ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 1990, p. 2307–2311
0066-4804/90/122307-05$02.00/0

Vol. 34, No. 12

Pharmacokinetics of Ceftazidime in Serum and Suction Blister Fluid during Continuous and Intermittent Infusions in Healthy Volunteers

JOHAN W. MOUTON,[1]* ALPHONSUS M. HORREVORTS,[1] PAUL G. H. MULDER,[2] EROLL P. PRENS,[3] AND MARC F. MICHEL[1]

Departments of Clinical Microbiology and Antimicrobial Therapy,[1] Statistics,[2] and Dermatology,[3] University Hospital Rotterdam, Erasmus University, 3015 GD Rotterdam, The Netherlands

Received 17 April 1990/Accepted 9 October 1990

The pharmacokinetics of ceftazidime were investigated during intermittent (II) and continuous (CI) infusion in eight healthy male volunteers in a crossover fashion. The total daily dose was 75 mg/kg of body weight per 24 h in both regimens, given in three doses of 25 mg/kg/8 h (II) or 60 mg/kg/24 h with 15 mg/kg as a loading dose (CI). After the third dose (II) and during CI, serum and blister fluid samples were taken. Seven new blisters were raised for each timed sample by a suction blister technique. Blisters took 90 min to form. Samples were then taken from four blisters (A samples) and 1 h later were taken from the remaining three (B samples). The concentration of ceftazidime was determined using a high-performance liquid chromatography method. After II, the concentrations in serum immediately after infusion (t = 30 min) and 8 h after the start of the infusion were 137.9 (standard deviation [SD], 27.5) and 4.0 (SD, 0.7) μg/ml, respectively. The half-life at α phase ($t_{1/2\alpha}$) was 9.6 min (SD, 4.6), $t_{1/2\beta}$ was 94.8 min (SD, 5.4), area under the concentration-time curve (AUC) was 285.4 μg · h/ml (SD, 22.7), total body clearance was 0.115 liter/h · kg (SD, 0.022), and volume of distribution at steady state was 0.178 liter/kg (SD, 0.023). The blister fluid (A) samples showed a decline in concentration parallel to that of the concentrations in serum during the elimination phase with a ratio of 1:1. The $t_{1/2}$ of the A samples was 96.4 min (SD, 3.2). The concentration of ceftazidime in the B blister fluid samples was significantly higher (27%) than in the A samples over time. This shows that blisters may behave as a separate compartment and establishes the need to raise new blisters for each timed sample. The mean AUC/h during continuous infusion was 21.3 μg · h/ml (SD, 3.0). The total body clearance was 0.113 liter/h · kg (SD, 0.018), the urinary clearance was 0.105 liter/h · kg (SD, 0.012), and the ceftazidime/creatinine clearance ratio was 0.885. The mean AUC of blister fluid per hour was 84.5% (18.0 μg · h/liter; SD, 3.6) compared with that of serum. The A samples did not differ significantly from the B samples. The implications of continuous infusion of beta-lactams for treatment of serious infections are discussed.

Time-kill studies of beta-lactam antibiotics on aerobic gram-negative rods show a bactericidal activity which is slow, proceeds with time, and is maximal at relatively low concentrations (23). The killing is exclusively related to the time that levels in serum and tissue exceed a certain threshold, whereas higher concentrations contribute no extra effect. When levels fall below this threshold, bacterial growth is immediately resumed. This interaction of beta-lactams with gram-negative rods has consequences for the way in which these drugs should be administered. It has been shown, in experimental infections, that a continuous infusion of ceftazidime leads to better results than intermittent administration (13). This effect was most pronounced in severe infections. There are a few clinical reports that ceftazidime given as a continuous infusion may lead to a better outcome (3). Since beta-lactam antibiotics are usually given intermittently, most pharmacokinetic data are based on this form of administration (4, 9, 10, 12, 19, 24, 25, 27). To study the pharmacokinetics of ceftazidime in serum and tissue fluid during continuous infusion, the pharmacokinetics of ceftazidime in eight volunteers were investigated in a crossover fashion during intermittent and continuous administration. Suction blister fluid samples were drawn as a measure of ceftazidime concentrations in tissue fluid. In addition, we investigated whether the concentration of ceftazidime in suction blister fluid is affected by the lifetime of the blister.

* Corresponding author.

