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Pharmacokinetics of Cefepime in Patients with Thermal Burn Injury

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The pharmacokinetics of cefepime following administration of a single 2-g dose were evaluated for 12 adult patients with thermal burn injury and suspected or documented infection. Serial blood and urine samples for cefepime concentration determination were obtained for 24 h following drug administration. Serum and urine cefepime concentrations were determined by high-performance liquid chromatography and serum concentrations were fit to a two-compartment pharmacokinetic model. Mean (standard deviation [SD]) age, actual body weight (ABW), percent total body surface area burned, and days postburn at the time of study were 41 (13) years, 84 (22) kg, 36 (17)%, and 9 (3) days, respectively. Mean (SD) measured creatinine clearance (CL_{CR}), total clearance (CL_T), renal clearance (CL_R), alpha phase half-life, beta phase half-life, and volume of distribution at steady state (V_{SS}) were 135 (31) ml/min, 8.8 (2.4) liters/h, 8.1 (2.0) liters/h, 0.33 (0.14) h, 2.8 (0.6) h, and 0.43 (0.10) liters/kg ABW, respectively. Cefepime CL_T and CL_R in burn patients were similar to previously reported values for healthy volunteers when normalized by CL_{CR}. Stepwise multiple regression was used to associate CL_T with CL_{CR} and days postburn ($r^2 = 0.861$), CL_R with CL_{CR} and days postburn ($r^2 = 0.773$), nonrenal clearance with percent third-degree (% 3°) burn and albumin concentration ($r^2 = 0.550$), and V_{SS} only with % 3° burn ($r^2 = 0.624$). Simulated steady-state serum concentrations obtained by using the patients' pharmacokinetic parameters exceeded the susceptibility interpretive standard (breakpoint) of cefepime for at least 60% of the dosing interval with dosing regimens of 1 g every 8 h (q8h), 2 g q8h, and 2 g q12h. Despite differences in pharmacokinetic parameters between our patients and healthy volunteers, it appears that these dosing regimens may be adequate in similar burn patients.

Numerous pathophysiological changes occur as a result of burn injury, and these changes may alter the pharmacokinetic characteristics and effectiveness of antimicrobial agents administered to burn patients (9, 21, 26). Several reports have demonstrated the necessity of larger and/or more frequently administered doses for antimicrobials which are primarily renally eliminated (2, 10, 11, 16, 17, 23, 28, 35, 37). Major reasons for this include increased renal elimination of drugs resulting from burn-induced increased glomerular filtration rate, alterations in fluid balance (affecting apparent distribution volume), increased metabolic rate, and altered protein binding (21, 24). Therefore, it is important to rigorously evaluate antimicrobials to determine what effect burn injury may have on the pharmacokinetic disposition and resultant dosing requirements in these patients.

Cefepime is a newer cephalosporin antibiotic possessing a wider spectrum of antibacterial activity and greater potency than most earlier cephalosporins (29). Its spectrum of activity includes pathogens such as *Pseudomonas aeruginosa* and *Staphylococcus aureus*, making it a potential candidate for treatment of bacterial infections in this population. Because of known alterations of drug disposition with other β-lactams and its potential usage in this patient population, the objective of this study was to characterize the pharmacokinetics of cefepime following a single dose in burn patients requiring antibiotics for suspected or documented infection.

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MATERIALS AND METHODS

Patients. All patients aged 18 to 80 years admitted to the Medical University of South Carolina Burn Unit with thermal burn injury having a percent total body surface area burned (% TBSAB) ≥15% (excluding first-degree burns) and requiring antimicrobial therapy (either suspected or documented infection) were eligible for study enrollment. The study was approved by the institutional review board, and written informed consent was obtained for all patients. Patients excluded from the study were the following: patients with a history of allergy to cefepime or cephalosporins or penicillins, patients with reduced renal function (estimated prestudy creatinine clearance [CL_{CR}] < 30 ml/min calculated by the method of Cockroft and Gault [12]), patients with hepatic impairment (serum bilirubin and alanine aminotransferase levels above the normal upper limit by factors of ≥2 and ≥4, respectively), or those undergoing any type of dialysis. All patients were studied following completion of fluid resuscitation and monitored in accordance with standard burn patient care at our institution.

Patient data. Information collected for all patients included age, sex, weight on day of study, height, date of burn, date of study, % TBSAB, percent second-degree burn (% 2° burn), percent third-degree burn (% 3° burn), review of systems and physical findings pertinent to the evaluation of liver and renal function, pre- and poststudy urinalysis, blood chemistry (SMA-7, SMA-25), and complete blood count with differential, dosage, schedule, and route of administration of concurrent medications, and fluid intake and output.

