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Comparative Study of the Effects of Four Cephalosporins against *Escherichia coli* In Vitro and In Vivo

MARC L. VAN OGTROP,[1,2] HERMAN MATTIE,[1]* HENRY F. L. GUIOT,[1,2] ELISABETH VAN STRIJEN,[1] ANNE-MARGREET HAZEKAMP-VAN DOKKUM,[1] AND RALPH VAN FURTH[1]

Department of Infectious Diseases, University Hospital, P.O. Box 9600, 2300 RC Leiden,[1] and J. A. Cohen Institute for Radiopathology and Radiation Protection, Leiden,[2] The Netherlands

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A thigh muscle infection induced with *Escherichia coli* in irradiated mice was used as a model to compare the in vivo pharmacodynamics of the antibacterial effect of four cephalosporins (i.e., cefepime, ceftriaxone, ceftazidime, and cefoperazone) with the in vitro antibacterial pharmacodynamics of these drugs. The following in vitro pharmacodynamic parameters were determined: the maximum effect as a measure for efficacy, the 50% effective concentration as a parameter for potency, and the slope of the concentration-effect relationship. For analysis of the in vivo antibacterial pharmacodynamics, the same parameters were applied for the dose instead of the concentration. For the detection of a relationship between concentration and antibacterial effect in vivo, we determined the pharmacokinetics of the four cephalosporins in the plasma of mice. The results showed that, in general, there is a direct relationship between the in vivo and in vitro pharmacodynamics of these cephalosporins. The maximum effects of cefepime, ceftazidime, and cefoperazone were approximately similar in vivo and in vitro. The sequence of potency of these drugs was, in descending order, cefepime, ceftazidime, and cefoperazone. Ceftriaxone differed from the other three cephalosporins in that it displayed unexpected in vivo pharmacodynamics. Ceftriaxone was just as efficacious as the other three in vitro, but its maximum effect in vivo was much lower. This relatively low maximum effect of ceftriaxone in vivo was not explained by the pharmacokinetic characteristics of the drug. From the present results it can be concluded that the in vitro efficacy of cephalosporins does not necessarily have a predictive value for the in vivo efficacy.

Cephalosporins are a group of antibacterial agents used increasingly for the empiric treatment of suspected infections as well as for the treatment of gram-negative infections in granulocytopenic patients (4).

The usual method for the in vitro comparison of antibacterial agents is to determine the MICs of the agents under study for several groups of bacteria. The MIC is, however, a static parameter of antibacterial effect because it does not take into account the pharmacodynamic characteristics of drug action (10), such as the potency of the drug, the slope of the curve of the concentration-effect relationship, and the maximum effect on bacterial growth. The MIC alone can be considered to be a measure of the in vitro potency of the antibiotic, but as a quantitative parameter it is rather inaccurate, because it is usually determined on the basis of twofold dilution steps.

For a valid comparison of in vitro and in vivo antibacterial pharmacodynamics, it is essential to determine the pharmacokinetics of the antimicrobial agents as well, because such data provide information on the relationship between the plasma concentration and the in vivo effect. The thigh infection model used in this study has the advantage that the concentration of the antimicrobial agent in the interstitial fluid of the thigh muscle corresponds with the concentration of free (unbound) drug in the plasma (6, 7).

For the present study on the in vitro and in vivo pharmacodynamic characteristics of the antibacterial effect of four cephalosporins, a strain of *Escherichia coli* was used. The antibacterial effect in vitro was determined in a short-term growth experiment, and a mathematical description of the proliferation of the test organism was used to quantify the in vitro effect of the drugs. The antibacterial effect of the drugs in vivo was quantified in a short-term thigh infection model in granulocytopenic mice. The in vivo and in vitro pharmacodynamic parameters were compared to determine the relevance of in vitro studies for the prediction of in vivo antibacterial efficacy.

MATERIALS AND METHODS

Antibiotics. Cefoperazone (sodium salt; activity, 96.4%) was kindly donated by Pfizer Pharmaceuticals, Rotterdam, The Netherlands; ceftazidime (activity, 84.2%) was from Glaxo, Nieuwegein, The Netherlands; ceftriaxone (activity, 83.95%) was from Hoffmann-La Roche, Basel, Switzerland; and cefepime (activity, 82.6%) was from Bristol Myers, Brussels, Belgium. Solutions of the drugs were prepared freshly in phosphate-buffered saline (PBS) by following the recommendations of the manufacturer.

