Once-Daily Amikacin Dosing in Burn Patients Treated with Continuous Venovenous Hemofiltration

Kevin S. Akers,1,2 Jason M. Cota,3 Christopher R. Frei,4,7 Kevin K. Chung,5 Katrin Mende,1,6 and Clinton K. Murray1,2,*

Infectious Disease Service, Brooke Army Medical Center, 3851 Roger Brooke Drive, Fort Sam Houston, Texas 78234-6200; Uniformed Services University of the Health Sciences, 4301 Jones Bridge Drive, Bethesda, Maryland 20814; Department of Pharmacy Practice, University of the Incarnate Word Feik School of Pharmacy, 4301 Broadway CPO #890, San Antonio, Texas 78209-6397; Pharmacotherapy Education and Research Center, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, MSC-6220, San Antonio, Texas 78229-3904; Burn Intensive Care Unit, United States Army Institute of Surgical Research, 3698 Chambers Pass, Fort Sam Houston, Texas 78234; Infectious Disease Clinical Research Program, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Drive, Bethesda, Maryland 20814; and College of Pharmacy, The University of Texas at Austin, 1 University Station, A1900, Austin, Texas 78229-3906

Received 19 March 2011/Returned for modification 20 May 2011/Accepted 31 July 2011

Aminoglycosides are an important therapeutic option in critically ill patients with sepsis, and achieving a pharmacodynamic target of ≥8 to 10 for the maximum concentration of drug in serum divided by the MIC (C_max/MIC) is recommended (14, 16). While aminoglycoside therapy has traditionally been given in multiple daily doses, limited clinical evidence supports once-daily maintenance dosing of 15 mg/kg of body weight for amikacin and offers advantages in cost and convenience (9, 12). However, aminoglycoside clearance can be enhanced in critically ill patients and patients with burn injury (8, 19, 21), making this target more difficult to achieve. Increased amikacin doses could therefore be required in this population to ensure clinical efficacy.

In our burn intensive care unit (ICU), we have observed that patients with severe burn injury often develop clinical sepsis or septic shock along with acute kidney injury, leading to concurrent antimicrobial and renal replacement therapies. Continuous venovenous hemofiltration (CVVH) is most often used since data from our center indicate a survival advantage over historical controls who largely did not receive any form of renal replacement (4, 5). However, the clinical impact of CVVH on aminoglycoside pharmacokinetics in burn patients is uncertain. We therefore conducted a Monte Carlo simulation using pharmacokinetic and MIC data from burn patients to determine whether CVVH compromised our ability to achieve a C_max/MIC of ≥8 to 10 using standard once-daily amikacin doses of 15 mg/kg.

MATERIALS AND METHODS

Clinical data. We reviewed the medical records of patients admitted to the burn ICU of the United States Army Institute for Surgical Research (USAISR) from 2006 to 2009. Patients were included if they received single daily amikacin doses of approximately 15 mg/kg. Patients were excluded if they were less than 18 years of age, pregnant, admitted for reasons other than a primary thermal burn injury, admitted within 72 h of the burn injury, or lacked sufficient amikacin serum concentrations to calculate pharmacokinetic parameters. Patients admitted after 72 h from the injury were included to ensure that pharmacokinetic measurements would take place in the second phase of burn injury, which is characterized by a hypermetabolic state. Amikacin doses, amikacin serum concentrations, CVVH treatment parameters, age, sex, and total body surface area burned (TBSA) were recorded. The study was approved by the Institutional Review Board.

Pharmacokinetic data. Amikacin serum concentrations were determined after the first dose in the course of routine clinical care by the automated fluorescence polarimetry method of the clinical laboratory. Each amikacin dose of approxi-
Once-daily amikacin dosing in burn patients treated with continuous venovenous hemofiltration

United States Army Institute of Surgical Research, JBSA Fort Sam Houston, TX

Approved for public release, distribution unlimited
TABLE 1. Clinical and pharmacokinetic variables in burn patients receiving amikacin

