ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 1991, p. 57–61
0066-4804/91/010057-05$02.00/0

Vol. 35, No. 1

Aztreonam Pharmacokinetics in Burn Patients

LAWRENCE V. FRIEDRICH,[1] ROGER L. WHITE,[1]* MICHAEL B. KAYS,[1]
DIANNE M. BRUNDAGE,[1] AND DABNEY YARBROUGH III[2]

College of Pharmacy[1] and Department of Surgery,[2] Medical University of South Carolina, 171 Ashley Avenue, Charleston, South Carolina 29425-0810

Received 30 May 1990/Accepted 2 November 1990

The pharmacokinetics of aztreonam in eight adult patients with severe burn injuries (total body surface area burn, 49% ± 21% [mean ± standard deviation]) were studied. The time of initiation of study following burn injury was 7.0 ± 1.4 days. Four patients at first dose and at steady state were studied. Aztreonam concentrations were measured by high-performance liquid chromatography, and a two-compartment model was used to fit the data. No significant differences in any pharmacokinetic parameters between first dose and steady state were observed. Volume of distribution of the central compartment after first dose (0.14 liters/kg) and volume of distribution at steady state (0.31 liters/kg) were approximately 30% higher than those reported for other patient populations. Total drug clearance and renal drug clearance when normalized to creatinine clearance (CL_{CR}) were similar to those previously reported for other critically ill patients. CL_{CR} was strongly correlated with renal drug clearance ($r = 0.94$) and total drug clearance ($r = 0.95$). The extent and degree of burn (percent second or third degree burn) were poorly correlated with all pharmacokinetic parameters with the exception of the volume of distribution at steady state, which was correlated with both total body surface area burn ($r = 0.95$) and percent second degree burn ($r = 0.83$). Aztreonam pharmacokinetics are altered as a result of thermal injury; however, CL_{CR} can be used to assess the clearance of aztreonam in burn patients.

Thermal burn injury and its subsequent treatment result in complex pathophysiologic changes in burned patients. Alterations in renal (16), cardiovascular (12), and hepatic (6, 12) function and plasma protein concentrations (17) may significantly alter the pharmacokinetics of antibiotics administered to these patients. Previous reports have been limited primarily to the aminoglycosides (16, 25–28) and vancomycin (1, 4, 10, 20). Clearance of these antibiotics, which are eliminated primarily via glomerular filtration, has been shown to be increased in these patients. Thus, more frequent and/or higher doses are usually recommended to maintain therapeutic concentrations. In contrast, there is a dearth of reported information regarding β-lactam antibiotics. Only reports on ceftazidime (24) and imipenem (3) are available.

Aztreonam, which is renally eliminated, possesses a spectrum of activity similar to that of aminoglycosides, with activity against gram-negative organisms including *Pseudomonas aeruginosa* (5, 13, 14). However, it lacks the toxicity often associated with aminoglycosides and does not require serum concentration monitoring. Thus, aztreonam is a reasonable alternative to aminoglycosides for the therapy of infections due to susceptible organisms.

Since there is documented evidence of changes in the pharmacokinetic parameters of other renally eliminated drugs in burn patients and no information is available for aztreonam, we evaluated the effect of thermal burn injury on aztreonam pharmacokinetics.

MATERIALS AND METHODS

Patients. Patients, aged 18 to 75 years, admitted to the Medical University Hospital Burn Unit with a total body surface area burn (TBSAB) (7) of greater than 20% (excluding first degree burns) and with suspected or documented gram-negative infection were eligible for study participation. Patients with a history of cystic fibrosis, allergy to aztreonam, history or evidence of alcoholic cirrhosis of the liver, or electrical burn injury or undergoing any type of dialysis were excluded from study. The study was approved by the Institutional Review Board of the hospital, and informed, written consent was obtained from all patients prior to the study.

Drug administration and sample collection. Two grams of aztreonam (lot no. 7K91598 [expiration date, 1 October 1989] and 8B01829 [expiration date, 1 February 1990]; E. R. Squibb & Sons, Princeton, N.J.) was diluted in 10 ml of sterile water for injection (Travenol, Deerfield, Ill.) and administered via a slow intravenous push over 10 min. A 6-h dosing interval was used in all patients except patient no. 7, in whom a 12-h interval was used. Blood samples (7 ml) were obtained at the following times around the first dose and at steady state (10th to 15th dose): immediately prior to aztreonam administration and 10, 20, 30, 45, 60, 120, 180, 240, and 330 min after the end of the aztreonam infusion. Blood samples were collected in nonanticoagulant (red-top) VACUTAINER tubes, allowed to clot, and centrifuged, and the serum was collected. All samples were processed and stored within 2 h of collection. A preliminary study revealed that no degradation of aztreonam occurred over this time period.

