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Altered Pharmacokinetics of Ceftazidime in Critically Ill Patients

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Many critically ill patients have increased extracellular fluid which might affect ceftazidime pharmacokinetics. We investigated the pharmacokinetics of ceftazidime in 15 adult intensive care patients receiving 2 g of ceftazidime intravenously three times a day. The ceftazidime mean (standard deviation) apparent volume of distribution and terminal-phase half-life were 56.91 (25.93) liters and 4.75 (1.85) h, respectively, significantly greater than values reported previously for healthy controls ($P < 0.001$). The mean ceftazidime clearance and area under the curve at steady state were not significantly different from those previously reported for controls. We conclude that ceftazidime pharmacokinetics in critically ill patients were altered by an increased volume of drug distribution and elevated elimination half-life.

Ceftazidime is a β-lactam antibiotic used in the treatment of serious gram-negative infections (20, 22, 26). It interferes with the transpeptidation enzymes that facilitate peptide cross-linking in peptidoglycan, thereby inhibiting cell wall synthesis (21, 24). The effect of ceftazidime is predominantly time dependent in that it requires continuous antibiotic presence above the MIC to achieve bacterial cell killing (9, 23). Its effect is independent of high peak levels (6), and there is no clinically significant postantibiotic effect (2, 7, 8, 13). In healthy individuals, ceftazidime is eliminated predominantly by glomerular filtration, with about 90% of the dose being excreted in the urine within 24 h of administration (14, 27). In patients with impaired renal function, the terminal-phase elimination half-life ($t_{1/2\beta}$) increases significantly (18).

Some critically ill patients receiving ceftazidime show poor clinical responses despite the in vitro sensitivity of the organism. Critically ill patients, particularly those with severe sepsis, often have reduced effective circulating volume, in part due to generalized increased capillary permeability (4, 11). Administration of fluids necessary to replete the intravascular compartment leads inevitably to some fluid extravasation, manifested clinically as peripheral edema. Therefore, by the nature of their illness, edema is a common problem in patients with sepsis.

We postulated that the edema often seen in critical illness has an effect on ceftazidime pharmacokinetics. We therefore conducted a prospective observational study to determine the pharmacokinetics of ceftazidime in intensive care patients without clinically overt deterioration of renal function but with considerable increases in extracellular fluid. We aimed to study the relationship, if any, between raised extracellular fluid and ceftazidime pharmacokinetics.

The study was approved by the Riverside Research Ethics Committee and took place in the Intensive Care Unit at Charing Cross Hospital, London, United Kingdom. All patients or the nearest relative gave written consent or assent, respectively. Fifteen adults (Table 1) with normal concentrations of creatinine in plasma received 2 g of ceftazidime (GlaxoWellcome, Stockley Park West, Middlesex, United Kingdom) in 20 ml of distilled water over 2 min intravenously (i.v.) every 8 h as part of a clinically indicated antibacterial regimen. Exclusion criteria were age less than 18 years, pregnancy, or lactation. Severity of illness was assessed by the acute physiology and chronic health evaluation (APACHE II) score (17) on the day of ceftazidime sampling. Blood was taken for drug assay immediately before and 5 min, 30 min, and 1, 2, 4, 6, and 8 h after drug administration. Patient sampling was undertaken after at least 24 h of treatment, and the data corresponded to conditions at steady state, except the data for patient 4, who was administered a single dose. Blood was collected from indwelling arterial cannulae into plain tubes and allowed to clot for 20 min. All patients had urinary catheters; urine was collected during the entire 8-h dosing interval for determination of creatinine and ceftazidime concentrations. Blood and urine samples were centrifuged at 4,000 rpm for 10 min, and the supernatants were stored at −20°C.

