Comparative Pharmacokinetics and Serum Bactericidal Activities of SCE-2787 and Ceftazidime

WOLFGANG PAULFEUERBORN, HANS-JOCHEN MÜLLER, KLAUS BORNER, PETER KOEPE, AND HARTMUT LODE

Department for Chest and Infectious Diseases, City-Hospital Zehlendorf, Institute of Clinical Chemistry and Clinical Biochemistry, and Department of Radiology, Klinikum Stieglitz, Freie Universität Berlin, Berlin, Germany

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Ceftazidime and the new SCE-2787 are parenteral cephalosporins with a broad antimicrobial spectrum. Pharmacokinetics, serum bactericidal activities, and side effects were investigated in a randomized crossover study. A total of 12 healthy volunteers received a 20-min infusion of 1.5 g of SCE-2787 or 2.0 g of ceftazidime. Serum and urine concentrations were determined by the bioassay method and by high-pressure liquid chromatography (HPLC). The mean (± standard deviation) drug concentrations in serum at the end of infusion of SCE-2787 and ceftazidime were 124.4 ± 23.8 and 233.1 ± 54.1 mg/liter, respectively. The urine recovery of SCE-2787 was 87.8% ± 5.5% of dose in 24 h and for ceftazidime was 85.8% ± 6.3% of dose in 24 h. Metabolites of SCE-2787 could not be detected by HPLC in serum or urine. Pharmacokinetic parameters were calculated both with a noncompartmental analysis and on the basis of an open two-compartment model (drugs are administered into and eliminated from a central compartment only). However, reversible drug distribution from the central space occurs simultaneously into one peripheral space. The area under the concentration time curve from 0 h to infinity of SCE-2787 was 197.9 ± 25.4 mg · h/liter, and that of ceftazidime was 334.2 ± 40.0 mg · h/liter. SCE-2787 had a mean terminal half-life in the elimination phase of 109.0 ± 15.3 min, while that of ceftazidime was 99.0 ± 13.4 min. The volume of distribution at steady state of SCE-2787 was 17.1 ± 1.6 liters/kg, and that of ceftazidime was 12.2 ± 1.3 liters/kg. The mean residence time of SCE-2787 was 136.4 ± 15.4 min, and that of ceftazidime was 122.9 ± 12.7 min. The renal clearance per 1.73 m² of SCE-2787 was 103.1 ± 12.3 ml/min, and that of ceftazidime was 80.6 ± 13.2 ml/min. The serum bactericidal activities were measured with the microdilution method of Straton and Reller (L. B. Reller and C. W. Straton, J. Infect. Dis. 136:196–204, 1977) against 40 clinically isolated strains. One hour after administration, we measured mean reciprocal bactericidal titers of SCE-2787 and ceftazidime, respectively, against Escherichia coli of 388 and 243, against Klebsiella pneumoniae of 395 and 138, against Pseudomonas aeruginosa of 13.0 and 12.7, and against Staphylococcus aureus of 32.2 and 4.0. No severe side effects were observed in this single drug administration.

β-Lactam antibiotics are in wide use for treatment of various infectious diseases because of their potent antimicrobial activities as well as their favorable adverse effect profile (28, 39, 54). A well-known parenteral broad-spectrum cephalosporin is ceftazidime, which is characterized by its broad antibacterial spectrum, including Pseudomonas aeruginosa (15, 17, 40, 49, 50, 52). SCE-2787 is a new cephalosporin with a broader and better-balanced antimicrobial spectrum ranging widely from gram-positive to gram-negative bacteria, including Staphylococcus aureus and Pseudomonas aeruginosa (23). The chemical structures of SCE-2787 and ceftazidime are shown in Fig. 1. Both drugs are stable against various β-lactamases and have low affinities to these enzymes (5, 6, 41). The present study with normal volunteers was performed to determine the basic pharmacokinetic data, the serum bactericidal activities, and the tolerance of SCE-2787 in comparison to ceftazidime in a single-dose administration design.