Drug administration and sample collection. All patients received 2 g of cefepime (lot D6V89A; expiration date January 1999; Bristol-Myers Squibb Company, Princeton, N.J.). Cefepime was reconstituted as directed by the manufacturer and added to a 100-ml 0.9% saline minibag. A sample was frozen at −70°C within 1 h of preparation for subsequent cefepime concentration determination. The contents of the cefepime minibag were infused intravenously over 30 min with a programmable pump, and the actual volume delivered was recorded. Immediately following the end of the infusion, the administration line was flushed with 0.9% saline. The calculation of the actual amount of drug administered was based on the assayed concentration of cefepime in the minibag and the volume delivered. The actual amount of drug administered was used for all subsequent pharmacokinetic calculations. Blood samples were collected at the following times: predose, and 30, 40, 50, and 60 min and 2, 3, 4, 6, 8, 10, 12, 18, and 24 h after the start of the infusion. Each sample was collected with an additive-free VACUTAINER tube (Becton Dickinson, Franklin Lakes, N.J.) either through a central or peripheral line. At each sample point, 5 ml of blood

was drawn through the line and placed in a separate container prior to collecting the sample. Samples were obtained by peripheral venipuncture only when an intravenous catheter was not available. Following collection, all blood samples were immediately placed on ice until they could be centrifuged at 2,000 × *g* (Centra-8R; IEC, Needham Heights, Mass.) for 6 min. The serum was removed and placed into polypropylene containers and frozen at −70°C. Serum samples were assayed within 7 months.

Urine samples were collected during the study period at the following intervals: immediately prior to drug administration and from 0 to 4, 4 to 8, 8 to 12, and 12 to 24 h after the start of the infusion. At each interval, the urine was thoroughly mixed and the volume was recorded. A 3-ml sample was removed for cefepime analysis and immediately placed on ice prior to pooling the remaining urine for a 24-h urine collection and CL_{CR} measurement. The 3-ml sample was mixed with 6 ml of 0.2 M sodium acetate buffer (pH 4.25) and immediately frozen at −70°C until the time of cefepime assay. Urine samples were assayed within 10 months of collection. Preliminary studies indicated that cefepime in serum and urine samples was stable (retention of ≥91% of the original concentration) during the period of frozen storage (unpublished data).

Cefepime serum assay. Cefepime serum and urine samples were analyzed by a modification of the method described by Barbhaiya et al. (3). High-performance liquid chromatography (HPLC) equipment used for the cefepime serum and urine assays consisted of a pump (model 510; Waters, Milford, Mass.), sample injector (715 Ultra WISP; Waters), UV light absorbance detector (Lambda-Max model 481; Waters), and an integrator (Chromatopac C-R3A; Shimadzu, Kyoto, Japan). Chromatographic separation was performed with a reverse-phase HPLC column (Nova-Pak C-18; 3.9 by 150 mm; Waters). The mobile phase consisted of an 86% 0.0023 M 1-octanesulfonic acid sodium salt in HPLC-grade water and 14% (vol/vol) acetonitrile adjusted to pH 2.3 with 85% phosphoric acid. Dissolved gases were removed from the final product by filtration through a 0.45-μm-pore-size nylon membrane filter (Whatman, Maldstone, England) while the sample was stirred under vacuum. The mobile-phase flow rate was 1 ml/min, the setting for full-scale absorbance units was 0.05, and the detection wavelength was 280 nm.

Patient serum samples were allowed to thaw at room temperature prior to analysis. When necessary, samples were diluted with pooled human serum into the range of the assay. Protein precipitation was accomplished by adding an equal volume of 5% trichloroacetic acid to all patient samples as well as standards, vortexing for 20 s, and centrifuging at 3,000 × *g* (IEC Centra-8R) for 10 min. Samples were injected in duplicate with an injection volume of 75 μl. The retention time of cefepime was approximately 10 min, and no interfering peaks were observed.

Serum standards were prepared from laboratory grade cefepime (batch CCB4V0189, lot 189; Bristol-Myers Squibb Company, Syracuse, N.Y.). Standards were prepared with pooled human serum (Abbott Laboratories, North Chicago, Ill.) to produce concentrations of 0.5, 1, 5, 8, 10, 25, 35, 50, and 75 μg/ml. Quality control samples had concentrations ranging from 0.5 to 75 μg/ml. Two standard curves were used to accommodate the wide range of anticipated concentrations while assuring linearity. They ranged from 0.5 to 10 μg/ml ($r^2 \geq 0.998$) and from 10 to 75 μg/ml ($r^2 \geq 0.999$). The intraday coefficients of variation were ≤7 and ≤1% for the low- and high-concentration standard-curve quality control samples, respectively; the corresponding interday coefficients of variation were ≤8 and ≤5%, respectively. A standard curve was considered acceptable if the quality control samples were within 15% of the nominal concentration.