A baseline urine sample was obtained immediately prior to drug administration. To quantitate aztreonam urinary excretion, urine was collected over the initial sampling period. After the total volume was measured, a 3-ml aliquot was obtained and immediately placed on ice. Urine was also collected for the 24 h immediately prior to or immediately following drug administration for creatinine clearance (CL_{CR}) measurement.

All serum and urine samples for aztreonam concentration determination were stored at −70°C until analyzed.

* Corresponding author.

Aztreonam assay. Aztreonam concentrations in serum and urine samples were assayed in duplicate by high-performance liquid chromatography by using a modification of the method described by Pilkiewicz et al. (19). Differences included a mobile phase consisting of 70% 0.0025 M tetrabutylammonium hydrogen sulfate–0.0025 M ammonium sulfate adjusted to a pH of 4.2 and 30% acetonitrile, with a flow rate of 1.2 ml/min. The chromatographic system consisted of a Waters WISP 710B autoinjector, Waters 510 pump, Waters Lambda-Max model 481 LC spectrophotometer, and Shimadzu C-R3A Chromatopac integrator with a C-18 reverse phase column and precolumn.

Serum samples were allowed to thaw at room temperature, and 100 μl of acetonitrile was added to an equal volume of the sample. Urine samples were thawed at room temperature and then diluted 1:10 with the mobile phase. All samples were vortexed for 1 min and centrifuged for 5 min at 1,244 × *g*, and the resultant supernatant was used for analysis. An injection volume of 20 μl was used.

Serum standards were prepared in pooled human serum (Biological Specialty Corporation, Lansdale, Pa.). To accommodate the wide range of expected concentrations in serum, two standard curves were prepared with the following concentrations: 5, 10, 25, 50, and 100 μg/ml (r = 0.9999) and 50, 100, 200, and 300 μg/ml (r = 0.9999). Absorbance units, full scale, were set at 0.02 and 0.10, respectively. Urine standards were prepared in the mobile phase at concentrations of 50, 100, 200, 300, 400, and 500 μg/ml (r = 0.9999), with an absorbance unit, full scale, of 0.20. All standard curves were prepared with laboratory grade standard powder (lot 05314-13733-600; Squibb). The intraday and interday coefficients of variation for the serum standard curves were <7 and ≤11%, respectively, for all concentrations. All urine samples were assayed within the same day, with an intraday coefficient of variation of ≤1% at all concentrations.

Pharmacokinetic analysis. The RSTRIP computer program (9) was used to obtain initial pharmacokinetic parameter estimates, and weighted least squares regression was used to fit the data (8). All datum points were weighted by the inverse of the assay variance. 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. Computer-fitted estimates of elimination rate constants k_{10}, k_{12}, and k_{21} (k_{10}, from central compartment; k_{12}, from central to peripheral compartment; k_{21}, from peripheral to central compartment) and V_1 (volume of distribution of the central compartment) were used to calculate the following parameters with standard pharmacokinetic equations: disposition rate constants α and β, distribution and elimination half-lives ($t_{1/2\alpha}$ and $t_{1/2\beta}$, respectively), zero time intercepts for the α phase and β phase, and steady-state volume of distribution (V_{ss}) (11). The area under the serum concentration-time curve (AUC) was calculated by using the linear trapezoidal rule. The AUC for the first dose was extrapolated to infinity as follows: $AUC_{0-\infty} = AUC_{0-\tau} + C_{last}/\beta$, where $AUC_{0-\tau}$ is the AUC for the sampling period, C_{last} is the last measured concentration, and β is the terminal elimination rate constant. The AUC at steady state (AUC_{ss}) was calculated over the dosing interval. The concentration at the end of the dosing interval was simulated from the fitted data for each patient and used in the AUC_{ss} calculation. Concentrations in serum immediately following the end of the infusion were simulated for each patient by using their respective fitted data and were used in both the $AUC_{0-\infty}$ and AUC_{ss} calculations. Aztreonam total clearance (CL_T), renal clearance (CL_R), and nonrenal clearance (CL_{NR}) for the first dose were calculated as follows: $CL_T = dose_{iv}/AUC_{0-\infty}$ (where $dose_{iv}$ is the intravenous dose), CL_R = amount of aztreonam recovered in the urine during the initial sampling period/$AUC_{0-\tau}$, and $CL_{NR} = CL_T - CL_R$. Aztreonam clearance at steady state (CL_{Tss}) was calculated as $CL_{Tss} = dose_{iv}/AUC_{ss}$. The percent aztreonam excreted in urine was calculated as (the amount of aztreonam recovered in the urine/$dose_{iv}$) × 100.