Ceftazidime concentration was measured by high-pressure liquid chromatography and UV spectrophotometry at 257 nm, as previously described (1). The assay was calibrated with standards between 10 and 200 μg/ml (correlation coefficient, 0.999). Results below the low standard were considered not detectable. When necessary, urine samples were diluted 1 in 10 in drug-free urine. The interday coefficients of variation for the 10-, 25-, and 50-μg/ml standards were 6.3, 5.0, and 9.2%, respectively. The intraday coefficients of variation for the same standards were 2.0, 2.6, and 6.1%, respectively. Levels of creatinine in plasma and urine were assayed by the Jaffe method (automated analyzer, BM/Hitachi 747; Boehringer Mannheim GmbH, Mannheim, Germany). For each patient the following pharmacokinetic parameters were computed by standard noncompartmental methods (10) with Win-NONLIN computer software (Scientific Consulting Inc.). The area under the curve at steady-state (AUC_{SS}) was calculated by the trapezoidal rule up to 8 h postdose for the steady-state data and extrapolated to infinity for patient 4. The total clearance (CL) of ceftazidime was calculated as the ratio of the dose to the AUC_{SS}. The elimination-phase rate constant (k_{el}) was estimated by linear regression of concentrations in the terminal linear phase of the semilogarithmic plot of the concentration in serum versus time

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TABLE 1. Patient characteristics

Patient	Age (yr)	Sex[a]	Diagnosis	APACHE II score	Tissue edema score	Concn of creatinine in plasma (μmol/liter)	CL_{CR} (ml/min)
1	64	M	Esophagectomy	6	4	97	109.6
2	29	F	Necrotizing fascitis	7	8	65	93.6
3	65	M	Femoral popliteal bypass	13	16	68	28.9
4	64	F	Fecal peritonitis	18	17	54	36.9
5	71	F	Meningioma	22	3	72	51.1
6	72	M	Subarachnoid hemorrhage	24	16	100	47.8
7	38	M	Subarachnoid hemorrhage	12	3	112	97.3
8	57	M	Fecal peritonitis	10	13	81	59.0
9	53	M	Perioperative cardiac arrest	23	6	81	Not available
10	82	F	Sigmoid volvulus	9	16	90	36.9
11	62	F	Aspiration pneumonia	8	18	85	65.3
12	66	F	Abdominal sepsis	12	18	44	54.7
13	76	M	Subdural hemorrhage	15	15	108	67.5
14	64	F	Gastrointestinal hemorrhage	15	18	52	35.7
15	46	F	Pancreatitis	9	18	58	70.2
Mean	59.3					77.8	61.1
SD	14.6					21.1	24.9
Median				12	16		

[a] M, male; F, female.

curve. The $t_{1/2\beta}$ was calculated as the ratio of the ln2 to the k_{el}. The apparent volume of distribution (V_β) was calculated as the ratio of the CL to the k_{el}.

Tissue edema was assessed clinically by us (either C.M.H.G. or J.J.C.) at six anatomical sites (sacrum, upper back, left and right hands, and pretibial areas) and quantified by using a simple score: 0 to 3 at each site, giving a maximum score of 18. Creatinine clearance (CL_{CR}) for the 8-h dosing interval was calculated by dividing the urinary creatinine excretion rate (urine flow times urine creatinine concentration) by the plasma creatinine concentration.

Descriptive statistics were used to summarize the values obtained (Excel 7.0; Microsoft). The mean pharmacokinetic parameters obtained in this study were compared with previously reported data (means ± standard deviations [SD]) from healthy volunteers (27) by the unpaired *t* test. The association between pharmacokinetic parameters and the pathophysiological descriptors (tissue edema, plasma creatinine, and CL_{CR}) was investigated by simple- and multiple-regression analyses (Statview SE & Graphics 1.02; Abacus Concepts Inc. Berkeley, Calif.). *P* values less than 0.05 were considered statistically significant.

All patients (Table 1) received standard supportive treatment appropriate to their condition; this included mechanical ventilation, vasoactive agents, and nutritional supplementation. The mean (SD) concentration of creatinine in plasma was 77.8 ± 21.1 μmol/liter, and all patients had a concentration of creatinine in plasma within the normal range for our laboratory (60 to 120 μmol/liter). The mean 8-h CL_{CR} was 61.0 ± 24.9 ml/min/1.73 m^2.