MATERIALS AND METHODS

Volunteers. Eight healthy male volunteers, aged 20 to 29 years, participated in the study. Body weights ranged from 63 to 103 kg. Before entering the study, each volunteer underwent a complete physical examination and was screened biochemically (Na, K, urea, creatinine, alanine transaminase, aspartate transaminase, alkaline phosphatase, gamma glutamyl transpeptidase, total protein, albumin, total bilirubin, and glucose) and hematologically (hemoglobin, hematocrit, packed cell volume, erythrocyte indices, leukocyte count, and platelet counts). A standard urine-screening test was performed. The study was approved by the Medical Ethical Committee of Erasmus University of Rotterdam, and informed consent was obtained from each volunteer.

Design. The pharmacokinetics of ceftazidime in each volunteer were studied during and after intermittent and continuous administration in a crossover fashion. For each volunteer, a minimum of 4 weeks was allowed to elapse between the two treatment regimens.

Drug. Ceftazidime was kindly provided by Glaxo (Nieuwegein, The Netherlands). The drug was reconstituted according to the manufacturer's instructions and further diluted to obtain the necessary concentration for each volunteer. The total volume used amounted to 50 ml per dose for intermittent administration. For continuous admin-

istration, the flow of the infusor was adjusted per individual to obtain the necessary dose per time unit.

Dosing. The total daily dose in both regimens amounted to 75 mg/kg of body weight. For intermittent administration, volunteers received 25 mg/kg every 8 h over 24 h. The infusion time was 25 min. For continuous administration, 15 mg/kg was given as a loading dose (infusion time, 25 min) and 60 mg/kg was given over 24 h with an infusor.

Blood samples. Venous blood samples for the ceftazidime assay were obtained from an indwelling needle from the arm opposite that used for the infusion of the antibiotic. From subjects receiving intermittent infusion, samples were taken prior to the third dose ($t = 0$) and at 10, 20, 30, 40, 50, and 60 min and 1.5, 2, 4, 6, and 8 h after the start of the third infusion. From subjects receiving continuous infusion, samples were taken prior to the start of the loading dose and continuous infusion ($t = 0$) and also at 10, 20, 30, 40, 50, and 60 min and 1.5, 2, 4, 8, 16, 20, and 24 h after the start of the infusions. After sampling, blood was allowed to clot on ice for 20 min and centrifuged, and the serum was stored at −70°C until assayed.

Blister fluid samples. Blisters were raised from the abdominal skin by the suction blister technique described by Kiistala and Mustakallio (8). In brief, perspex cups containing seven perforations with a diameter of 6 mm each, connected to a vacuum source, were used. The cups were placed on the skin and kept in place by applying a negative pressure of 300 mm Hg (400×10^2 Pa). Fifteen minutes after positioning of the cups, the suction pressure was lowered to −225 mm Hg (-300×10^2 Pa). This pressure was maintained until 1.5 h after placement of the cups; seven full blisters, each containing 20 to 60 μl of fluid, were formed by then. The flow of fluid into the newly formed blister occurred during the last 10 to 15 min of this 1.5-h period. Blister samples were drawn from four of the seven blisters, yielding a total sample volume of 50 to 150 μl. These samples were called the A samples. Two and a half hours after placement of the cup, samples from the remaining three blisters, the B samples, were drawn. Samples were stored at −70°C until assayed.

The cups were placed at the following times: 1.5, 2.5, 4.5, and 6.5 h after the third infusion for intermittent doses and 17.5, 18.5, 20.5, and 22.5 h after the start of the infusion for continuous doses.

Urine samples. Volunteers were encouraged to drink, and urine samples were collected whenever possible; the volume of each void was measured, and an aliquot (1 ml) was stored at −70°C until assayed to determine the urinary clearance. The urinary clearance during continuous administration was determined during the last 8 h of infusion.

Analysis. Samples were assayed by a high-performance liquid chromatography method, using an octyldecylsilane column (Chrompack, Middelburg, The Netherlands) with a 0.05 M ammonium diphosphate solution (pH 2.0) containing 11.5% (vol/vol) acetonitrile as a mobile phase. A perchloric acid solution, containing 50 μg of cefaclor per ml as an internal standard, was added to an equal volume of sample and centrifuged, and the supernatant was filtered through a membrane filter (Millipore Corp.) (type HV; 0.45 μm). The lower limit of assay sensitivity was 0.5 μg/ml. The between-sample between-day variation was less than 7%. All samples were assayed in duplicate. Control runs were performed regularly.