TABLE 1. Patient demographic characteristics

Patient	Age (yr)	Wt (kg)	% Burn injury[a]			Days post-burn[b]
			TBSAB	2°	3°	
1	56	85	22	20	2	5
2	37	98	35	25	10	7
3	45	68	25	21	4	6
4	34	91	75	10	65	7
5	62	80	60	0	60	9
6	27	84	62	52	10	6
7	74	70	41	9	32	9
8	36	84	74	15	59	7
Mean (SD)	46 (16)	83 (10)	49 (21)	19 (16)	30 (27)	7 (1.4)

[a] Percent TBSAB was determined by using the Lund and Browder chart (7). 2°, Second degree burn; 3°, third degree burn.
[b] Days post-burn injury at the time of first dose.

Statistical analysis. A two-tailed, paired Student's t test was used to determine the statistical significance between pharmacokinetic parameters in those patients studied after the first dose and at steady state. Linear regression, by using the method of least squares, was used to assess relationships between variables of interest, with statistical significance determined by using the F test. A P value of <0.05 was considered to be statistically significant.

RESULTS

Nine patients (eight male and one female) were studied. One patient experienced a hypotensive episode immediately prior to the initial dose. The episode, which lasted approximately 2 h, required the use of pressor agents. Thus, this patient was omitted from any further analysis and the reported results are for the remaining eight patients (seven male and one female). The mean (standard deviation) dose administered to all patients was 24.7 (3.2) mg/kg of actual body weight. Patient demographic parameters are shown in Table 1. Four patients were studied following the first dose and at steady state. Six patients were treated for pneumonia, and one each was treated for fever of unknown origin and catheter line sepsis. All patients were studied at least 3 days after fluid resuscitation was completed.

A two-compartment open model was used to fit the observed concentration-time data for all patients. The pharmacokinetic parameters for all patients studied following the first dose are shown in Table 2. The aztreonam excreted in the urine during the initial 6-h dosing interval was 45% ± 18%, mean ± standard deviation. CL_{CR} was significantly correlated with CL_R (r = 0.94, P = 0.0018) and CL_T (r = 0.95, P = 0.0012) but not with the percent aztreonam excreted in the urine (r = 0.72, P = 0.0700), although it did approach statistical significance. CL_R was significantly cor-

TABLE 2. Aztreonam pharmacokinetic parameters following first dose[a]

Patient	A (mg/liter)	B (mg/liter)	α (h^{-1})	β (h^{-1})	V_1 (liters/kg)	V_{ss} (liters/kg)	$t_{1/2\beta}$ (h)	$AUC_{0-\infty}$ (mg · h/liter)	CL_T (liters/h)	CL_R (liters/h)	CL_{CR} (ml/min)
2	108.6	43.4	3.17	0.39	0.13	0.29	1.79	148	13.5	9.7	191
3	103.5	70.3	1.24	0.29	0.17	0.25	2.42	334	6.0	4.8	117
4	134.0	61.1	1.67	0.24	0.11	0.22	2.91	339	5.9	3.3	95
5	80.4	89.9	1.76	0.15	0.15	0.24	4.55	406	4.9	2.4	44
6	111.2	43.7	1.68	0.20	0.15	0.33	3.38	284	7.1	3.4	115
7	108.9	97.4	1.99	0.08	0.14	0.27	9.05	1,336	1.5	0.8	19
8	101.2	67.6	2.40	0.21	0.14	0.28	3.35	350	5.7	2.6	79
Mean (SD)	106.8 (15.8)	67.6 (20.8)	1.99 (0.63)	0.22 (0.10)	0.14 (0.02)	0.27 (0.04)	3.92 (2.42)	457 (396)	6.4 (3.6)	3.9 (2.8)	94 (56)

[a] A and B, Zero time intercepts for the α phase (A) and β phase (B).

related with CL_T ($r = 0.96$, $P = 0.0005$). $t_{1/2\beta}$ was significantly correlated with CL_{CR} ($r = -0.82$, $P = 0.0255$) and CL_T ($r = -0.77$, $P = 0.0447$); however, it was not significantly correlated with CL_R ($r = -0.70$, $P = 0.0776$). The TBSAB and percent third degree burn were poorly correlated with all pharmacokinetic parameters. The percent second degree burn was significantly correlated with V_{ss} ($r = 0.83$, $P = 0.0201$), but not with any other pharmacokinetic parameters.