Cefepime urine assay. The HPLC equipment used for the cefepime urine assay was the same as that listed above. Chromatographic separation was performed with a reverse-phase HPLC column (Partisil 5 ODS-3 C18; 4.6 by 100 mm; Whatman). The mobile phase consisted of 49.7% HPLC grade methyl alcohol, 40.4% of a 0.01 M sodium dodecyl sulfate solution (pH 3; adjusted with glacial acetic acid), 5.3% tetrahydrofuran, 3.9% of a 5% trichloroacetic acid solution, and 0.7% of a 2.49 M (vol/vol) phosphoric acid solution. The mobile phase was filtered through a 0.45-μm-pore-size nylon membrane filter (Whatman) while the sample was stirred under vacuum to remove dissolved gases. The mobile-phase flow rate was 2.8 ml/min, the detection wavelength was 280 nm, and the settings for full-scale absorbance units were 0.02 and 0.05 for the low-concentration and high-concentration standard curves, respectively.

Patient urine samples were allowed to thaw at room temperature prior to analysis. They were diluted with an equal volume of 0.2 M sodium acetate buffer into the range of the assay when necessary. Samples were injected in duplicate, and the injection volume was 10 μl. The retention time of cefepime was approximately 10 min.

Urine standards were prepared from laboratory grade cefepime powder (batch CCB4V0189, lot 189; Bristol-Myers Squibb Company). Standards were prepared in 0.2 M sodium acetate buffer (pH 4.25) to produce concentrations of 1.6, 3.1, 6.3, 12.5, 25, 50, 100, 200, 400, 600, and 800 μg/ml. Quality control samples had concentrations ranging from 1.6 to 800 μg/ml. Two standard curves were used for the urine assay to assure linearity over the wide range of concentrations to be measured. The low-concentration standard curve ranged from 1.6 to 12.5 μg/ml ($r^2 \geq 0.999$), and the high-concentration standard curve ranged from 12.5 to 800 μg/ml ($r^2 \geq 0.999$). The intraday coefficients of variation were ≤2 and ≤3% for the low- and high-concentration standard-curve quality control samples, respectively; the corresponding interday coefficients of variation were ≤4 and ≤8%, respectively. A standard curve was considered acceptable if the quality control samples were within 15% of the nominal concentration.

TABLE 1. Patient demographics

Patient	Sex	Age (yr)	ABW (kg)	% TBSAB	% 2° Burn	% 3° Burn	Days postburn
1	Male	21	107	30	25	5	2
2	Male	60	88	30	17	13	7
3	Male	38	84	18	18	0	10
4	Female	42	122	30	10	20	10
5	Male	30	61	27	9	18	7
6	Male	31	71	40	35	5	10
7	Male	53	116	40	0	40	8
8	Male	44	71	65	50	15	9
9	Male	50	56	18	10	8	13
10	Male	61	78	22	22	0	14
11	Female	26	96	45	5	40	8
12	Male	32	67	70	0	70	7
Mean (SD)		41 (13)	84 (22)	36 (17)	17 (15)	20 (21)	9 (3)

Pharmacokinetic analysis. The serum concentration-time profile for each patient was fit to a two-compartment model with a weighting selection of $1/y^2$ (where y is the observed concentration) by using RSTRIP (15). Determination of the optimal compartmental model was based on visual inspection of the concentration-time curves, minimization of the residual sum of squares, and the model selection criterion obtained from RSTRIP, which is an adaptation of the Akaike information criterion (34). Pharmacokinetic parameters included the area under the concentration-time curve (AUC) from 0 h to the last measured serum concentration (AUC_{0-t}), AUC from 0 h to infinity ($AUC_{0-\infty}$), alpha phase rate constant (α), and beta phase rate constant (β). β was also calculated as the negative slope of the terminal elimination phase by linear least-squares regression of at least four points. The alpha phase half-life was calculated as $t_{1/2\alpha} = 0.693/\alpha$, and the beta phase half-life was calculated as $t_{1/2\beta} = 0.693/\beta$. The AUC was calculated by the linear trapezoidal method and extrapolated to infinity as follows: $AUC_{0-\infty} = AUC_{0-t} + C_{last}/\beta$ where C_{last} is the last measured serum concentration. In addition, a noncompartmental analysis was performed. The area under the first moment of the concentration-time curve and the volume of distribution at steady state (V_{SS}) were calculated with standard pharmacokinetic equations (18). Total clearance (CL_T), renal clearance (CL_R), and nonrenal clearance (CL_{NR}) were calculated as follows: CL_T = (actual dose administered)/$AUC_{0-\infty}$, CL_R = (amount of cefepime recovered in urine during 0 to 8 h)/AUC from 0 to 8 h, and $CL_{NR} = CL_T - CL_R$. CL_T, CL_R, CL_{NR}, CL_{CR}, and V_{SS} were divided by actual body weight (ABW), lean body weight (LBW), a formula for corrected body weight that accounts for obesity (LBW + 0.4 [ABW − LBW]), and body surface area to normalize these parameters for differences in body weight among the patients studied. By least-squares analysis, the normalization factor that provided the strongest relationship between a pharmacokinetic parameter and the patient demographic factors was identified, and then this factor was used in subsequent analyses. Urinary excretion of cefepime as a percent of the dose recovered in 24 h was calculated as (amount of cefepime recovered in the urine/actual dose administered) × 100.