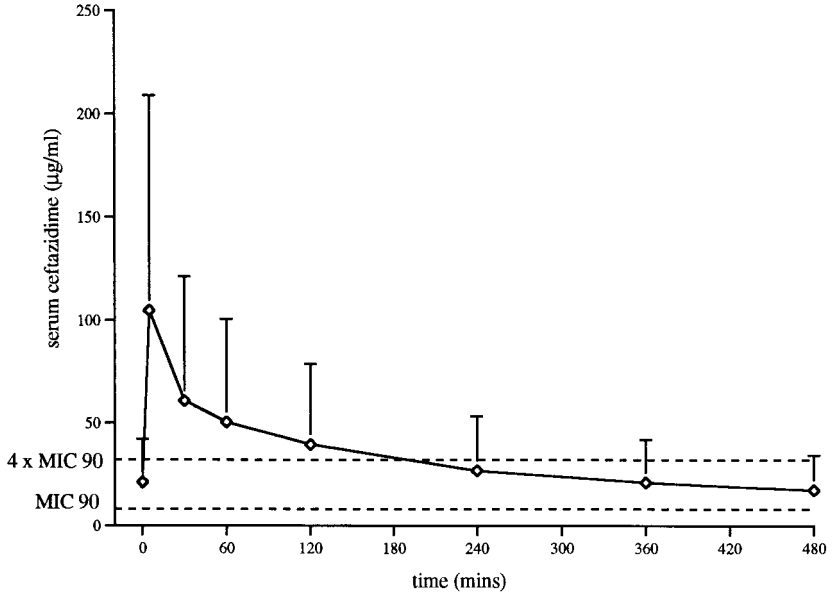

FIG. 1. Mean (SD) ceftazidime concentrations over an 8-h dosing interval (n = 15).

TABLE 2. Pharmacokinetics of ceftazidime in critically ill patients and historical controls

Subjects	Mean (SD)[a]			
	AUC (mg · h/liter)	CL (liter/h)	V_β (liters)	$t_{1/2\beta}$
Study patients	277.31 (138.98)[b]	9.06 (4.79)	56.91 (25.93)*	4.75 (1.85)*
Historical controls[d]	153.5 (23.1)[c]	6.64 (0.97)	13.6 (1.9)*	1.8 (0.14)*

[a] *, $P < 0.001$ by the unpaired t test.
[b] AUC_{SS}.
[c] AUC from 0 h to infinity after a 1-g i.v. dose.
[d] Data for controls are from reference 27.

Figure 1 shows the mean (SD) concentrations of ceftazidime in serum at each sampling interval in relation to the MIC at which 90% of the isolates are inhibited (MIC_{90}) and to four times the MIC_{90} for *Pseudomonas aeruginosa*. Table 2 shows the mean (SD) values for AUC_{SS}, CL, V_β, and $t_{1/2\beta}$. In our patients ceftazidime mean V_β and mean $t_{1/2\beta}$ were, respectively, 56.91 ± 25.93 liters and 4.75 ± 1.85 h, more than 4- and 2.5-fold greater than values for healthy controls ($P < 0.001$) (27). Mean values for ceftazidime CL and AUC_{SS} did not differ significantly between the same groups. In the study patients, $t_{1/2\beta}$ did not correlate with V_β, CL, or AUC_{SS}. Figure 2 illustrates the numbers of patients at each time interval with serum ceftazidime concentrations below the MIC_{90}s and four times the MIC_{90}s for *P. aeruginosa* and other relatively common gram-negative rods.