Pharmacokinetic parameters at steady state are presented in Table 3. No statistically significant differences between any pharmacokinetic parameters in those patients studied after the first dose and at steady state were noted. CL_{Tss} was significantly correlated with CL_{CR} ($r = 0.95$, $P = 0.0143$) and $t_{1/2\beta}$ ($r = -0.92$, $P = 0.0294$). CL_{CR} was significantly correlated with $t_{1/2\beta}$ ($r = -0.89$, $P = 0.0435$). The percent second and third degree burn was not correlated with any pharmacokinetic parameters; however, the TBSAB was significantly correlated with V_{ss} ($r = 0.95$, $P = 0.0149$) but not with V_1 ($r = 0.81$, $P = 0.0981$).

DISCUSSION

Boucher et al. (3) reported the pharmacokinetics of imipenem in 11 burn patients. No statistically significant differences for any pharmacokinetic parameters were noted when compared with those reported for normal volunteers. Imipenem clearance was significantly related to CL_{CR} ($P < 0.0001$); however, the severity of burn injury did not correlate with any pharmacokinetic parameters. The authors concluded that imipenem pharmacokinetics in burn patients were similar to those in normal volunteers. Ceftazidime pharmacokinetics in burn patients have also been reported (24). The authors found that, compared with those of other patients, the apparent volume of distribution, CL_{NR}, and CL_T were higher, while $t_{1/2\beta}$, CL_R, and urinary recovery of ceftazidime were lower in burn patients. However, the CL_R was significantly related to CL_{CR} ($r = 0.95$). The severity of burn injury did not correlate with the apparent volume of distribution.

Similar to the results reported by Walstad et al. (24), we noted changes in the volume of distribution of aztreonam in burn patients. Both V_1 and V_{ss} were higher than previously reported in normal subjects (21–23) (V_1, 0.05 to 0.11 liters/kg; V_{ss}, 0.11 to 0.22 liters/kg) and in critically ill patients (15) (V_{ss}, 0.16 liters/kg). In contrast to the findings of Walstad et al. (24) with ceftazidime, the CL_T and CL_R of aztreonam in burn patients were similar to those previously reported in other patient populations.

Other investigators have documented alterations in volumes of distribution in critically ill patients receiving aztreonam. These changes were attributed to lower protein binding secondary to low serum albumin concentrations (2, 15, 18). Burn injury is well known to result in decreased serum albumin concentrations. Serum albumin concentrations were low in our patients (2.5 ± 0.7 and 2.1 ± 0.2 g/dl [mean ± standard deviation] at first dose and steady state, respectively), and albumin concentrations were poorly correlated with V_1 ($P = 0.5012$) and V_{ss} ($P = 0.7208$) following the first dose. At steady state, albumin and V_1 were poorly correlated ($P = 0.2831$); however, albumin was significantly correlated with V_{ss} ($r = -0.99$, $P = 0.0085$). Thus, it is possible that serum protein binding decreased, resulting in alterations in the volume of distribution, although this was not directly evaluated in this study. This effect would be expected to be more pronounced with those drugs that exhibit a higher

TABLE 3. Aztreonam pharmacokinetic parameters at steady state[a]

Patient	A (mg/liter)	B (mg/liter)	α (h^{-1})	β (h^{-1})	V_1 (liters/kg)	V_{ss} (liters/kg)	$t_{1/2\beta}$ (h)	AUC_{ss} (mg · h/liter)	CL_T (liters/h)	CL_{CR} (ml/min)
1	122.2	86.1	4.60	0.33	0.11	0.23	2.12	293	6.8	120
2	59.4	70.0	3.00	0.47	0.16	0.23	1.48	173	11.6	191
5	87.8	62.8	1.80	0.07	0.17	0.36	9.95	963	2.1	46
6	60.1	33.0	0.87	0.17	0.26	0.42	4.04	263	7.6	80
7	101.9	89.7	1.71	0.05	0.15	0.30	14.87	1,986	1.0	12
Mean (SD)	86.3 (27.1)	68.3 (22.7)	2.40 (1.45)	0.22 (0.18)	0.17 (0.06)	0.31 (0.08)	6.49 (5.75)	736 (767)	5.8 (4.3)	90 (69)

[a] A and B, Zero time intercepts for the α phase (A) and β phase (B).