<table>
<thead>
<tr>
<th>Without CVVH</th>
<th>With CVVH</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (No.)</td>
<td>48</td>
<td>12</td>
</tr>
<tr>
<td>Age (years)</td>
<td>37.9 ± 20.2</td>
<td>28.3 ± 8.4</td>
</tr>
<tr>
<td>TBSA (%)</td>
<td>38.4 ± 21.8</td>
<td>74.0 ± 15.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>94.9 ± 20.7</td>
<td>83.3 ± 20.9</td>
</tr>
<tr>
<td>Dose (mg)</td>
<td>1320.0 ± 286.4</td>
<td>1158.3 ± 357.9</td>
</tr>
<tr>
<td>Dose (mg/kg)</td>
<td>14.2 ± 2.9</td>
<td>13.9 ± 2.6</td>
</tr>
<tr>
<td>Vₐmax (µg/ml)</td>
<td>36.3 ± 10.2</td>
<td>29.1 ± 14.5</td>
</tr>
<tr>
<td>Cₐmax (µg/ml)</td>
<td>1.6 ± 4.3</td>
<td>1.5 ± 1.6</td>
</tr>
<tr>
<td>T₁/₂ (h)</td>
<td>4.75 ± 5.24</td>
<td>5.49 ± 2.35</td>
</tr>
<tr>
<td>CLₐmik (L/h)</td>
<td>7.8 ± 3.7</td>
<td>8.8 ± 8.9</td>
</tr>
<tr>
<td>AUC₀→t (mg · h/L)</td>
<td>239.0 ± 262.7</td>
<td>214.8 ± 113.8</td>
</tr>
<tr>
<td>V (L/kg)</td>
<td>0.60 ± 0.10</td>
<td>0.84 ± 1.06</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD, unless otherwise noted.

TBSA, % total body surface area burned; Cₐmax, maximum concentration; Cₐmin, minimum concentration; kₑ, rate constant of elimination; T₁₁/₂, half-life of elimination; CLₐmik, amikacin clearance; AUC₀→t, area under the curve; V, apparent volume of distribution.

RESULTS

Patient and infection characteristics. Sixty patients received amikacin and had sufficient dosing and postinfusion data to calculate pharmacokinetic parameters (Table 1). In-hospital mortality was 35%, and 20 patients (51.3%) developed recurrent bacteremia after amikacin therapy. The majority of patients also received imipenem therapy. In the 48 patients who did not receive CVVH, the mean and standard deviation for serum creatinine were 1.0 ± 0.3 mg/dl, and the mean creatinine clearance was 134 ± 35 ml/min. Twelve patients were simultaneously treated with CVVH. Of these, 10 patients were treated using the Prismaflex system with an HF1400 polyarylethersulfone (PAES) filter with a 1.4-m² surface area (Gambro, Lakewood, CO) and 2 were treated using the NxStage system using a CAR-500 polysulfones (PES) filter with a 1.5-m² surface area (NxStage Medical, Inc., Lawrence, MA). The mean hemofiltration rate was 30.0 ± 13.5 ml/kg/h (range, 10.6 to 55.6 ml/kg/h; median, 26.9 ml/kg/h). Clearance of amikacin in CVVH recipients correlated with effluent rates (r = 0.82).

One hundred seventy-two Gram-negative bloodstream isolates were recovered from 39 patients within 30 days of the amikacin dose. The predominant pathogens and amikacin MIC data for 82 isolates are listed in Table 2. The other isolates recovered included Stenotrophomonas maltophilia (11 isolates), Enterobacter aerogenes (9 isolates), Aeromonas hydrophilia (6 isolates), Serratia marcescens (4 isolates), Pantoea agglomerans (2 isolates), Haemophilus influenzae (2), Serratia liquefaciens (2), Klebsiella oxytoca (2), Proteus mirabilis (1), and Enterobacter cloacae (1).

Pharmacokinetic data. Among those patients receiving CVVH therapy, the amikacin Cₐmax and Cₐmin were significantly lower and T₁₁/₂ was significantly longer (Table 1). Cₐmax was noted to be significantly lower in association with more rapid amikacin clearance and a larger volume of distribution as the total body surface area burned (TBSA) exceeded 25% (Table 3). Considering the amikacin Cₐmax values in individual patients relative to the MICs of bacteria recovered from them, the target ratio of Cₐmax/MIC of ≥10 was satisfied for only 7 of 82 isolates (8.5%) collected from 7 different patients. The amikacin MICs of those isolates were 2 or 4 µg/ml, in contrast to ≥8 µg/ml for the remaining 75 isolates for which a Cₐmax/MIC ratio of ≥10 was not satisfied.