The median edema score was 16 (range, 0 to 18). Edema scores correlated negatively with the k_{el} ($r = 0.60$, $P = 0.02$) (Fig. 3), as well as with the CL_{CR} ($r = 0.65$, $P = 0.01$). There were no associations between tissue edema scores and any other pharmacokinetic parameters, including V_βs. Levels of creatinine, CL_{CR}s, edema scores, and k_{el}s were compared by multivariate analysis, as independent predictor variables, with

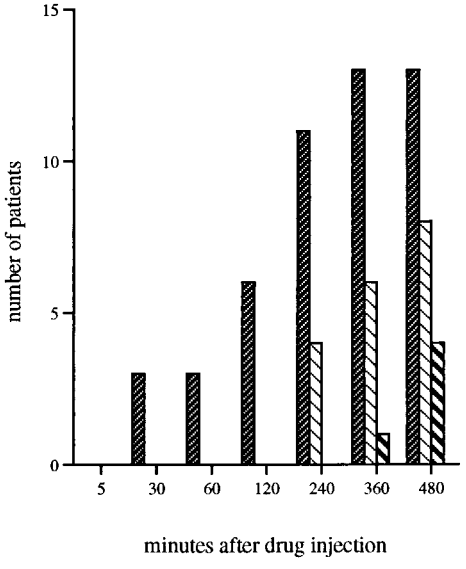

FIG. 2. Numbers of patients with serum ceftazidime concentrations below target levels. ▨, ceftazidime concentration of <32 μg/ml (which is four times the MIC_{90} for *P. aeruginosa*); ▧, ceftazidime concentrations of <16 μg/ml (which is four times the MIC_{90} for other gram-negative rods, including *E. cloacae*); ▩, ceftazidime concentrations of <8 μg/ml (which is the MIC_{90} for *P. aeruginosa*). All patients had concentrations in serum greater than 4 μg/ml (MIC_{90} for *E. cloacae*).

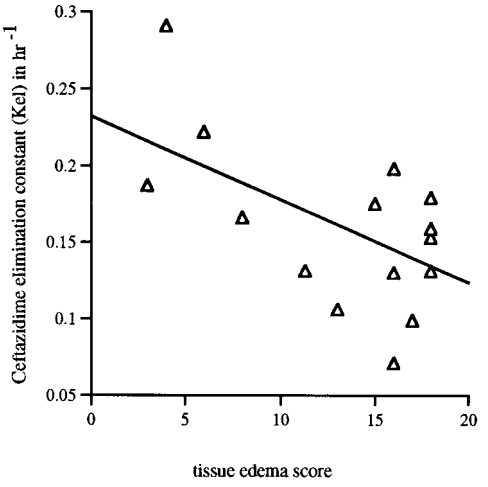

FIG. 3. Inverse correlation between the tissue edema scores and k_{el}s ($r = 0.60$, $P = 0.02$).

V_βs. None showed a statistically significant association with V_βs (all P values were >0.12). CL_{CR}s correlated with k_{el}s ($r = 0.67$, $P = 0.008$) (Fig. 4).

The main finding of our study is an important increase in the mean V_β and mean $t_{1/2\beta}$ of ceftazidime relative to those for healthy volunteers (27). As ceftazidime CL was not significantly altered in our patients, the increased V_β was the primary cause of the prolonged $t_{1/2\beta}$. This elevated extracellular volume in our patient group, in effect a large drug reservoir, appeared to influence ceftazidime concentrations differently throughout the dosing interval. Initially, it contributed to lower concentrations of the drug in serum, but in the second half of the dosing interval, the delayed elimination, and thus the increased $t_{1/2}$, increased drug concentrations relative to those in healthy volunteers (Fig. 5). This explains why the AUC_{SS} in our study group was not significantly different from that of healthy volunteers (27). Our mean $t_{1/2\beta}$ was also increased relative to those reported from previous studies of critically ill patients (3, 28). There are no previous calculations of total V_βs (12) in the critically ill, and so we were unable to compare our results with those of others for this parameter.