MATERIALS AND METHODS

Volunteers. A total of 12 healthy subjects (6 females and 6 males) participated in this study. They all were by ethnic origin Caucasians and had no known allergies to antimicrobial agents. Informed written consent was obtained from all volunteers. The study was approved by the local ethical committee according to German law. None of the females was pregnant (low human chorionic gonadotropin in urine), and none of the volunteers took any other antimicrobial agent or drug during 4 weeks preceding the study or during the study. Subjects had normal biochemical and hematological profiles, normal blood pressures, heart rates, and body temperatures, all of which were measured before the study, between days 1 and 2, and after the study. The volunteers fasted 12 h before drug administration (solid food as well as fluids), no tobacco products were allowed, and they avoided all alcoholic beverages the previous 24 h before antibiotic infusion. Mean age was 28 ± 6 years, mean body weight was 70.8 ± 8.7 kg, mean body surface was 1.86 ± 0.17 m², and mean creatinine clearance was 99 ± 12 ml/min/1.73 m² (clearance: drug concentration in urine × volume of urine [24 h] × 1.73/drug concentration in serum × 1,440 × body surface) (all data are ± standard deviation).

Dosing. In a randomized crossover study design, the volunteers received 1.5 g of SCE-2787 supplied by Takeda Pharma GmbH, Stolberg, Germany (batch CH-B-ZS43H122) or 2.0 g of ceftazidime supplied by Glaxo GmbH, Bad Oldesloe, Germany (batch CH-B9 G871) and the correspon-
dent drug after a washout time of 1 week. For intravenous administration, both drugs were dissolved in 40 ml of 0.9% sodium chloride and constantly infused over a 20-min period into a peripheral vein by an infusion pump (B. Braun, Melsungen, Germany). The volunteers took 200 ml of mineral water before infusion and 500 ml of liquids over the next 6 h after intravenous administration. The fasting state (solid food) was maintained for 3 h after drug administration.

Sampling. Samples for antibiotic assays in serum after intravenous administration were taken before dosing and 0, 15, 30, 45, 60, and 90 min and 2, 3, 4, 6, 8, 10, 12, and 24 h after venous infusion. All samples were stored for 15 min at room temperature and 30 min at 4°C, centrifuged, and afterwards immediately shock frozen (−20 to −30°C). All volunteers started with empty bladders, and they all voided to provide the last urine sample. The urine samples were collected in time periods of 0 to 3, 3 to 6, 6 to 12, and 12 to 24 h after the end of infusion and were shock frozen immediately.

High-pressure liquid chromatography (HPLC). The concentration of SCE-2787 was detected as described by Borner et al. (9). The analyte SCE-2787 was separated by reversed-phase chromatography in a mobile phase containing heptane sulfonic acid as an ion pair-forming reagent. The A254 of the eluate was recorded. Peak areas were used for calculation of concentrations referring to external calibrators. The analyte was extracted from serum by precipitation of serum proteins with acetonitrile and subsequent back-extraction of acetonitrile with dichloromethane. Urine samples only were diluted with 15 mmol of heptanesulfonic acid, pH 3.2, per liter. The detection limit of SCE-2787 was 0.62 mg/liter in serum and 3.5 mg/liter in urine. Linearity was in the range of 1.0 to 200 mg/liter for serum and 5.0 to 1,000 mg/liter for urine. Precision within series (coefficient of variation) was 11.3% to 0.7% in serum (concentration range, 0.7 to 160 mg/liter) and 10.7% to 1.5% in urine (concentration range, 5 to 500 mg/liter). Precision between series was 7.5% to 3.2% in serum (concentration range, 3.5 to 75 mg/liter) and 4.2% to 2.7% in urine (concentration range, 50 to 300 mg/liter).

Recovery from serum was 96 to 103%, and that from urine was 99 to 104%. Specificity was confirmed by spectral analysis of the peak and complete enzymatic degradation with β-lactamase type II from Bacillus subtilis. The extent of the degradation was 99% from serum and 95% from urine. The ceftazidime concentrations were measured by HPLC on the basis of previously described methods (8, 25). The analyte ceftazidime was separated by reversed-phase chromatography in a mobile phase which consisted of sodium acetate buffer plus acetonitrile. The A254 of the eluate was recorded. Sera were deproteinized by adding acetonitrile to the sample. Results were calculated with peak areas and external standardization. The detection limit was about 0.8 mg/liter. Linearity was given for concentrations of up to 250 mg/liter. The precision of the HPLC method was 4% at 117 mg/liter (coefficient of variation). The mean recovery was 91.4%. The identity of the peaks was confirmed by complete enzymatic degradation with β-lactamase type II and by spectral analysis.

