estimated by the method of Smith and Schentag (20), which provides a means for calculating AUMCi_{v,0-\infty} from steady-state data.

Vancomycin CLs was calculated as follows:

\[ CL_s = \frac{Ae_{0-\tau}}{\text{AUCsso-\tau}} \]

where Ae_{0-\tau} is the amount of unchanged drug excreted in urine over the dosing interval.

Clearance of unbound drug and steady-state volume of distribution of unbound drug were determined by dividing the pharmacokinetic parameter for total drug by the measured f_u in serum. The filtration clearance of unbound vancomycin (CLF) was estimated as the product of f_u and the glomerular filtration rate (assumed to be equal to CLCR). Urinary recovery (percentage) of unchanged drug was calculated by dividing the amount recovered in urine by the dose administered. Vancomycin net renal secretory clearance (CLg) was calculated by subtracting CLF from CLR.

The CLR/CLF ratio was calculated to elucidate the mechanisms of vancomycin renal excretion.

Differences in patient characteristics and pharmacokinetic parameters for the three groups were determined by analysis of variance. Tukey’s test was used to identify differences between burn patients, IVDA, and controls. Differences between trough (i.e., the sample prior to dosing) vancomycin concentrations and C_{min} (i.e., the last sample) were compared with a paired Student t test to ascertain that patients had indeed reached the steady state. Statistical significance was defined as P < 0.05. Data are presented as means ± SDs unless otherwise indicated.

**RESULTS**

The demographic characteristics, including burn patient descriptions, are shown in Table 1. Infection diagnosis consisted of sepsis (burn, n = 10; IVDA, n = 3; control, n = 5), cellulitis (IVDA, n = 6; control, n = 4), osteomyelitis (IVDA, n = 3; control, n = 1), septic arthritis (IVDA, n = 1), and endocarditis (IVDA, n = 1). The time postburn in which patients in the burn group were started on vancomycin therapy ranged from 7 to 45 days. There were no significant differences among groups in age, actual body weight, or serum creatinine. Overall, serum albumin levels were low in all three groups, ranging from 1.0 to 3.8 mg/dl (all groups combined, 2.4 ± 0.7 mg/dl) but were significantly lower in the burn patients (1.7 ± 0.5 mg/dl). Burn patients tended to be more aggressively dosed initially, accounting for the significant difference between vancomycin dosages prescribed for burn and nonburn patients. There were no significant differences between C_{min} and trough vancomycin concentrations in serum, indicating the achievement of the steady state.

Mean values for steady-state vancomycin pharmacokinetic parameters are shown in Table 2. CLCR and vancomycin CL were found to be significantly greater in burn patients than in either IVDA or controls. CLR was significantly greater in burn patients than in controls. Although there was a trend for vancomycin CL and CLR to be greater in the IVDA group than in the control group, it did not reach statistical significance. The proportion of vancomycin eliminated by nonrenal mechanisms was found to be small and not statistically different among the three groups. There were no differences in V_{ss} among the three groups. Vancomycin serum protein binding did not differ among the three groups, with f_u ranging from 0.41 to 0.77. Hence, changes in

**TABLE 1. Patient demographics**

<table>
<thead>
<tr>
<th>Group (n)</th>
<th>Age (yr)a</th>
<th>No. of males/females</th>
<th>Vancomycin dose (mg/kg)a</th>
<th>CLCR (ml/min)a</th>
<th>Albumin (mg/dl)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVDA (14)</td>
<td>36.0 ± 6.2</td>
<td>9/5</td>
<td>28.9 ± 6.4</td>
<td>85.5 ± 23.0</td>
<td>2.6 ± 0.3</td>
</tr>
<tr>
<td>Control (10)</td>
<td>38.0 ± 11.9</td>
<td>8/2</td>
<td>29.4 ± 6.0</td>
<td>68.3 ± 30.4</td>
<td>2.8 ± 0.6</td>
</tr>
<tr>
<td>Burn (10)</td>
<td>36.4 ± 14.9</td>
<td>5/5</td>
<td>42.7 ± 18.3</td>
<td>111.0 ± 28.3</td>
<td>1.7 ± 0.5</td>
</tr>
</tbody>
</table>

a Mean ± standard deviation.
b 30.9% ± 14.4% of total body surface area was burned, and 18.3 ± 11.7 days elapsed before treatment with vancomycin was begun.
c P < 0.05.
unbound kinetic parameters were consistent with those observed for total drug (data not shown). Differences in $f_u$ within a patient determined at 1, 6, and 11 h for patients receiving vancomycin every 12 h ($n = 30$) and at 1, 3, and 7 h for four burn patients receiving vancomycin every 8 h were no higher than 10%. Therefore, an average of all three values for a given patient was used in all subsequent calculations involving $f_u$. Vancomycin urinary recovery for the three groups was not significantly different ($82\% \pm 0.3\%$). Estimated vancomycin CL$_{ur}$ was significantly greater for burn patients than for either IVDA or controls.