Protein binding. Blister fluid samples of the eight volunteers, obtained after intermittent administration, were pooled for each time point, yielding four pooled A and four pooled B blister fluid samples. The serum samples were also pooled for the last four timed samples. In one part of each pooled sample, the total ceftazidime concentration was determined as described above. In the remnant, the non-protein-bound ceftazidime concentration was determined by using the Amicon micropartition system (MPS-1 4010; Amicon, Lexington, Mass.). Protein binding is expressed as 1 minus the free ceftazidime/total ceftazidime ratio × 100%.

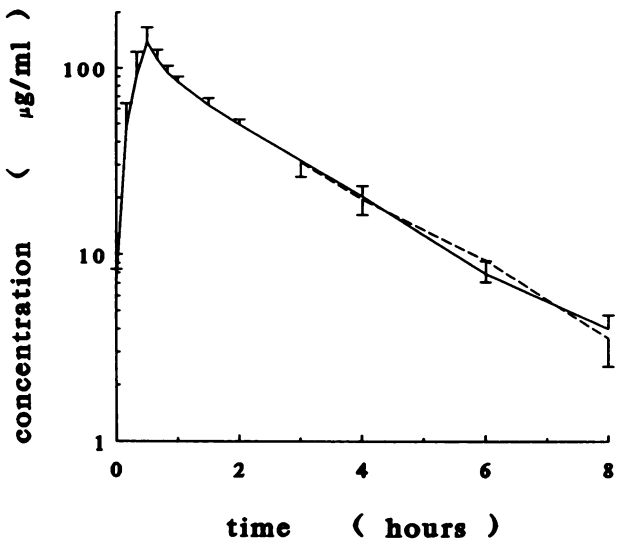

FIG. 1. Mean (± SD) ceftazidime concentrations in serum (——) and blister fluid (---) plotted versus time after intermittent dosing (25 mg/kg per dose).

Other assays. A 24-h creatinine urinary clearance assay was performed on each study day to compare with the ceftazidime urinary clearance.

Pharmacokinetic and statistical analysis. Concentrations in serum were plotted versus time in a semilogarithmic plot. Pharmacokinetic parameters were estimated by using the SAS NLIN computer program package with a two-compartment open model with a weighted least-squares adjustment (16). The equations used were those of Allen et al. (1). The Wilcoxon matched-pairs test was used to compare results between treatments (18). Repeated-measurement analysis of variance from the BMDP 5V program package (20) was used to obtain the half-lives and to test the difference between A and B blister fluid samples. The concentration in blister fluid/concentration in serum ratio of the A blister fluid samples during continuous infusion was determined from the area under the concentration-time curve (AUC) ratio during the time period at which the blister fluid concentrations were known, i.e., the last 5 h of infusion. The results are expressed as arithmetic means ± standard deviations (SD), except for the half-lives, which are expressed as harmonic means ± SD.

RESULTS

Concentrations in serum and blister fluid are plotted versus time in Fig. 1 (intermittent administration) and Fig. 2 (continuous administration). Concentrations in blister fluid declined parallel to the concentrations in serum (Fig. 1). The decline in concentration in the blisters was usually lagging slightly in time and the concentration itself was thus relatively higher at the same time point compared with concentrations in serum. The penetration in tissue of less than 100%

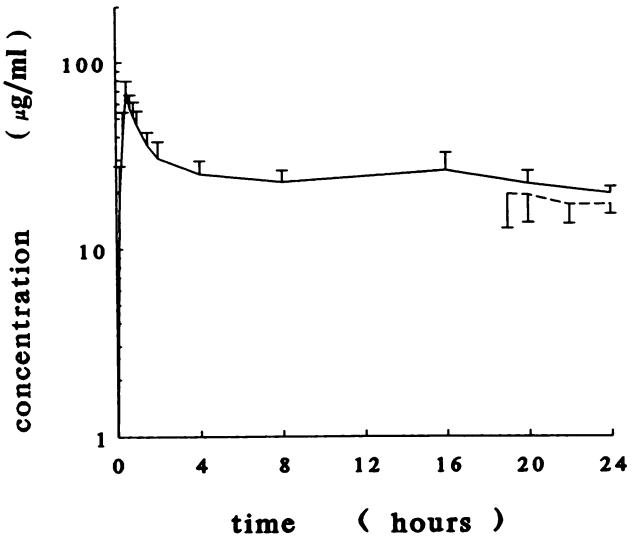

FIG. 2. Mean (± SD) ceftazidime concentrations in serum (——) and blister fluid (---) plotted versus time during continuous administration (60 mg/kg/24 h and 15 mg/kg as a loading dose).

seems to compensate the time lag almost exactly. There might also be a very short time lag due to the mere drawing of the blisters.