Although the amikacin 15 mg/kg CFR given a Cₐmax/MIC of ≥10 was higher for patients not receiving CVVH, it was less
than 50% for all isolates (Table 4). The CFRs remained less than 60% for all isolates for a theoretical 20-mg/kg amikacin dose using a lower threshold of $C_{\text{max}}$/MIC of $\geq 10$. Amikacin 20 mg/kg CFRs were modeled for $AUC_{24}$/MIC ratios of 100, 125, and 150 since some studies have proposed these as potential pharmacodynamic targets. CFRs were less than 15% for all isolates at an $AUC_{24}$/MIC of 100 and less than 5% for an $AUC_{24}$/MIC of 150 (data not shown).

## DISCUSSION

Optimizing antimicrobial therapy is critical to ensure favorable clinical outcomes for life-threatening bacterial infections. Previous studies have indicated that critical illness (17, 18) and burn injury (21) are risk factors for inadequate aminoglycoside dosing, even when 20 mg/kg of amikacin is administered as a single daily dose (8). Based on previous data indicating significant survival advantages in burn patients who develop acute renal insufficiency (4, 5), CVVH is often used for renal replacement therapy in our burn ICU. However, it is unclear whether and to what extent CVVH therapy affects aminoglycoside clearance and whether increased clearance might offset the survival benefits of CVVH therapy. With this in mind, we used data previously collected for clinical care to calculate pharmacokinetic parameters for amikacin in severely burned patients with and without exposure to concurrent CVVH therapy and then used a Monte Carlo simulation to estimate the CFR for these patients.

For aminoglycosides, which exert concentration-dependent bactericidal activity, optimal efficacy is achieved when the $C_{\text{max}}$/MIC ratio is $\geq 8$ to 10 (14, 16). Our data show that this pharmacodynamic target was achieved infrequently, for only 8.5% of the isolates when using an average dose of 14.1 mg/kg. Amikacin $AUC_{24}$/MIC ratios of $> 150$ were nearly unattainable using a 15-mg/kg dose. We did observe increased amikacin clearance with more extensive burns. Patients had lower $C_{\text{max}}$ values due to large volumes of distribution and increased clearance. This resulted in more difficult attainment of a $C_{\text{max}}$/MIC of $\geq 10$. This finding agrees with prior observations of increased amikacin clearance above a total body surface area burned (TBSA) threshold of 15% (8).

The lack of pharmacodynamic target attainment in many of our patients may also be due in part to high MICs of isolates for which this target was not met. An isolate with a MIC of up to 16 $\mu$g/ml is considered susceptible by CLSI guidelines, whereas the European susceptibility breakpoint is $\leq 8$ $\mu$g/ml. In order to achieve a $C_{\text{max}}$/MIC of 8 for CLSI susceptible isolates, the amikacin peak would have to be unacceptably high at 128 $\mu$g/ml. Monte Carlo simulation data incorporating MIC and pharmacokinetic data from within our burn ICU indicate that a 20-mg/kg amikacin dose would not be sufficient to significantly improve the CFR for accepted $C_{\text{max}}$/MIC or $AUC_{24}$/MIC indices. While achieving a $C_{\text{max}}$ of 64 $\mu$g/ml for isolates with MICs of 8 $\mu$g/ml may be considered safe, daily doses greater than 35 mg/kg would likely be required given the V of 0.6 liters/kg in our burn patients. Such doses may increase the likelihood of toxicity resulting from continuously elevated trough concentrations. However, it is notable that once-daily doses of amikacin as high as 50 mg/kg were recently used to cure refractory $P. aeruginosa$ infections in two patients, apparently without toxic effects of therapy. In these patients, continuous venovenous hemodiafiltration (CVVHDF) was used adjunctively to achieve low trough concentrations between doses (13).