Pharmacodynamic analysis. We assessed the time the serum concentration exceeded the MIC ($T > MIC$). The steady-state serum concentration-time profile for each patient was simulated assuming a one-compartment open model with a 0.5-h infusion time by using patient-specific $t_{1/2\beta}$ and V_{SS}. Theoretical regimens simulated consisted of 1 g every 8 h (q8h), 2 g q8h, 1 g q12h, and 2 g q12h. The percentage of a dosing interval that the serum concentrations remained above a given MIC ($\%T > MIC$) was calculated as [($T > MIC$) × 100]/dosing interval. MICs utilized in this analysis were 8 (National Committee for Clinical Laboratory Standards susceptibility interpretive standard for cefepime), 4, 2, and 1 μg/ml (25). All calculations were verified by visual inspection of the serum concentration-time profiles.

Statistical analysis. Descriptive statistics were used to summarize the pharmacokinetic parameters. Simple and stepwise multiple linear regression, by the method of least squares, was used to describe the relationships between pharmacokinetic parameters and demographic characteristics of interest (i.e., measured CL_{CR}, % 2° burn, % 3° burn, age, days post-burn-injury, and albumin concentration [in grams per deciliter]). These relationships were analyzed with the StatView statistical software package, version 4.51 (Abacus Concepts, Inc., Berkeley, Calif.). A P value ≤0.05 was considered to be statistically significant.

RESULTS

Thirteen adult patients (10 male and 3 female) were enrolled. One patient was excluded from the study when venous access was lost. The analysis is based on the remaining twelve patients. Patient demographics are displayed in Table 1. All

TABLE 2. Pharmacokinetic parameters

Patient	CL_{CR} (ml/min)	$AUC_{0-\infty}$ (μg · h/ml)	V_{SS} (liters/kg ABW)	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	CL_T (liters/h)	CL_R (liters/h)	24-h urinary excretion (%)
1	182	135	0.37	0.39	2.8	14.0	12.5	90
2	122	196	0.36	0.19	2.2	10.0	9.4	95
3	189	193	0.33	0.37	1.9	9.2	8.2	96
4	191	163	0.48	0.45	3.3	11.1	9.4	82
5	125	258	0.38	0.10	1.9	6.9	6.7	99
6	139	251	0.31	0.63	2.2	7.2	7.8	107
7	164	223	0.43	0.29	4.0	8.4	8.4	98
8	104	294	0.43	0.35	3.0	6.3	5.8	90
9	150	266	0.55	NC[a]	2.5	7.0	6.3	88
10	NA[b]	333	0.34	0.28	2.8	5.6	NA	NA
11	184	157	0.50	0.31	3.5	11.3	9.3	82
12	130	215	0.66	0.27	3.1	8.8	5.7	63
Mean (SD)	135 (31)	224 (59)	0.43 (0.10)	0.33 (0.14)	2.8 (0.6)	8.8 (2.4)	8.1 (2.0)	90 (12)

[a] NC, not calculated for this patient.
[b] NA, urine data not available for this patient.

patients were studied following completion of fluid resuscitation and within 14 days of burn injury. The severity of the burn injury varied widely among patients with % 2° burn ranging from 0 to 50% and % 3° burn ranging from 0 to 70%. The mean (standard deviation [SD]) dose of cefepime administered was 1,844 (55) mg.

The pharmacokinetic parameters for all patients are shown in Table 2. Serum concentration-time data were best fit to a two-compartment model with a weighting factor of $1/y^2$ except for two patients (patients 4 and 9). In these patients, the β phase was better described by a weighting factor of $1/y$. For patient 9, we were unable to characterize the α phase due to incomplete sample collection immediately following cefepime administration. We were unable to measure CL_{CR} and to calculate CL_R for one patient due to incomplete urine collection. In the remaining patients, the 24-h mean (SD) percent urinary excretion was 90 (12)%.