Bioassay. The bioassay method was based on an agar plate diffusion technique described by Reeves and Bywater (43). Serum samples were assayed against standards prepared in activity-free pooled human serum. Phosphate buffer (pH 7.0) was used for the predilution of urine and urine standards. All samples and standards were tested in triplicate. SCE-2787 was detected in the concentration range from 180 to 0.6 mg/liter by using the test organism Escherichia coli NIH (IFO 14249) and Difco N agar (pH 7.4). The coefficient of variation was 2.65% at 5 mg/liter and 8% at 2.5 mg/liter. The detection limit was 0.45 mg/liter in serum and urine. The test organism Providencia retgeri ATCC 9250 and MacConkey agar (pH 8.0) were used in the concentration range from 0.6 to 0.06 mg/liter. The coefficient of variation was 5.81% at 0.625 mg/liter, and the detection limit was 0.06 mg/liter in serum and 0.03 mg/liter in urine. Ceftazidime was evaluated in the concentration range from 0.9 to 0.3 mg/liter by using the test organism E. coli V 6311 and Difco N agar (pH 7.4). The coefficient of variation was 3.52% at 25 mg/liter and 2.5% at 5.25 mg/liter. The detection limit was 0.16 mg/liter in serum and urine. In the concentration range from 260 to 0.9 mg/liter, we used the test organism E. coli ATCC 25922 and Difco N agar (pH 7.4). The coefficient of variation was 2.75% at 6.25 mg/liter, and the detection limit was 0.6 mg/liter in serum and urine.

Protein binding. The protein binding of SCE-2787 was measured by micropartition system MPS-1 (Amicon GmbH, Witten, Germany) by using spiked samples containing 5 and 10 mg of SCE-2787 per liter. The concentration of the free fraction of SCE-2787 in the ultrafiltration partition was determined with the agar plate diffusion technique. The coefficient of variation was 5.8% at 5 mg/liter and 8.5% at 10 mg/liter. The centrifuge speed was 1,500 × g, the centrifuge time was 30 min, and the temperature was 25°C. The quantitative partitioning capability is reflected by retention of >99.9% of serum protein and <5% of t-thyroxine. The drug did not adsorb to the filter, and the ultrafiltration partition of SCE-2787 in buffer was 100%.

SBA. The serum bactericidal activity (SBA) was detected by using the microdilution method of Reller and Stratton (44). All samples were serially diluted with heat-decomplemented (56°C, 30 min) pooled human serum from 1:2 to 1:512 and incubated 18 h at 37°C with a final inoculum size of 5 × 10⁵ strains per ml. The serum inhibiting titer was the highest dilution that showed no visible growth. A 1-μl sample from each well showing no visible growth was subcultured onto MH agar media and incubated 12 h at 37°C. The dilution that
TABLE 1. Adverse effects

<table>
<thead>
<tr>
<th>Type of adverse effect</th>
<th>No. of subjects with complaint after 20-min infusion of</th>
<th>SCE-2787 (1.5 g)</th>
<th>Ceftazidime (2 g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headaches</td>
<td></td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Gastrointestinal complaints&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Central nervous complaints&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Local and peripheral affections&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>No side effects</td>
<td></td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

<sup>a</sup> Nausea (n = 1) and watery stool (n = 6).

<sup>b</sup> Visual disturbance, increased sensitivity to light (n = 1); dizziness (n = 1); poor ability to concentrate (n = 4); and fatigue (n = 1).

<sup>c</sup> Flush (n = 4) at the puncture site (n = 3), itching eyes (n = 1), and itching nose (n = 2).