Interestingly, the amikacin serum concentrations, pharmacokinetic parameters, and CFRs in burn patients undergoing CVVH were similar to those in non-CVVH patients. One reason for this finding may be the greater relative %TBSA-to-body weight ratio in the CVVH group. Indeed, our study and others have demonstrated that a greater %TBSA may lead to increased loss of aminoglycosides through the burn wound. The prescribed CVVH doses and filter membranes used at our institution may also result in amikacin clearances similar to those in patients without acute kidney injury. These findings are notable because a maximum empirical amikacin dose of 7.5 mg/kg every 24 h is recommended for nonburn critically ill patients undergoing CVVH (10, 20). Following these empirical dosing guidelines would likely result in peaks of less than 15 $\mu$g/ml, which is a $C_{\text{max}}$ below the target for all isolates in our study which had MICs of $\geq 2$ $\mu$g/ml. The 20-mg/kg modeled amikacin dose would increase CFR in CVVH recipients, and the $C_{\text{min}}$ would likely remain below 2 to 4 $\mu$g/ml. One challenge to high-dose amikacin in CVVH patients would be unplanned clotting of the continuous renal replacement therapy (CRRT) circuit. If this were to occur shortly after the administration of a dose, a patient would be exposed to prolonged concentrations of amikacin until CVVH could be resumed. After comparing the high efficiency of amikacin drug removal observed with CVVH in this study to the solute clearance observed in other reports, we strongly recommend that aminoglycoside dosing guidelines in patients undergoing CRRT be institution specific. Using Monte Carlo simulations that incorporate these CRRT factors in addition to institution-specific
MIC distributions should further guide empirical dosing recommendations.

This study has limitations. The number of patients receiving concurrent CVVH therapy was small, reducing the sensitivity for detecting an increase in amikacin clearance attributable to CVVH (a type II error). While it would be interesting to perform a population pharmacokinetic model on our amikacin serum concentrations, the more precise estimates from such modeling would be unlikely to significantly change the study conclusions. We also described the amikacin pharmacokinetics using a 1-compartment model, which would underestimate the amikacin peak concentration. However, amikacin peak concentrations according to a 2-compartment model would probably remain less than 50 to 60 mg/liter, and few isolates had MICs of less than 8 μg/ml. Widely accepted pharmacodynamic targets would still not be met in CVVH and non-CVVH burn patients receiving once-daily amikacin doses of 15 mg/kg. Pharmacokinetic calculations are exquisitely sensitive to the elapsed time from the start and end of infusion, and we were unable to verify the accuracy of the times recorded on laboratory samples. However, the resulting pharmacokinetic parameters are largely consistent with those of other studies (3, 8, 11). We deliberately used only bloodstream isolates for the calculation of C_{max}/MIC ratios, and thus, these findings cannot be directly extrapolated to isolates recovered from other body compartments. The evaluation of clinical pharmacodynamic targets for amikacin in bacteremic patients is of significant interest. However, many of the patients included in this study received concomitant antimicrobial therapy.

In conclusion, critically ill burn patients are at increased risk for inadequate dosing with amikacin. Although increased clearance and volume of distribution may be contributing factors with larger surface area burns, the low CFR for a C_{max}/MIC of ≥10 that we observed is also attributable to high MICs among the recovered bacterial isolates. In addition, it appears that high-dose daily aminoglycoside dosing may be appropriate given the high efficiency of drug removal observed while receiving CVVH according to our institution’s CRRT prescribing practices. It should be noted that the CVVH recipients in this study had TBSAs greater than 60%. As therapeutic options are progressively limited by increasing antimicrobial resistance and rising MICs, new dosing strategies may be necessary in order to deliver effective antimicrobial therapy to critically ill and severely burned patients. It might be possible to give higher amikacin doses and use CRRT to enhance drug removal and minimize toxicity. Clinical trials are needed to further assess this idea.

ACKNOWLEDGMENTS

We thank Kristelle Cheatle for her assistance with the preparation of microbiological data.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or reflecting the views of the Department of the Army, Department of Defense, or the U.S. Government.

C.R.F. is supported by the U.S. National Institutes of Health (NIH) in the form of an NIH/KL2 career development award (RR025766).

REFERENCES