To determine whether ceftazidime diffuses freely between blisters and tissue, B blister samples were drawn 1 h after the original (A) samples from as-yet-intact blisters. After we tested that the time trend did not differ significantly between A and B blister samples, the concentration of ceftazidime in the B blister samples was established to be 27% higher (95% confidence interval, 24 to 31%, repeated-measurement analysis of variance) than in the A samples (Fig. 3). This may indicate that blisters behave as a separate compartment.

Since protein binding might be responsible for the differences found between serum and blister fluid ceftazidime concentrations, this binding was measured in serum and blister fluid. Protein binding in serum was found to be 18.7% ± 2.9%, and binding was 14.9% ± 4.9% and 21.0% ± 6.4% in the A and B blister fluid samples, respectively. The concentration-time curve for serum after intermittent infusion showed a biphasic decline, representing a distribution phase and an elimination phase with mean half-lives of 9.6 ± 4.6 min at α phase and 94.8 ± 5.4 min at β phase, respectively. The mean concentration in serum obtained immediately after infusion was 137.9 ± 27.5 μg/ml, and the mean concentration at the end of the dosing interval was 4.0 ± 0.7 μg/ml. The mean AUC was 285.4 ± 22.7 μg · h/ml, the total body clearance (TBC) was 0.115 ± 0.022 liter/h · kg, and the volume of distribution at steady state was 0.178 ± 0.023 liter/kg (Table 1).

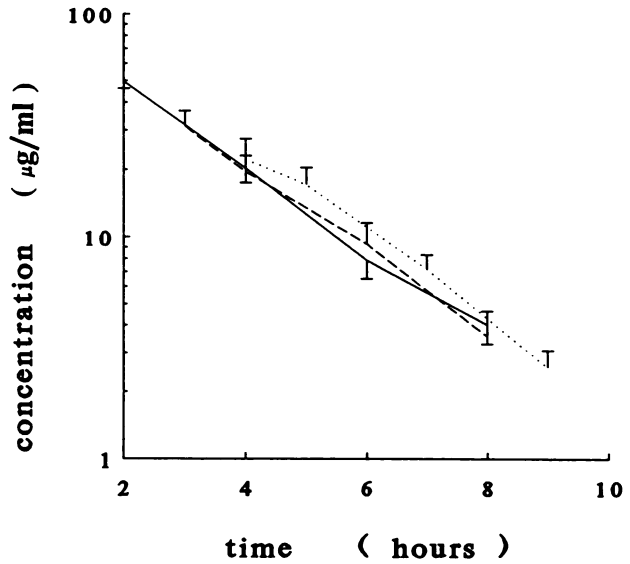

FIG. 3. Mean (± SD) ceftazidime concentrations (plotted versus time) in serum (——) and blister fluid A (---) and B (·····) samples during the elimination phase.

The concentrations in blister fluid (A samples) showed a decline similar to that in serum with a mean half-life of 96.4 ± 3.2 min (repeated-measurement analysis of variance), and a blister fluid/serum concentration ratio of 101.5% ± 18.3% during the elimination phase.

Pharmacokinetic parameters obtained after continuous infusion are summarized in Table 2. The TBC was 0.113 ± 0.018 liter/h · kg, the urinary clearance was 0.105 ± 0.012 liter/h · kg during the last 8 h of infusion, and the ceftazidime/creatinine clearance ratio 88.5% ± 4.4%. The urinary clearance of the free fraction was 108.9% ± 5.4%, which is not significantly different from 100%, indicating that there is probably no net tubular handling of the drug.

The mean AUC during continuous infusion was 21.3 μg · h/ml, and the mean blister fluid AUC was 18.0 μg · h/ml, corresponding to 84.5% of that of serum (blister/serum). There was no significant difference between concentrations in A and B blister fluid during continuous infusion.