In the analysis of the relationships between pharmacokinetic parameters and patient demographics, CL_T, CL_R, CL_{NR}, and CL_{CR} were normalized by LBW whereas V_{SS} was normalized by ABW. CL_T was significantly associated with CL_{CR} by simple linear regression ($r^2 = 0.575$; $P = 0.0068$). This is depicted in Fig. 1. With stepwise multiple regression, the inclusion of days postburn in addition to CL_{CR} enhanced the explanation of variability in CL_T ($r^2 = 0.861$; $P = 0.0004$). CL_R was significantly associated with CL_{CR} ($r^2 = 0.519$; $P = 0.0124$). With stepwise multiple regression, inclusion of days postburn in addition to CL_{CR} helped explain the variability in CL_R ($r^2 =$

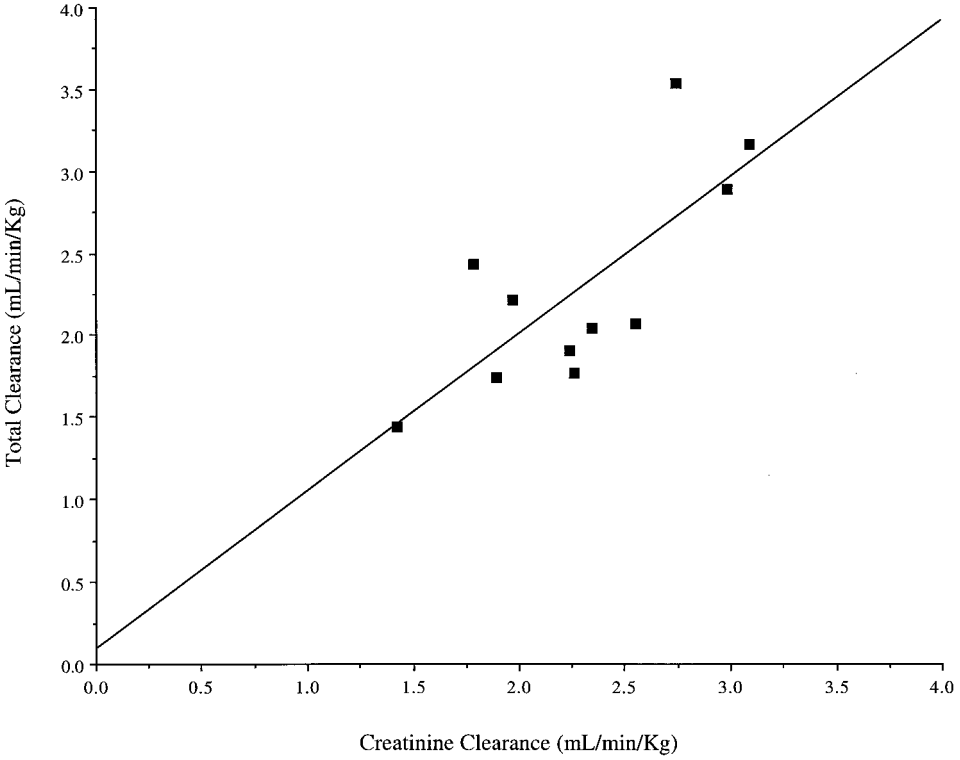

FIG. 1. Relationship between CL_{CR} and cefepime CL_T. $CL_T = 0.08810 + 0.9568(CL_{CR})$; $r^2 = 0.575$; $P = 0.0068$.