PHARMACOKINETICS AND SBA OF SCE-2787 AND CEFTAZIDIME

killed >99.6% of the initial inoculum was the SBA. In this study, the following freshly isolated pathogens were tested against sera from all volunteers 1 h after end of infusion (peak) and 8 h after end of infusion (trough): S. aureus (10 strains), E. coli (10 strains), Klebsiella pneumoniae (10 strains), and P. aeruginosa (10 strains). All strains were freshly isolated from clinical materials by the Department of Microbiology (Klinikum Steglitz).

Pharmacokinetic analysis. Pharmacokinetic parameters were calculated both (i) with a noncompartmental analysis and (ii) on the basis of an open two-compartment model (16, 45). (i) The area under the curve (AUC) was calculated by the log trapezoidal rule, corrected for body weight and reference dose. (ii) We calculated the pharmacokinetic constants for infusion time as described by Loo and Riegelmann by using the open two-compartment model: drugs were administered into and eliminated from a central compartment only. However, reversible drug distribution from the central space occurs simultaneously into one peripheral space (34).

An iterative relative least-squares method was used to fit the constants to the experimental data of the serum concentration-time curve (29–31). Serum drug concentrations were normalized for a body weight of 70 kg before determination of pharmacokinetic parameters. The area under the curve (AUC) was calculated by using the compartmental model (AUC<sub>0-∞</sub>) as the half-lives in distribution and elimination phases. The volume of distribution at steady state (V<sub>ss</sub>) in liters/70 kg = V<sub>ss</sub> percentage of body weight) was detected by using the noncompartmental analysis. The alternative for biological half-lives, the mean residence time (MRT), was determined by using both pharmacokinetic models (10, 27). The renal clearance (CL<sub>R</sub>) was total clearance × percent urine recovery/100. The total urine recovery is the result of the regression straight line, whose slope defines the data; they may be smaller than the urine recovery found by HPLC (e.g., see SCE-2787 [Table 2]).

Statistical analysis. Wilcoxon's test (signed-rank test for paired samples, two tailed) was used for statistical comparison. A probability (P) of ≤0.05 was considered significant.

RESULTS

Tolerance. No abnormal physical or laboratory findings were observed. All adverse effects were of a mild or moderate severity, were of short period, improved spontaneously, and recovered completely (Table 1).

One volunteer developed a drug exanthema 2 and 9 days after infusion of ceftazidime and SCE-2787, respectively—a well-known intolerance effect of cephalosporins, which lasted for 2 days in this case.

Non-specific circulatory disorders (chills, tachycardia, hypotension, nausea, dyspnea, cold perspiration, weak concentration, and dizziness) 6 h after receiving SCE-2787 led to discontinuation of blood sample collection from one volunteer; the relation to the study drug was unclear. The serum concentration data of SCE-2787 from 8 to 24 h and the serum bactericidal titer 8 h after end of infusion are representative of 11 volunteers only.

Single-dose kinetics. Drug concentrations and pharmacokinetic results in all tables are given on the basis of the HPLC. Comparison of the results obtained by bioassay and HPLC methods showed an excellent correlation for drug concentrations of SCE-2787 in serum (slope/intercept, 0.945/−0.42; n = 170 [Fig. 2]) and urine (slope/intercept, 0.975/−1.48; n = 48) (2). Predose samples of blood and urine showed no detectable activity. No metabolites of SCE-2787 or ceftazidime could be detected with the HPLC method. The control materials were blank serum and urine of the volunteers. The extent of degradation was 99% in serum and 95% in urine after enzymatic degredation with β-lactamase from B. subtilis type II.

A dose of 1.5 g of SCE-2787 resulted in a mean peak level of 124.4 ± 23.8 mg/liter after the 20-min infusion, with decreases to 45.2 ± 6.2 mg/liter after 1 h, 5.82 ± 1.3 mg/liter after 6 h, and 0.75 ± 0.31 mg/liter after 12 h. A 2-g ceftazidime dose showed a mean peak level of 233.1 ± 54.1 mg/liter after the 20-min infusion, with decreases to 78.6 ± 11.2 mg/liter after 1 h, 8.7 ± 2.0 mg/liter after 6 h, and 0.73 ± 0.38 mg/liter after 12 h (Fig. 3).