The TBC during and after intermittent administration was not significantly different from the TBC during continuous administration.

DISCUSSION

The aim of this study was to determine pharmacokinetic parameters of ceftazidime in serum and in tissue during continuous infusion and intermittent administration. As a representative of the concentration of ceftazidime in tissue, concentrations in suction blister fluid were measured. Suction blisters were drawn as originally described by Kiistala and Mustakallio (8). Schreiner et al. (17) demonstrated the use of the method for studies of extravascular antimicrobial activity. We used a modification of this technique by forming new blisters before every sample to eliminate, as far as possible, a possible diffusion barrier between blister and tissue, thus reducing the time lag of the concentrations in blisters versus tissue to almost zero during intermittent administration.

The penetration of ceftazidime in the blisters during intermittent infusion was 101% during the elimination phase. This is in agreement with results of Wise et al. (27), who found a penetration of nearly 100% using cantharide blisters. Walstad et al. (24), who also used suction blisters, found a penetration of 80%. Investigators who used subcutaneous threads found lower values, i.e., 50% (6, 14). The difference between these values is rather high and probably depends on the method used (15, 26). The determination of the penetration in blisters in steady state should be independent of the method used. We found a penetration of 84.5%. This cannot be explained by the protein binding, as the difference between the protein binding in serum and blister fluid was found to be rather small.

TABLE 1. Pharmacokinetic parameters[a] of ceftazidime after intermittent administration

No.	Volunteer data: Age (yr)	Wt (kg)	Ht (cm)	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (min)	AUC (μg · h/ml)	TBC (liter/h · kg)	V_{ss} (liter/kg)	Blister/serum concn (%)
1	25	76.5	175	7.0	94.9	257.8	0.124	0.193	96.0
2	24	103.5	190	12.3	92.8	273.4	0.158	0.178	139.8
3	22	61.0	176	9.7	100.6	313.9	0.081	0.180	80.8
4	28	81.5	182	13.7	103.4	306.9	0.111	0.169	96.2
5	23	81.0	189	17.7	94.8	261.5	0.129	0.215	115.1
6	21	73.0	183	4.0	87.2	283.4	0.107	0.160	93.3
7	21	76.0	181	6.2	88.7	312.3	0.101	0.139	89.7
8	25	74.0	182	6.1	95.8	274.0	0.113	0.193	101.3
$\bar{x}$	23.6	78.3	182.3	9.6	94.8	285.4	0.115	0.178	101.5
SD	2.4	12.0	5.0	4.6	5.4	22.7	0.022	0.023	18.3

[a] $t_{1/2\alpha}$ and $t_{1/2\beta}$, Half-lives at α and β phases, respectively; V_{ss}, volume of distribution at steady state.

To study the effect of a possible diffusion barrier on the concentration of ceftazidime in the blisters, a second sample (B sample) was drawn 1 h after the first one (A sample) from the same set of, but other, blisters. If no diffusion barrier existed, the concentrations in the second sample would equal those in serum, as they did in the first drawings. In fact, they were 27% higher. This demonstrates that the blisters may behave as a separate compartment and establishes the need to raise new suction blisters for each timed sample. This view is supported by a persistently high concentration of ceftazidime in blister fluid from one volunteer, drawn 2 and 3 h after the collection of the A blister samples (results not shown). The half-lives of ceftazidime were not significantly different in serum and the two blister samples and were log linear. In earlier studies, the time concentration curves in blisters seemed to be biexponential (24). In these studies, the blisters were drawn at the onset of the study, and the blisters from which the later samples were taken could have undergone histological changes and thus formed a diffusion barrier, explaining the relatively high concentrations found at the later time points. Also, the elimination of ceftazidime from the blisters is dependent on the volume of the blister with respect to the surface area.

One explanation of the discrepancy between concentrations in serum and blister fluid might be lower protein binding in the blister fluid samples due to a lower protein content of blister fluid (22). Although protein binding in the A samples was slightly lower, this cannot fully explain the differences found. Also, the higher values found in the B samples cannot explain the relatively higher concentrations in the B samples.