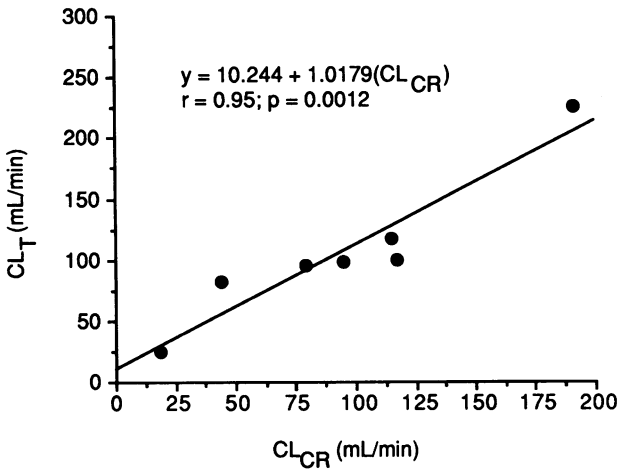

FIG. 1. Relationship between CL_{CR} and aztreonam CL_T following first dose.

degree of protein binding than aztreonam, which is approximately 60% protein bound.

As expected with a drug that is primarily eliminated via glomerular filtration, a statistically significant linear correlation was demonstrated between the CL_{CR} and CL_T of aztreonam (Fig. 1). This relationship is similar to that reported in other critically ill patients receiving aztreonam with a similar range of CL_{CR} (15, 18). The CL_T and CL_R in our patients were higher than previously reported. However, when normalized to individual patients' CL_{CR}, CL_T/CL_{CR} (1.11) and CL_R/CL_{CR} (0.68) ratios are similar to those reported for nonburned patient populations. Therefore, it appears that any differences in clearance were likely due to higher CL_{CR}s in our patients. Although drug loss across the burn wound may have contributed to the CL_T observed, this was not measured in our study.

Interestingly, we noted statistically significant relationships between the extent of burn injury (TBSAB) as well as percent second degree burn and the volume of distribution. This is in contrast to previous investigations with other β-lactams.

Aztreonam disposition in burn patients is altered as a result of thermal injury, with the major effect being an increase in the volume of distribution. Moreover, aztreonam clearance (CL_T, CL_R) did not appear to be affected and remained strongly associated with the CL_{CR}. On the basis of these results, larger doses of aztreonam may be necessary in this patient population; however, more frequent dosing intervals may not be warranted. Further work is necessary to better delineate the pharmacokinetic changes that occur and their possible effects on dosing regimens in this patient population.

ACKNOWLEDGMENTS

This work was supported in part through a grant from E. R. Squibb & Sons.

We acknowledge Marjorie Robinson for her expertise and assistance in the high-performance liquid chromatography analysis of the samples. In addition, we are indebted to the entire Burn Unit staff, without whom this project would not have been possible.