The pharmacokinetics of both drugs could be described by an open two-compartment model with a rapid initial distribution phase (t<sub>1/2α</sub> of SCE-2787, 15.7 ± 5.6 min; of ceftazidime, 13.7 ± 7.3 min) and a slow terminal elimination phase (t<sub>1/2β</sub> of SCE-2787, 109.0 ± 15.3 min; of ceftazidime, 99.0 ± 13.4 min). The mean AUC<sub>0-∞</sub> of SCE-2787 was 197.9 ± 25.4 mg·h/liter, and that of ceftazidime was 334.2 ± 40.0 mg·h/liter. These results are in close agreement with the AUC<sub>0-∞</sub> of both substances to a mean dosage of 1,000 mg resulted in an AUC<sub>0-∞</sub> of 131.9 mg·h/
litter for SCE-2787 and an AUC₀₋∞ of 167.1 mg · h/liter for ceftazidime. The mean Vₐ of SCE-2787 was 17.1 ± 1.6 liters/70 kg, and that of ceftazidime 12.2 ± 1.3 liters/70 kg, the mean volume of distribution by the area method (Vₐ(area)) of SCE-2787 was 20.0 ± 2.3 liters/70 kg, and that of ceftazidime was 14.3 ± 1.8 liters/70 kg. The MRT of SCE-2787 was 136.4 ± 15.4 min, and that of ceftazidime 122.9 ± 12.7 min, which are close to the results of the noncompartmental analysis (MRT*). The total body clearance (CLTOT) of SCE-2787 was 118.4 ± 12.8 ml/min, and that of ceftazidime was 93.8 ± 11.5 ml/min. The CLₚ of SCE-2787 was 103.1 ± 12.3 ml/min, and that of ceftazidime was 80.6 ± 13.2 ml/min. The mean protein binding of SCE-2787 was 30.8% ± 5.4%. Nearly two-thirds of the dose of both drugs was eliminated within 3 h (SCE-2787, 66.3% ± 5.4%; ceftazidime, 64.2% ± 6%). Twenty-four h after the end of infusion, the mean urine recovery of SCE-2787 was 87.8% ± 5.5% of the administered dose, and that of ceftazidime was 85.8% ± 6.3% (Fig. 4).

The mean concentration at the end of the infusion showed a significant difference between 1.5 g of SCE-2787 and 2.0 g of ceftazidime (Table 2; Fig. 3) and also could be calculated significant differences of AUC, AUD, MRT, MRT*, Vₐ*, Vₐ(area), CLTOT, and CLₚ (Table 2). SCE-2787 and ceftazidime

![FIG. 3. Mean concentration ± standard deviation of SCE-2787 (○) and ceftazidime (△) in serum.](image-url)

![FIG. 4. Cumulative renal elimination of SCE-2787 (■) and ceftazidime (▲).](image-url)

![FIG. 5. SBA of SCE-2787 (■) and ceftazidime (▲) against K. pneumoniae and E. coli (mean 1/liter, 0 to 500).](image-url)

<table>
<thead>
<tr>
<th>Parameter (unit)</th>
<th>Value (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀₋∞ (mg · h/liter)</td>
<td>SCE-2787 (1.5 g/70 kg)</td>
</tr>
<tr>
<td>AUD₀₋∞ (mg · h/liter)</td>
<td>197.9 ± 25.4</td>
</tr>
<tr>
<td>C₂₀₋∞ (mg/liter)</td>
<td>200.2 ± 25.8</td>
</tr>
<tr>
<td>t₁₂α (min)</td>
<td>124.4 ± 23.8</td>
</tr>
<tr>
<td>t₁₂β (min)</td>
<td>15.7 ± 5.6</td>
</tr>
<tr>
<td>V₉ (liters/70 kg)</td>
<td>109.0 ± 15.3</td>
</tr>
<tr>
<td>V₉* (% body weight)</td>
<td>17.1 ± 1.6</td>
</tr>
<tr>
<td>MRT (min)</td>
<td>24.5 ± 2.2</td>
</tr>
<tr>
<td>MRT* (min)</td>
<td>136.4 ± 15.4</td>
</tr>
<tr>
<td>Vₐ(area) (liters/70 kg)</td>
<td>20.0 ± 2.3</td>
</tr>
<tr>
<td>Vₐ(area) (liters/100 kg)</td>
<td>28.5 ± 3.3</td>
</tr>
<tr>
<td>CLTOT (ml/min/1.73 m²)</td>
<td>118.4 ± 12.8</td>
</tr>
<tr>
<td>CLₚ (ml/min/1.73 m²)</td>
<td>103.1 ± 12.3</td>
</tr>
<tr>
<td>CLEXT* (ml/min/1.73 m²)</td>
<td>15.3 ± 6.3</td>
</tr>
<tr>
<td>Urine recovered (%/24 h)</td>
<td>87.1 ± 5.2</td>
</tr>
<tr>
<td>Protein binding (%)</td>
<td>30.8 ± 5.4</td>
</tr>
</tbody>
</table>