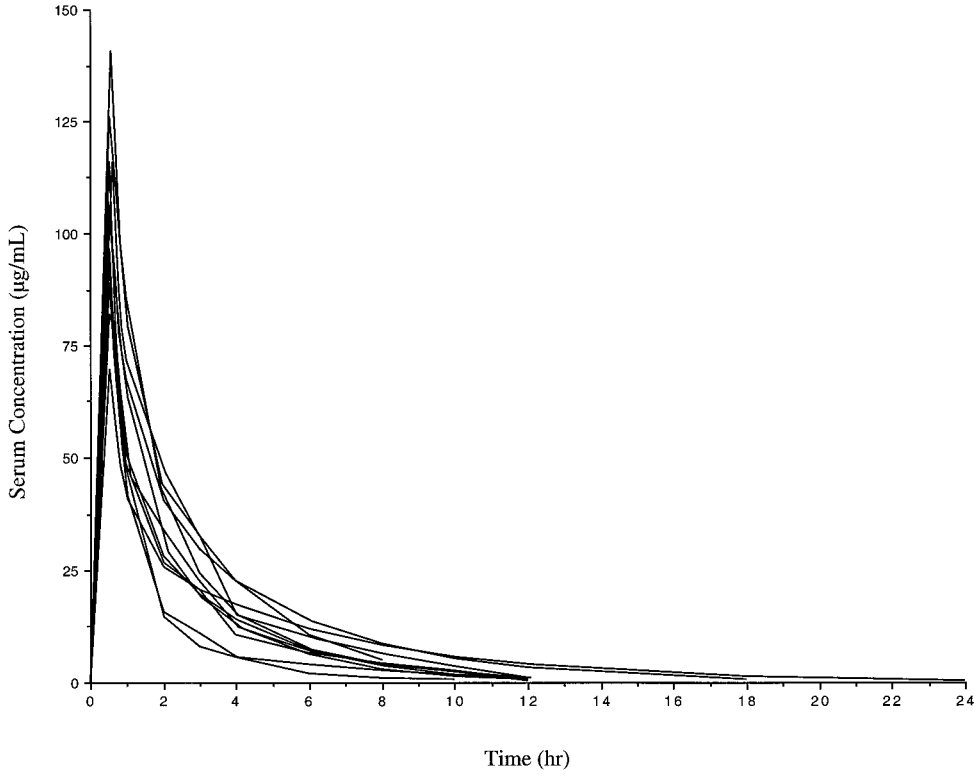

FIG. 2. Fitted serum concentration-time profile for each patient after a single 2-g dose of cefepime administered over 0.5 h (patient 4 was omitted due to a 1-h infusion).

0.773; $P = 0.0026$). CL_{NR} was significantly associated with % 3° burn ($r^2 = 0.376$; $P = 0.0448$) by simple linear regression. With stepwise multiple regression, the inclusion of albumin concentration in addition to % 3° burn better explained the variability in CL_{NR} ($r^2 = 0.550$; $P = 0.0411$). By simple linear regression and stepwise multiple regression, only % 3° burn was significantly associated with V_{SS} ($r^2 = 0.624$; $P = 0.0022$). Patient demographics included in each stepwise multiple-regression relationship were individually statistically significant with the exception of albumin concentration, which was included in the CL_{NR} relationship because it contributed considerably to the explanation of variability for this parameter.

The fitted serum concentration-time profiles for the patients are shown in Fig. 2. The mean (SD) observed serum concentration at the end of the infusion was 110 (23) μg/ml, whereas the observed concentrations at 8 and 12 h after the start of the infusion (SD) were 5.5 (2.6) μg/ml and 2.3 (1.6) μg/ml, respectively. The estimated $\%T >$ MIC values for dosing regimens consisting of 1 g q8h, 2 g q8h, 1 g q12h, and 2 g q12h administered over 0.5 h, obtained by using patient-specific pharmacokinetic parameters, are shown in Table 3. Simulated steady-state serum concentration-time profiles based on mean pharmacokinetic parameters with the same dosing regimens are shown in Fig. 3. In each panel, the *x* axis represents the time after the start of the infusion. All dosing regimens except 1 g q12h maintained a %T > MIC of at least 60% throughout the dosing interval for all MICs at or below 8 μg/ml, a susceptibility interpretive guideline for cefepime (25).

DISCUSSION

Burn injury results in numerous pathological changes in the body that can affect the disposition of antimicrobials (9, 21, 26). Since infection is a common complication of burn injury and since drug disposition may be altered in these patients, it is important to examine newer agents used in this patient population. Most of the published information regarding drug disposition in burn patients has been limited to aminoglycosides (7, 19, 20, 23, 27, 30, 35–37) and vancomycin (2, 11, 17, 28). Few studies have focused on the drug disposition of β-lactams in burn patients (1, 8, 10, 16, 32, 33). Consistent throughout these reports is the fact that drug disposition is influenced in this patient population. Similarly, we found cefepime pharmacokinetics to be altered in our burn patients.

Overall, the two cefepime pharmacokinetic parameters that appear to be most affected in burn patients are clearance and volume of distribution. The CL_T and CL_R for the study patients were approximately 10 and 20 to 30% higher, respectively, than those previously reported for healthy volunteers (4, 6). The patients in our study population also demonstrated an above-normal CL_{CR} with a mean (range) of 153 (104 to 191) ml/min. Similarly, Loirat et al. (23) demonstrated a significant increase in CL_{CR} among patients between the 4th and 35th days following burn injury compared to that for healthy controls. However, when normalized by CL_{CR}, the ratios of CL_T/

TABLE 3. Estimate of %T > MIC

MIC (μg/ml)	Mean $\%T >$ MIC (range) for regimen:			
	1 g q12h	2 g q12h	1 g q8h	2 g q8h
8	45 (36–56)	68 (52–85)	73 (56–89)	96 (79–100)
4	68 (52–85)	89 (67–100)	96 (79–100)	100 (100)
2	89 (68–100)	97 (83–100)	100 (100)	100 (100)
1	97 (83–100)	100 (98–100)	100 (100)	100 (100)