Values for CL_{CR} from plasma varied markedly within this

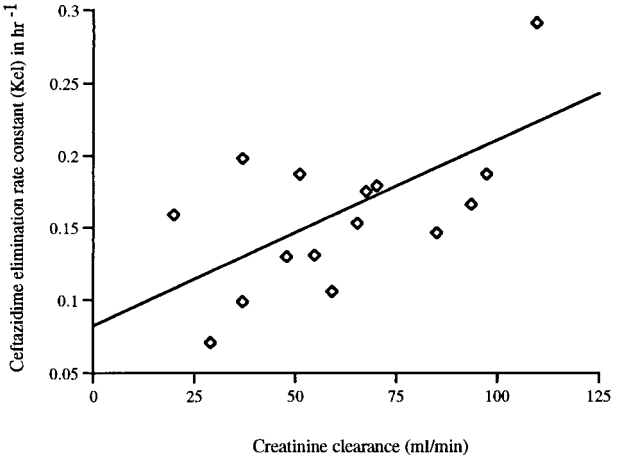

FIG. 4. Ceftazidime k_{el} versus CL_{CR} ($r = 0.67$, $P = 0.008$).

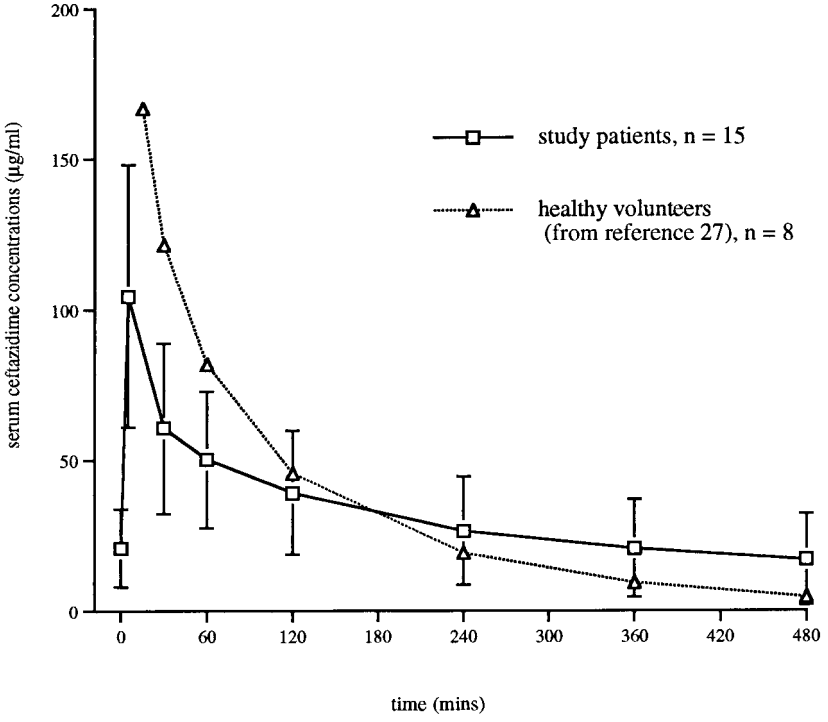

FIG. 5. Mean ceftazidime concentrations (after i.v. bolus) in study patients compared to those in healthy volunteers (27).

patient group. A level of creatinine in plasma within the normal laboratory range was a poor indicator of renal function, partly due to the dilutional effect of increased extracellular volume on plasma creatinine concentrations. In contrast to Young et al. (28), we found a correlation between CL_{CR} and k_{el} (Fig. 4) but not between the CLs of creatinine and ceftazidime.

The tissue edema score was designed to provide a simple bedside estimate of extracellular volume. Although we observed an inverse relationship between the edema score and k_{el} (Fig. 3), it was not possible with this small number of patients to associate this arbitrary edema score with the raised V_β for ceftazidime.

We also observed an inverse correlation between the edema score and CL_{CR}, although not between the V_β and CL_{CR}. The greatly increased extracellular volume might have been caused by subtle and otherwise unimportant decreases in renal function, but specific abnormalities of critical illness—such as capillary leak—seem more plausible. In particular, both a deterioration in renal function and increased extracellular water may be related to severity of illness. Finally, it is also possible that the more ill patients, with concomitantly worse renal function, required more fluid to maintain circulatory stability.