TABLE 2. Pharmacokinetic parameters[a] of ceftazidime during continuous infusion

Volunteer no.	TBC (liter/h · kg)	CL_u (liter/h · kg)	$CL_{ceftazidime}/CL_{CR}$ (%)	Serum AUC (mean μg · h/ml)	Blister AUC/serum AUC (%)
1	0.123	0.118	89.9	19.8	75.4
2	0.094	0.086	92.9	24.0	85.0
3	0.086	0.104	81.4	27.1	78.6
4	0.135	0.121	89.0	18.4	76.4
5	0.097	0.094	87.8	22.0	99.1
6	0.120	0.098	84.4	19.8	86.0
7	0.117	0.108	95.1	20.9	102.3
8	0.130	0.112	87.6	18.2	72.8
$\bar{x}$	0.113	0.105	88.5	21.3	84.5
SD	0.018	0.012	4.4	3.0	11.0

[a] CL, Clearance; *u*, urinary; CR, creatinine.

The pharmacokinetic data from serum obtained during intermittent administration are in agreement with data from earlier studies (4, 9, 12, 19, 24, 25, 27). The data best fit a two-compartment open model.

The bactericidal action of beta-lactam antibiotics on gram-negative rods is related to the duration of exposure above a certain threshold (23). In conventional treatment regimens, beta-lactams are as a rule given intermittently. This may lead to concentrations in plasma below this threshold during part of the dosing interval and thus may impair efficacy. In tissue, this effect may be even more marked, as antibiotic concentrations in tissue are generally lower. During continuous infusion, a level above this threshold may be easily maintained. A continuous infusion of ceftazidime has been shown to be more efficacious than intermittent administration in leukopenic animal models during treatment of gram-negative-rod infections (13). A decrease in the dosing interval was shown to be more efficacious for ticarcillin (5, 11). For humans, there are a few reports that continuous infusion may lead to a better outcome. Daemen and de Vries-Hospers (3) were able to cure serious infections by *Pseudomonas aeruginosa* with a continuous infusion of ceftazidime, whereas the same drug had failed to do so when given intermittently. Bodey et al. (2) found that continuous infusion of cefamandole, administered together with carbenicillin, was more efficacious than intermittent infusion when treating febrile episodes in cancer patients. Since the antibiotic activity of ceftazidime on gram-negative rods is related to the duration of active drug levels present at the site of infection, this should have consequences for the way in which ceftazidime, or any beta-lactam, should be administered. The present paper provides pharmacokinetic data which may serve as a model as to which doses should be applied. More clinical trials are needed to determine the efficacy of continuous dosing versus intermittent dosing in humans.

LITERATURE CITED

1. **Allen, L., K. Kimura, J. MacKichan, and W. A. Rittschel.** 1982. Manual of symbols, equations and definitions in pharmacokinetics. J. Clin. Pharmacol. **22**(Suppl.):1S–23S.
2. **Bodey, G. P., S. J. Ketchel, and V. Rodriguez.** 1979. A randomized study of carbenicillin plus cefamandole or tobramycin in the treatment of febrile episodes in cancer patients. Am. J. Med. **67**:608–616.