Animals. Female specific-pathogen-free Swiss mice (Broekman Institutes, Someren, The Netherlands) were used throughout the study.

Bacteria. A strain of *E. coli* serotype O.90, isolated from the feces of a Swiss mouse, was used as the test strain. The strain is serum resistant. The MICs of cefoperazone, ceftazidime, ceftriaxone, and cefepime for this microorganism, determined by the agar dilution method on Iso-Sensitest agar (Oxoid, Basingstoke, United Kingdom), were 0.125, 0.125, 0.032, and 0.032 μg/ml, respectively. The MICs and MBCs of these four drugs, determined by the tube macrodilution method in brain heart infusion broth (Oxoid) in the presence of 10% murine plasma, were 0.25 and 0.5 μg/ml for cefoperazone, 0.25 and 0.25 μg/ml for ceftazidime, 0.063 and 0.063 μg/ml for ceftriaxone, and 0.125 and 0.125 μg/ml for cefepime, respectively.

An overnight culture of the bacterium was prepared in

* Corresponding author.

brain heart infusion broth, snap-frozen in liquid nitrogen, and stored at −70°C. Before each experiment, portions were rapidly thawed in a water bath at 37°C.

Effect of the cephalosporins on the growth rate of *E. coli* in vitro. A 1:3,000 dilution of an overnight culture of *E. coli* in brain heart infusion broth was incubated in a shaking water bath at 37°C for 1 h and then distributed in 20-ml portions in 50-ml flasks. Samples were taken at 45-min intervals over a period of 3 h and were washed once with ice-cold PBS to prevent carryover of the antimicrobial agents. The washing procedure was as follows: a 200-μl sample was diluted with 1,800 μl of PBS and centrifuged at 2,000 × *g* for 10 min at 4°C, after which the upper 0.9 volume was pipetted off. The recovery of the bacteria with this procedure was 99.8% (standard deviation, 17.7%). Appropriate dilutions in PBS were plated on diagnostic sensitivity test agar (Oxoid) and incubated overnight at 30°C, after which the CFU were counted.

The effect of a given concentration of the cephalosporins on bacterial numbers was expressed as the difference between the logarithms (base 10) of the numbers of CFU in the absence and presence of the antimicrobial agent (E_N). The values of E_N were fitted by multiple-regression analysis to the following equation (H. Mattie, A.-M. van Dokkum, L. Brus-Weijer, A. M. Krul, and E. van Strijen, J. Infect. Dis., in press):

$$E_N = i_1 t + i_2 t^2 + i_3 e^{-t} + i_4 \quad (1)$$

The net killing rate was defined as the first derivative of E_N. For further calculations, the highest value of the net killing rate during the 3 h of exposure (E_R) was used. The concentration-effect relationship was then established by using the Hill equation (12):

$$E_R = E_{R,\max} \times C^s/[(EC_{50})^s + C^s] \quad (2)$$

where $E_{R,\max}$ is the maximum effect of the antibiotic on the growth rate of the test strain estimated from experimental results, C is the concentration of the drug, s is a parameter reflecting the steepness of the curve of the concentration-effect relationship, and EC_{50} is the concentration of the drug at which 50% of the maximum effect is obtained. The parameters of this pharmacodynamic model were calculated by nonlinear least-squares regression techniques (Systat 5.0; Systat Inc., Evanston, Ill.). This program uses a Quasi-Newton nonlinear squares estimator. No weighting was performed.