The efficacy of ceftazidime is greatest when its concentration in serum is adequate throughout the dosing interval, best expressed as time above the MIC (5, 8, 16). The exact concentration in serum necessary for an effective bactericidal action varies with the individual pathogen strain, site of infection, and host response. Many organisms responsible for hospital-acquired infections display various susceptibilities to ceftazidime (15). This is reflected in a wide range and a scattered population distribution of MICs and in considerable differences between the MIC_{90}s for different organisms as well as for different strains of the same organism. Indeed many species of *P. aeruginosa*, *Enterobacter cloacae*, and *Klebsiella pneumoniae* show MICs up to 128, 64, and 32 μg/ml, respectively (25). Furthermore, maximal killing, especially for multiresistant bacteria, is highest at about four to five times the MIC (6, 19), an arbitrary point which is considered to separate susceptible from resistant bacteria (1a, 19). For these reasons we report our results relative to usual MIC_{90}s and to four times the MIC_{90}s (Fig. 1 and 2).

In summary, this study is the first to show that the pharmacokinetics of ceftazidime in critically ill edematous patients may be altered, specifically by an increased V_β.

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REFERENCES

1. **Ayrton, J.** 1981. Assay of ceftazidime in biological fluids using high pressure liquid chromatography. J. Antimicrob. Chemother. **8**(Suppl. B)**:**227–231.
1a. **Archer, G. L., and R. E. Polk.** 1994. Treatment and prophylaxis of bacterial infections. *In* K. J. Isselbacher, E. Braunwald, J. D. Wilson, J. B. Martin, A. S. Fauci, and D. L. Kasper (ed.), Harrison's principles of internal medicine. McGraw Hill Inc, New York, N.Y.
2. **Bakker Woudenberg, I. A., and R. Roosendaal.** 1990. Impact of dosage schedule of antibiotics on the treatment of serious infections. Intensive Care Med. **16:**S229–S234.
3. **Benko, A. S., D. M. Cappelletty, J. A. Kruse, and M. J. Rybak.** 1996. Continuous infusion versus intermittent administration of ceftazidime in critically ill patients with suspected gram-negative infections. Antimicrob. Agents Chemother. **40:**691–695.
4. **Bone, R. C.** 1991. The pathogenesis of sepsis. Ann. Intern. Med. **115:**457–469.
5. **Craig, W. A.** 1998. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin. Infect. Dis. **26:**1–12.
6. **Craig, W. A., and S. C. Ebert.** 1992. Continuous infusion of beta-lactam antibiotics. Antimicrob. Agents Chemother. **36:**2577–2583.