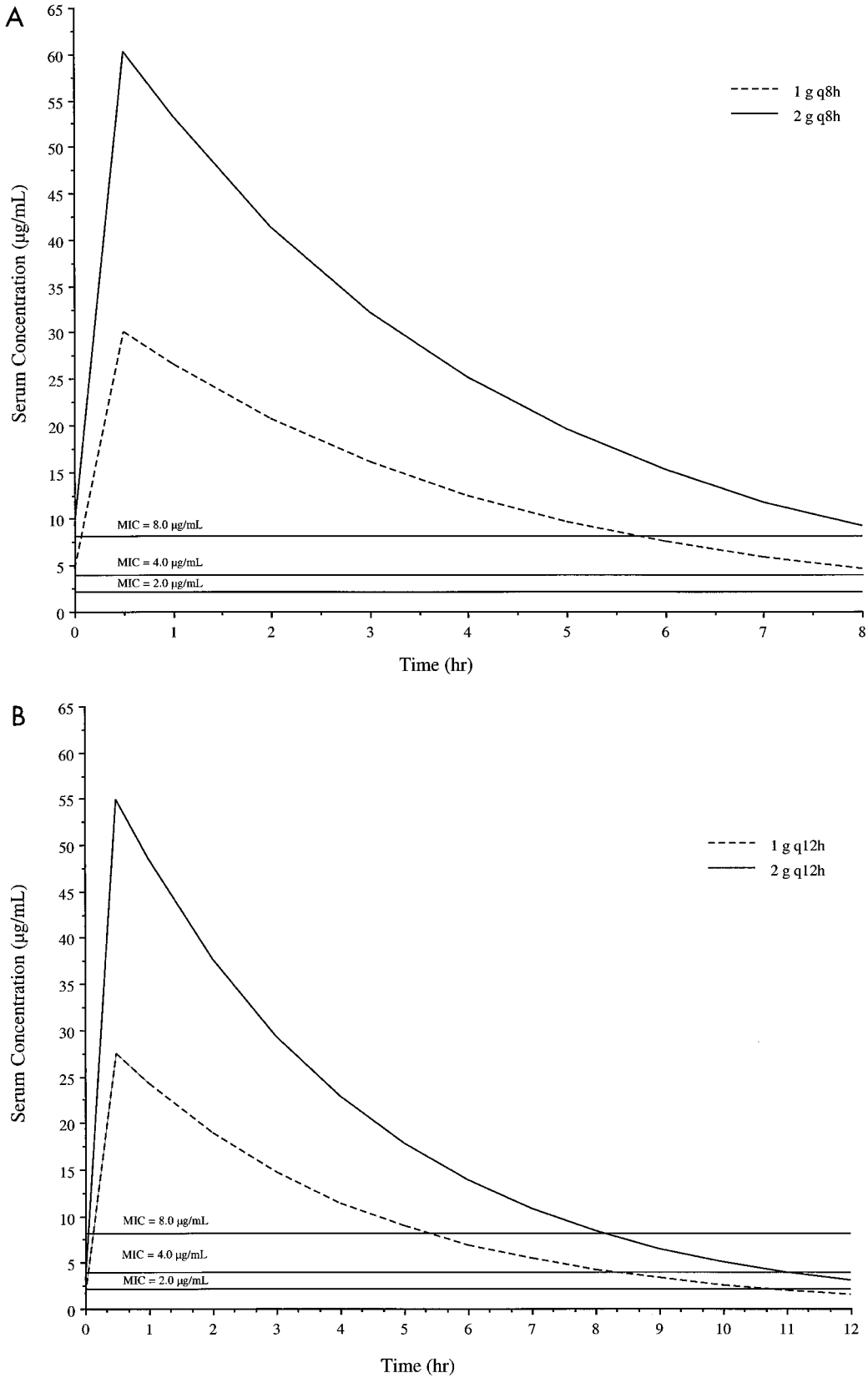

FIG. 3. Simulated steady-state serum concentration-time profiles of cefepime at 1 and 2 g q8h (A) and q12h (B) administered over 0.5 h based on mean pharmacokinetic parameters. Overlaid lines representing possible MICs are for showing $T >$ MIC.

CL_{CR} and CL_R/CL_{CR} in our study were found to be similar to ratios calculated from a study of healthy volunteers (5). Thus, it appears that the increased CL_T we observed was likely due to an elevated glomerular filtration rate in our patient population. Not all burn patients will have a CL_{CR} elevated above normal. Patients with preexisting renal impairment may experience an increase in the glomerular filtration rate over their baseline, although their increased renal function may still be below normal levels.

As is expected with a drug that is eliminated primarily by glomerular filtration, we found a statistically significant association between CL_T or CL_R and CL_{CR} by simple linear regression. When analyzed by stepwise multiple regression, days post-burn-injury also helped explain the variability in CL_T and CL_R. An inverse relationship between CL_T or CL_R and days post-burn-injury was found. Perhaps wound healing results in decreased drug clearance. CL_{NR} was positively associated with both % 3° burn and albumin concentration. Because the mechanisms of CL_{NR} were not assessed, we are unable to physiologically explain this finding. Lastly, the association between V_{SS} and % 3° burn that we found may be related to the physiological effects resulting from thermal burn injury, an effect directly related to the medical interventions, or some combination of the above.