3. **Daemen, S., and U. de Vries-Hospers.** 1988. Cure of *Pseudomonas aeruginosa* infection in neutropenic patients by continuous infusion of ceftazidime. Lancet **i**:937.
4. **De Klerk, S., L. Walters, M. van Wyck, S. M. Harding, A. M. Paton, and J. Ayrton.** 1983. Pharmacokinetics of ceftazidime in male and female volunteers. Antimicrob. Agents Chemother. **23**:892–896.
5. **Gerber, A. U., W. A. Craig, H. P. Brugger, C. Feller, A. P. Vastola, and J. Brandel.** 1983. Impact of dosing intervals on activity of gentamicin and ticarcillin against *Pseudomonas aeruginosa* in granulocytopenic mice. J. Infect. Dis. **147** (Suppl.):910–917.
6. **Hoffstedt, B., and M. Walder.** 1981. Penetration of ceftazidime into extracellular fluids in patients. J. Antimicrob. Chemother. **8**(Suppl. B):289–293.
7. **Horrevorts, A. M.** 1987. In vitro activity of new antimicrobial agents against *Pseudomonas aeruginosa* isolates from cystic fibrosis patients. Eur. J. Clin. Microbiol. **6**:323–324.
8. **Kiistala, U., and K. K. Mustakallio.** 1967. Dermo-epidermal separation with suction. J. Invest. Dermatol. **48**:466–477.
9. **Lebel, M., G. Barbeau, F. Vallee, and M. G. Bergeron.** 1985. Pharmacokinetics of ceftazidime in elderly volunteers. Antimicrob. Agents Chemother. **28**:713–715.
10. **Lebel, M., and M. Spino.** 1988. Pulse dosing versus continuous infusion of antibiotics. Clin. Pharmacokinet. **14**:71–95.
11. **Mordenti, J. J., R. Quintiliani, and C. H. Nightingale.** 1985. Combination antibiotic therapy: comparison of constant infusion and intermittent bolus dosing in an experimental animal model. J. Antimicrob. Chemother. **15**(Suppl.):313–321.
12. **Naber, K. G., F. Kees, and H. Grobecker.** 1983. Ceftazidime: pharmacokinetics in young volunteers versus elderly patients and therapeutic efficacy with complicated urinary tract infections. J. Antimicrob. Chemother. **12**(Suppl. A):41–45.
13. **Roosendaal, R., I. A. J. Bakker-Woudenberg, M. van den Berghe-van Raffe, J. C. Vink-van den Berg, and M. F. Michel.** 1989. Impact of the dosage schedule on the efficacy of ceftazidime, gentamicin and ciprofloxacin in *Klebsiella pneumoiae* pneumonia and septicemia in leukopenic rats. Eur. J. Clin. Microbiol. Infect. Dis. **8**:878–887.
14. **Ryan, D. M., U. Mason, and S. M. Harding.** 1981. The penetration of ceftazidime into extravascular fluid. J. Antimicrob. Chemother. **8**(Suppl. B):283–288.
15. **Ryan, D. M., B. Hodges, G. R. Spencer, and S. M. Harding.** 1982. Simultaneous comparison of three methods for assessing ceftazidime penetration into extravascular fluid. Antimicrob. Agents Chemother. **22**:995–998.
16. **SAS Institute, Inc.** 1982. SAS user's guide. SAS Institute, Inc., Cary, N.C.
17. **Schreiner, A., K. B. Hellum, A. Digranes, and I. Bergman.** 1978. Transfer of penicillin G and ampicillin into human skinblisters induced by suction. Scand. J. Infect. Dis. **14**(Suppl.):223–237.
18. **Snedecor, G. W., and W. G. Cochran.** 1980. Statistical methods, 7th ed. Iowa State University Press, Ames.
19. **Tjandramaga, T. B., A. van Hecken, A. Mullie, R. Verbesselt, P. J. de Schepper, and L. Verbist.** 1982. Comparative pharmacokinetics of ceftazidime and moxalactam. Antimicrob. Agents Chemother. **22**:237–241.
20. **University of California Press.** 1988. BMDP statistical software manual. University of California Press, Berkeley.
21. **van Klingeren, B.** 1988. Antibiotic resistance in *Pseudomonas aeruginosa*, *Haemophilus influenzae* and *Staphylococcus aureus*. Chest **94**(Suppl.):103–108.
22. **Vermeer, J. V., F. C. Reman, and C. M. van Gent.** 1979. The determination of lipids and proteins in suction blister fluid. J. Invest. Dermatol. **73**:303–305.
23. **Vogelman, B., and W. A. Craig.** 1986. Kinetics of antimicrobial activity. J. Pediatr. **108**:835–840.
24. **Walstad, R. A., K. B. Hellum, S. Blika, L. G. Dale, T. Fredriksen, K. I. Myre, and G. R. Spencer.** 1983. Pharmacokinetics and tissue penetration of ceftazidime: studies on lymph, aqueous humour, skinblister, cerebrospinal, and pleural fluid. J. Antimicrob. Chemother. **12**(Suppl. A):275–282.
25. **Warns, H., H. Lode, C. M. Harnoss, B. Kemmerich, P. Koeppe, and J. Wagner.** 1983. Multiple dose pharmacokinetics and therapeutic results with ceftazidime. J. Antimicrob. Chemother. **12**(Suppl. A):235–240.
26. **Wise, R.** 1986. Methods for evaluating the penetration of β-lactam antibiotics into tissues. Rev. Infect. Dis. **8**(Suppl. 3):325–332.
27. **Wise, R., G. C. Armstrong, R. M. Brown, and J. M. Andrews.** 1981. The pharmacokinetics and tissue penetration of ceftazidime and cefamandole in healthy volunteers. J. Antimicrob. Chemother. **8**(Suppl B):277–282.