7. **Craig, W. A., and S. Gudmundsson.** 1996. Postantibiotic effect, p. 314–316. *In* V. Lorian (ed.), Antibiotics in laboratory medicine, 4th ed. Williams & Wilkins Co., Baltimore, Md.
8. **Drusano, G. L.** 1988. Role of pharmacokinetics in the outcome of infections. Antimicrob. Agents Chemother. **32:**289–297.
9. **Fantin, B., R. Farinotti, A. Thabaut, and C. Carbon.** 1994. Conditions for the emergence of resistance to cefpirome and ceftazidime in experimental endocarditis due to Pseudomonas aeruginosa. J. Antimicrob. Chemother. **33:** 563–569.
10. **Gibaldi, M., and D. Perrier.** 1989. Pharmacokinetics. Marcel Dekker, New York, N.Y.
11. **Glauser, M. P., G. Zanetti, J. D. Baumgartner, and J. Cohen.** 1991. Septic shock: pathogenesis. Lancet **338:**732–735.
12. **Greenblatt, D. J., and J. Koch-Weser.** 1975. Clinical pharmacokinetics. N. Engl. J. Med. **293:**702–705.
13. **Hanberger, H., L. E. Nilsson, M. Nilsson, and R. Maller.** 1991. Post-antibiotic effect (PAE) of beta-lactam antibiotics on gram-negative bacteria in relation to morphology, initial killing and MIC. Eur. J. Clin. Microbiol. Infect. Dis. **10:**927–934.
14. **Harding, S. M., J. Ayrton, J. E. Thornton, A. J. Munroe, and M. I. J. Hogg.** 1981. Pharmacokinetics of ceftazidime in normal subjects. J. Antimicrob. Chemother. **8**(Suppl. B)**:**261–262.
15. **Harding, S. M., and P. B. Harper.** 1983. The pharmacokinetic behaviour of ceftazidime in man and the relationship between serum levels and the in vitro susceptibility of clinical isolates. Infection **11:**S49–S53.
16. **Hatano, K., Y. Wakai, Y. Watanabe, and Y. Mine.** 1994. Simulation of human plasma levels of beta-lactams in mice by multiple dosing and the relationship between the therapeutic efficacy and pharmacodynamic parameters. Chemotherapy **40:**1–7.
17. **Knaus, W. A., E. A. Draper, D. P. Wagner, and J. E. Zimmerman.** 1985. APACHE II: a severity of disease classification system. Crit. Care Med. **13:**818–829.
18. **Leroy, A., F. Leguy, F. Borsa, G. R. Spencer, J. P. Fillastre, and G. Humbert.** 1984. Pharmacokinetics of ceftazidime in normal and uremic subjects. Antimicrob. Agents Chemother. **25:**638–642.
19. **Mouton, J. W., and J. G. den Hollander.** 1994. Killing of *Pseudomonas aeruginosa* during continuous and intermittent infusion of ceftazidime in an in vitro pharmacokinetic model. Antimicrob. Agents Chemother. **38:**931–936.
20. **O'Callaghan, C. H., P. Acred, P. B. Harper, D. M. Ryan, S. M. Kirby, and S. M. Harding.** 1980. GR 20263, a new broad-spectrum cephalosporin with anti-pseudomonal activity. Antimicrob. Agents Chemother. **17:**876–883.
21. **Tipper, D. J., and J. L. Strominger.** 1965. Mechanism of action of penicillin: a proposal based on their structural similarity to acyl-D-alanyl-D-alanine. Proc. Natl. Acad. Sci. USA **54:**1133–1141.
22. **Verbist, L., and J. Verhaegen.** 1980. GR-20263: a new aminothiazolyl cephalosporin with high activity against *Pseudomonas* and *Enterobacteriaceae*. Antimicrob. Agents Chemother. **17:**807–812.
23. **Vogelman, B., S. Gudmundsson, J. Leggett, J. Turnidge, S. Ebert, and W. A. Craig.** 1988. Correlation of antimicrobial pharmacokinetic parameters with therapeutic efficacy in an animal model. J. Infect. Dis. **158:**831–847.
24. **Waxman, D. J., and J. L. Strominger.** 1983. Penicillin-binding proteins and the mechanism of action of beta-lactam antibiotics. Annu. Rev. Biochem. **52:**825–869.
25. **Wiedemann, B., and H. Grimm.** 1996. Susceptibility to antibiotics: species incidence and trends. *In* V. Lorian (ed.), Antibiotics in laboratory medicine. Williams & Wilkins, Baltimore, Md.
26. **Wise, R., J. M. Andrews, and K. A. Bedford.** 1980. Comparison of in vitro activity of GR 20263, a novel cephalosporin derivative, with activities of other beta-lactam compounds. Antimicrob. Agents Chemother. **17:**884–889.
27. **Wise, R., G. C. Armstrong, R. M. Brown, and J. M. Andrews.** 1981. The pharmacokinetics and tissue penetration of ceftazidime and cefmandole in healthy volunteers. J. Antimicrob. Chemother. **8**(Suppl. B)**:**277–282.
28. **Young, R. J., J. Lipman, T. Gin, C. D. Gomersall, G. M. Joynt, and T. E. Oh.** 1997. Intermittent bolus dosing of ceftazidime in critically ill patients. J. Antimicrob. Chemother. **40:**269–273.