*#, P ≤ 0.05. Lit., 19, 12, 25, 32, 51. * Results were analyzed model free.

had similar initial and terminal half-lives, total urine recoveries, and nonrenal clearances (Table 2).

**SBA.** One hour after end of infusion, the serum concentrations of SCE-2787 and ceftazidime resulted in high mean reciprocal titers against E. coli and K. pneumoniae. The mean reciprocal SBA titers of SCE-2787 and ceftazidime, respectively, were 388 and 243 against E. coli and 395 and 138 against K. pneumoniae. Both antibiotics had a high mean peak titer of 13.0 (SCE-2787) and of 12.7 (ceftazidime) against P. aeruginosa. SCE-2787 showed an increased mean peak titer against S. aureus of 32.2, while ceftazidime showed a lower titer of 4.0 (Fig. 5 and 6).

The mean minimal bactericidal concentration of SCE-2787 1 h after end of infusion was 0.12 mg/liter against E. coli, 0.11 mg/liter against K. pneumoniae, 3.5 mg/liter against P. aeruginosa, and 1.4 mg/liter against S. aureus. The results of ceftazidime were 0.32 mg/liter against E. coli, 0.57 mg/liter against K. pneumoniae, 6.19 mg/liter against P. aeruginosa, and 19.6 mg/liter against S. aureus.
Eight hours after end of infusion, the trough sera of
SCE-2787 and ceftazidime were still effective against E. coli
and K. pneumoniae. They showed respective reduced mean
reciprocal titer against E. coli of 35 and 21 and against K.
pneumoniae of 29 and 12. Low respective SBA titers of both
cephalosporins were determined against P. aeruginosa of 2.2
and 2.3, and against S. aureus of 3.3 and 2.0 (Fig. 5 and 6).

All serum bactericidal titers were statistically significantly
different between SCE-2787 and ceftazidime (P ≤ 0.05),
except for the results against P. aeruginosa (peak and trough
level).

**DISCUSSION**

**Tolerance.** Both drugs were well tolerated, though nine
volunteers who received 1.5 g of SCE-2787 and seven
volunteers who received 2.0 g of ceftazidime complained of
several minor adverse drug reactions. Most of the reported
side effects showed no correlation with physical or labora-
tory findings or high concentrations of both drugs in urine or
blood. The adverse effects referring to the central nervous
system were atypical for this class of substances (13, 15, 37,
39). Only local and peripheral reactions (flush at the punctu-
ture site and itching eyes and nose) were probably drug
related, because they were recorded during or directly after
the 20-min infusion, and they are well-known adverse effects
of cephalosporins (1, 4, 14, 38). Also, a well-known rare side
effect of cephalosporins is the drug-induced exanthema that
appeared 2 and 9 days, respectively, after infusion of ceftazi-
dime and SCE-2787 in one subject (3, 22, 24, 36, 46).

Seven volunteers who received 1.5 g of SCE-2787 and five
volunteers who received 2.0 g of ceftazidime reported head-
aches. They may be enhanced or provoked by the long
fasting state (about 15 h) or by the withdrawal of tobacco and
caffeine-containing products from the subjects during the
day of the study. These were also possible explanations for
the nonspecific circulatory disorder in one volunteer, who
didn't eat anything during the day of the study.