We found a strong relationship between CL_{CR} and CL_T with cefepime in this population. Other authors have found strong relationships between CL_{CR} and CL_T with other β-lactam antibiotics in burn patients. Boucher et al. (8) observed a significant relationship between CL_{CR} and CL_T with imipenem ($r^2 = 0.60$; $P = 0.0001$) and Friedrich et al. (16) noted a similar significant relationship with aztreonam in burn patients ($r = 0.95$; $P = 0.0018$). In a study of the pharmacokinetics of piperacillin-tazobactam in burn patients, Bourget et al. (10) found a significant relationship between the CL_T of piperacillin-tazobactam and CL_{CR} ($r = 0.83$, $P = 0.03$), and Shikuma et al. (32) found a relationship between the CL_T of piperacillin and CL_{CR} ($r = 0.49$). In contrast to the findings of the previous authors, Walstad et al. (33) failed to find a relationship between CL_{CR} and CL_T of ceftazidime ($r = 0.13$), although a significant correlation between CL_{CR} and CL_R was found ($r = 0.96$). The authors report that this finding may be explained by an elevated CL_{NR} in patients with large burns. Therefore, the CL_T of β-lactams is variable in burn patients but appears to be associated with CL_{CR}. Although the CL_{CR} range observed in the patients we studied was limited (104 to 191 ml/min), the ratio of CL_T/CL_{CR} we observed in our study patients was consistent with that reported for healthy volunteers (5).

Although the calculated CL_R for patient 6 appears to exceed the CL_T, this is unlikely to occur physiologically and may be explained by experimental error, especially in the case of a drug for which the CL_R approaches the CL_T. In contrast, the low CL_R relative to the CL_T we observed for patient 12 may be related to the % 3° burn, which was the highest among all patients. This, coupled with the needed debridement surgery during the study, may explain an increased CL_{NR} due to an associated increase in insensible fluid loss.

Similar to other investigators who noted an increase in the V_{SS} of β-lactams, we noted an increase in the V_{SS} of cefepime in burn patients. The V_{SS} in our burn patient population (0.43 liters/kg) was approximately twice that previously reported for volunteers (0.18 to 0.24 liters/kg) with or without renal impairment (5, 6, 14). Walstad et al. (33) observed an increase in the V_{SS} of ceftazidime in burn patients compared to that in other patients. The increase was almost twice that seen with ceftazidime in healthy volunteers (22). Bourget et al. (10), Boucher et al. (8), Friedrich et al. (16), and Adam et al. (1) reported similar increases in V_{SS} with piperacillin-tazobactam, imipenem, aztreonam, and ticarcillin-clavulanate, respectively, in burn patients. Shikuma et al. (32) described approximately a threefold increase in V_{SS} of piperacillin in burn patients compared to that in healthy subjects. Thus, it appears that the V_{SS} of cefepime is increased, as has been previously described for other β-lactams. The increase in the V_{SS} of cefepime may also be partially attributed to alterations in protein binding; other studies have shown changes in plasma protein levels and drug binding following burn injury (24). Plasma albumin levels in our patients were sometimes low, ranging from 1.7 to 3.4 g/dl. However, because the protein binding of cefepime is less than 20% (3), it is unlikely to explain the observed increase in V_{SS}.

The $\%T >$ MIC for β-lactams has been associated with outcome in both animal infection models (13) and humans (31). Using a neutropenic-mouse thigh infection model, researchers have previously demonstrated, with cephalosporins against gram-negative organisms, that maintaining drug concentrations above the MIC for 60 to 70% of the dosing interval may be necessary to maximize bactericidal activity (13). Therefore, it is reasonable to design cephalosporin dosing regimens for humans based on this pharmacodynamic parameter. According to our pharmacokinetic simulations with MICs ≤8 μg/ml, a $\%T >$ MIC of at least 60% was accomplished with all assessed dosing regimens except 1 g q12h. It should also be noted that the 1-g-q8h regimen produced a %T > MIC similar to that produced by the 2-g-q12h regimen and represents a reduction in the total daily dose.

In conclusion, the CL_T and V_{SS} of cefepime were increased in our study population compared to those for healthy volunteers. The CL_T may be explained by an increase in the glomerular filtration rate, whereas V_{SS} is associated with the burn severity. Nonetheless, it appears that the dose does not need to be adjusted in similarly affected burn patients and that 1 g q8h and 2 g q12h provide similar %T > MIC, while the 1-g-q8h regimen allows a reduction in the daily dose.

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