**Discussion**

The increased frequency of methicillin-resistant staphylococcal strains has led to a more widespread use of vancomycin in various patient populations. This has created a need to examine more carefully the factors which influence the variability in vancomycin pharmacokinetics. Previous reports have indicated that burn patients exhibit altered vancomycin pharmacokinetics as compared with nonburn patients. Brater et al. (3) found enhanced vancomycin CL in burn patients which correlated with an increased CL$_{Cr}$. Garrelts and Peterie (6) found a 78% increase in the vancomycin dosage required to produce therapeutic concentrations in serum in burn patients as compared with nonburn patients. This increased dosage requirement occurred even though there was only a 12% increase in CL$_{Cr}$ in burn versus nonburn patients. In the present investigation, we found that vancomycin CL was significantly greater in burn patients than in the control group or the IVDA group. This was associated with a significant increase in CL$_{Cr}$.

Several possible mechanisms for enhanced vancomycin and aminoglycoside elimination in burn patients have been proposed, including (i) increased nonrenal elimination (particularly through the burn wound), (ii) increased glomerular filtration rate, and (iii) altered protein binding (2, 3, 12, 18, 19). Our data indicate that there is no significant difference in the urinary recovery of vancomycin in burn patients as compared with nonburn patients. This would appear to rule out enhanced nonrenal elimination in burn patients as a mechanism of increased clearance, assuming that the assay used is not interfered with by any as-yet-unidentified metabolites or degradation products. Although there have been studies documenting differences in vancomycin concentrations determined by high-pressure liquid chromatography or fluorescence polarization immunoassay in anuric patients undergoing peritoneal dialysis, studies in patients with normal renal function (as in this investigation) are lacking (13, 22). The fact that protein binding did not differ among the three groups also indicates that altered binding is not a plausible mechanism for the altered elimination observed in burn patients. These observations indicate that the probable mechanism for increased vancomycin elimination in burn patients is secondary to altered renal elimination.

There are conflicting data in the literature regarding whether the mechanism(s) of vancomycin renal elimination involves filtration only or filtration and secretion. Golper and associates (8) performed the most rigorous evaluation of vancomycin renal elimination mechanisms published to date. Based upon their observations, these investigators concluded that vancomycin was eliminated only via filtration and nonrenal mechanisms. Unfortunately, technical difficulties prevented the investigators from determining protein binding, and they assumed a value of 10 to 20%. The assumption of protein binding values similar to those measured in the present study would have led Golper et al. to
conclude that the renal mechanisms of vancomycin elimination include both filtration and secretion. Our finding that the \( \text{CL}_{\text{R}} / \text{CL}_{\text{F}} \) ratio was greater than 1 in all three patient groups supports the conclusion that secretion contributes to the renal elimination of vancomycin. This conclusion is consistent with the observations of other investigators (5, 14, 16; T. A. Golper, L. Elzinga, H. Noonan, J. Anderson, D. N. Gilbert, and W. M. Benner, Program Abstr. 26th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 1260, 1986). Thus, burn patients may exhibit an increased filtration fraction, an increased secretory component, or both. The data in Table 2 suggest that both filtration and secretion may be enhanced in burn patients, although because of the large intersubject variability, only the increase in secretory clearance was statistically significant. The fact that the small proportion of drug eliminated by the nonrenal route was not statistically different among the three groups further supports this observation. Further studies are needed to confirm these observations and to probe the physiological and biochemical mechanisms of such changes.

The extensive use of vancomycin in IVDA and the report by King et al. (10) of altered aminoglycoside pharmacokinetics in this patient population led us to examine this subgroup for possible altered kinetics. While the mean vancomycin CL was 31% higher in IVDA than in controls, the difference was not statistically significant. We recently reported (M. J. Rybak, S. A. Lerner, D. P. Levine, L. M. Albrecht, P. L. McNeil, G. A. Thompson, and M. T. Kenny, 29th ICAAC, abstr. no. 1343, 1989) increased dosage requirements in IVDA receiving teicoplanin (an investigational glycopeptide antibiotic similar to vancomycin) to the trend towards an increased vancomycin CL and the observations with teicoplanin and clarithromycin. Our finding that the proportion of drug eliminated by the nonrenal route was not significantly altered in IVDA patients who received teicoplanin supported the conclusion that secretion contributes to the nonrenal elimination of vancomycin.

The data in Table 2 suggest that both filtration and secretion may contribute to the nonrenal elimination of vancomycin. This conclusion is consistent with the observations of other investigators (5, 14, 16; T. A. Golper, L. Elzinga, H. Noonan, J. Anderson, D. N. Gilbert, and W. M. Benner, Program Abstr. 26th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 1260, 1986). Thus, burn patients may exhibit an increased filtration fraction, an increased secretory component, or both. The data in Table 2 suggest that both filtration and secretion may be enhanced in burn patients, although because of the large intersubject variability, only the increase in secretory clearance was statistically significant. The fact that the small proportion of drug eliminated by the nonrenal route was not statistically different among the three groups further supports this observation. Further studies are needed to confirm these observations and to probe the physiological and biochemical mechanisms of such changes.

LITERATURE CITED