Four volunteers who received 1.5 g of SCE-2787 and one
volunteer who received 2.0 g of ceftazidime recorded prob-
able drug-related local and peripheral reactions. This may
show a higher allergic potential of SCE-2787 compared with
ceftazidime, but this observation was not reproduced in
another randomized, placebo-controlled and double-blind
multiple dose study from our own research department
(37a).

**Pharmacokinetics.** The different dosages of 1.5 g of SCE-
2787 and of 2.0 g of ceftazidime caused significant differ-
ences in the mean concentrations at the end of infusion and
of course in AUC (same as the AUD), too. Different AUCs
remained after both drugs were normalized to a mean dosage
of 1,000 mg. Results by other authors were in the same range
as those in our study (11, 20, 25, 51). The validity of the
pharmacokinetic model is indicated by a good agreement
with the results analyzed by a non compartmental and by an
open two-compartment model. SCE-2787 and ceftazidime
had comparable relative long terminal half-lives of 109 and
99 min, respectively, so as determined by pharmacokinetics,
they could be administered twice a day, although the serum
bactericidal titers may support a time gap of 8 h. They were
predominantly eliminated by the kidneys, though they have a
significant difference in CLG and CLTOT. The clearance
data of ceftazidime are in agreement with reports by other
authors, even if ceftazidime was given in different dosages
(19, 33, 35). SCE-2787 showed a protein binding of 30.8% ±
5.4%. Other authors have detected a protein binding of
ceftazidime ranging from 16 to 22.8% (12, 19, 25, 32, 51)
(Table 2).

**SBA.** The SBA test has been used for many years to
monitor antibiotic therapy, but there are many technical
variables that influence the measurement of the SBA, and
even in patients the drug levels fluctuate (42, 53). However,
a serum bactericidal titer of ≥1:8 is suggested to be associ-
ated with a significantly better therapeutic outcome in febrile
cancer patients (26), and in patients with granulocytopenia
a titer of ≥1:16 seems to be necessary in gram-negative bac-
ceremia (47). In this study the SBA test took into account
the ability of healthy volunteers to distribute, eliminate, and
metabolize the antibiotic so as to influence the bacterial
growth by additional serum activity.

Though SCE-2787 and ceftazidime were eliminated
together, they revealed high SBA titers against E. coli and K.
pneumoniae 8 h after end of infusion. Standiford et al. and
other authors described comparable SBA results 1 and 6 h
after infusion of ceftazidime (8, 12, 48). These authors also
described the same efficacy of ceftazidime against P. aerugi-
nosa and S. aureus. The in vitro properties of ceftazidime
against these four strains were first described by Wise et al.
(52). Our results were in the same range and were also
reported by others (7, 18, 19, 21, 49).

SCE-2787 showed a minimal bactericidal concentration
against P. aeruginosa after 440 min following the end of
infusion, while ceftazidime showed it after 360 min. We
observed an increased reciprocal titer of SCE-2787 of 32
against S. aureus 1 h after end of infusion compared with a
low reciprocal titer of ceftazidime of 4 (8, 11, 48). Iwahil et
al. reported comparable results of the in vitro and in vivo
(in mice) activities of SCE-2787 against these four pathogens
(23).

SCE-2787 developed a minimal bactericidal concentration
against S. aureus for a duration time longer than 600 min
according to a twice-daily application, while ceftazidime
showed one for about 250 min. The serum bactericidal titers
of SCE-2787 were generally better than those of ceftazidime
against K. pneumoniae, E. coli, and S. aureus and were
equal against P. aeruginosa.

SCE-2787 and ceftazidime had similar pharmacokinetics
with relative long elimination half-lives, were predominantly
eliminated by the kidneys, and were well tolerated. Although
SCE was administered in a lower dosage, both drugs offered

FIG. 6. SBA of SCE-2787 (●) and ceftazidime (□) against
P. aeruginosa and S. aureus (mean 1/titer, 0 to 40).
approximately equal antibacterial efficacy against the tested gram-negative bacteria. The increased SBA titer of SCE-2787 against S. aureus demonstrated the broader antibacterial spectrum of this new cephalosporin, which could be of clinical importance in the treatment of serious nosocomial infections.

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