REFERENCES

1. **Bailie, G. R., B. H. Ackerman, J. Fischer, L. D. Solem, and J. C. Rotschafer.** 1984. Increased vancomycin dosage requirements in young burn patients. J. Burn Care Rehab. **5**:376–378.
2. **Boccazzi, A., M. Langer, M. Mandelli, and A. M. Ranzi.** 1989. The pharmacokinetics of aztreonam and penetration into bronchial secretions of critically ill patients. J. Antimicrob. Chemother. **23**:401–407.
3. **Boucher, B. A., W. L. Hickerson, D. A. Kuhl, A. M. Bombassaro, and G. S. Jaresko.** 1990. Imipenem pharmacokinetics in patients with burns. Clin. Pharmacol. Ther. **48**:130–137.
4. **Brater, D. C., R. E. Bawdon, S. A. Anderson, G. F. Purdue, and J. L. Hunt.** 1986. Vancomycin elimination in patients with burn injury. Clin. Pharmacol. Ther. **39**:631–634.
5. **Brogden, R. N., and R. C. Heel.** 1986. Aztreonam: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. Drugs **31**:91–130.
6. **Ciaccio, E. I., and R. J. Fruncillo.** 1979. Urinary excretion of D-glucaric acid by severely burned patients. Clin. Pharmacol. Ther. **25**:340–344.
7. **Curreri, P. W., and A. Luterman.** 1989. Burns, p. 285–305. *In* S. I. Schwartz, G. T. Shires, and F. C. Spencer (ed.), Principles of surgery, 5th ed. McGraw-Hill Book Co., New York.
8. **D'Argenio, D. Z., and A. Schumitzky.** 1979. A program package for simulation and parameter estimation in pharmacokinetic systems. Comput. Programs Biomed. **9**:115–134.
9. **Fox, J. L., and M. L. Lamson.** 1987. RSTRIP user handbook, version 3.0. Micromath Inc., Salt Lake City, Utah.
10. **Garrelts, J. C., and J. D. Peterie.** 1988. Altered vancomycin dose vs. serum concentration relationship in burn patients. Clin. Pharmacol. Ther. **44**:9–13.
11. **Gibaldi, M., and D. Perrier.** 1982. Pharmacokinetics. Marcel Dekker, Inc., New York.
12. **Gump, F. E., J. B. Price, and J. M. Kinney.** 1970. Blood flow and oxygen consumption in patients with severe burns. Surg. Gynecol. Obstet. **130**:23–28.
13. **Hopefl, A. W.** 1985. Aztreonam—an overview. Drug Intell. Clin. Pharm. **19**:171–175.
14. **Jacobus, N. V., M. C. Ferreira, and M. Barza.** 1982. In vitro activity of azthreonam, a monobactam antibiotic. Antimicrob. Agents Chemother. **22**:832–838.
15. **Janicke, D. M., R. F. Cafarell, S. W. Parker, M. A. Apicella, and W. J. Jusko.** 1985. Pharmacokinetics of aztreonam in patients with gram-negative infections. Antimicrob. Agents Chemother. **27**:16–20.
16. **Loirat, P., J. Rohan, A. Baillet, F. Beaufils, R. David, and A. Chapman.** 1978. Increased glomerular filtration rate in patients with major burns and its effect on the pharmacokinetics of tobramycin. N. Engl. J. Med. **299**:915–919.
17. **Martyn, J. J., D. R. Abernethy, and D. J. Greenblatt.** 1984. Plasma protein binding of drugs after severe burn injury. Clin. Pharmacol. Ther. **35**:535–539.
18. **Mattie, H., and A. Matze-van der Lans.** 1986. Pharmacokinetics of aztreonam in infected patients. J. Antimicrob. Chemother. **17**:215–217.
19. **Pilkiewicz, F. G., B. J. Remsburg, S. M. Fisher, and R. B. Sykes.** 1983. High-pressure liquid chromatographic analysis of aztreonam in sera and urine. Antimicrob. Agents Chemother. **23**:852–856.
20. **Rybak, M. J., L. M. Albrecht, J. R. Berman, L. H. Warbasse, and C. K. Svensson.** 1990. Vancomycin pharmacokinetics in burn patients and intravenous drug abusers. Antimicrob. Agents Chemother. **34**:792–795.
21. **Scully, B. E., E. A. Swabb, and H. C. Neu.** 1983. Pharmacology of aztreonam after intravenous infusion. Antimicrob. Agents Chemother. **24**:18–22.
22. **Swabb, E. A., S. M. Singhvi, M. A. Leitz, M. Frantz, and A. A. Sugerman.** 1983. Metabolism and pharmacokinetics of aztreonam in healthy subjects. Antimicrob. Agents Chemother. **24**: 394–400.
23. **Swabb, E. A., A. A. Sugerman, and D. N. McKinstry.** 1983. Multiple-dose pharmacokinetics of the monobactam azthreonam (SQ 26,776) in healthy subjects. Antimicrob. Agents Chemother. **23**:125–132.
24. **Walstad, R. A., L. Aanderud, and E. Thurmann-Nielsen.** 1988. Pharmacokinetics and tissue concentrations of ceftazidime in burn patients. Eur. J. Clin. Pharmacol. **35**:543–549.

25. **Zaske, D. E., J. L. Bootman, L. D. Solem, and R. G. Strate.** 1982. Increased burn patient survival with individualized dosages of gentamicin. Surgery **91**:142–149.
26. **Zaske, D. E., R. J. Cipolle, L. D. Solem, and R. G. Strate.** 1978. Rapid individualization of gentamicin dosage regimens in 66 burn patients. Burns **7**:215–220.
27. **Zaske, D. E., R. J. Sawchuk, D. N. Gerding, and R. G. Strate.** 1976. Increased dosage requirements of gentamicin in burn patients. J. Trauma **16**:824–828.
28. **Zaske, D. E., R. J. Sawchuk, and R. G. Strate.** 1978. The necessity of increased doses of amikacin in burn patients. Surgery **84**:603–608.