Effect of the cephalosporins on the number of *E. coli* in an experimental thigh muscle infection. An experimental thigh muscle infection model (5) was used to assess the therapeutic effect of the cephalosporins in vivo. Mice were rendered granulocytopenic by total body irradiation at 6 Gy (6-MV linear accelerator, model SL 75/6; Philips, Eindhoven, The Netherlands). At 5 days after the irradiation, when the experimental infection was induced, the mean number of granulocytes had reached its minimum, i.e., 65/μl. The mice were infected by injecting 5×10^6 to 6×10^6 CFU of *E. coli* into a thigh muscle, and 1 h later the antimicrobial agent was administered subcutaneously at various dosages. The dose range studied was 0.04 to 10 mg/kg for ceftriaxone, 1.6 to 100 mg/kg for cefepime, 2.5 to 160 mg/kg for ceftazidime, and 6.25 to 1,600 mg/kg for cefoperazone. Control mice received the diluent. The dose range of each drug was chosen empirically so that a maximum antibacterial effect on the number of bacteria in the thigh muscle could be estimated. At 4 h after the injection of the drug, the mice were killed by cervical dislocation and the thigh muscle was excised and then homogenized in 5 ml of sterile, ice-cold PBS with a tissue homogenizer (Ystral, type X-1020; International Laboratorium Apparate GmbH, Dottingen, Federal Republic of Germany). For counting of the CFU in the homogenate, samples were processed as described for the in vitro experiments.

The effect of a single dose of the cephalosporins was expressed as the difference between the logarithms (base 10) of the numbers of CFU in the thighs of untreated and treated mice (E_N). The dose-effect relationship was then established by use of the Hill equation:

$$E_N = E_{N,\max} \times D^s/[(ED_{50})^s + D^s] \quad (3)$$

where $E_{N,\max}$ is the maximum effect of a single dose of the antibiotic on the number of bacteria in the infected thigh muscle estimated from experimental results, D is the dose of the drug, and ED_{50} is the dose of the drug at which 50% of the maximum effect is obtained.

Pharmacokinetic study of the cephalosporins in mice. Single-dose pharmacokinetics in plasma were analyzed for the following doses: cefoperazone, 1,600 mg/kg; ceftazidime, 160 mg/kg; ceftriaxone, 5 mg/kg; and cefepime, 100 mg/kg. Blood samples were taken by cardiac puncture with heparinized syringes after the animals had been killed by exposure to 100% CO_2. The samples were centrifuged at 1,500 × *g* for 10 min at room temperature, after which the plasma was removed and the drug concentration was measured. With these values, the half-life was determined by linear regression analysis of the descending slope of the time versus log-concentration curve, and the area under the concentration-time curve was calculated by use of the trapezoidal rule.

Protein binding of the cephalosporins in murine plasma was determined by equilibrium dialysis in a Dianorm dialysis apparatus (Diachema AG, Zurich, Switzerland) at 37°C (8). The dialysis chambers have a volume of 1 ml and are separated by a membrane measuring 4.5 cm^2. One chamber contained 0.7 ml of plasma, and the other contained a solution of the antibiotic in PBS (pH 7.0). The concentrations studied were 5, 10, and 20 μg/ml for all four drugs. The chamber was placed in a rotator, and dialysis was carried out at 16 rpm at 37°C for 4 h. At this time, equilibrium was obtained. The stabilities of the drugs after 4 h at 37°C were 87% for cefoperazone, 94% for ceftazidime, 98% for ceftriaxone, and 95% for cefepime. The concentrations of the drugs in both chambers were determined by using appropriate standards.

High-pressure liquid chromatography analysis of the cephalosporin concentrations. Acetonitrile, dichloromethane, and sodium acetate were of analytical grade and were supplied by Merck (Darmstadt, Federal Republic of Germany). The liquid chromatographic system consisted of a constant-flow pump (model 1000; Sykam, Analytica BV, Rijswijk, The Netherlands), a Rheodyne model 7125 injection valve equipped with a 20-μl sample loop (Chrompack, Middelburg, The Netherlands), a stainless-steel column (10 cm long by 3 mm internal diameter), and a Spectroflow 773 absorbance detector (Kipp & Zn., Delft, The Netherlands). The detector was set at 254 nm for monitoring ceftazidime, 274 nm for ceftriaxone, 254 nm for cefoperazone, and 280 nm for cefepime. The column was home packed with 5 μm of Hypersil ODS (Shandon SPL, Cheshire, United Kingdom) by using a pressurized slurry technique.

The extraction procedure used for the plasma samples containing cefoperazone, ceftazidime, or ceftriaxone was as follows: a 500-μl volume of plasma was vigorously mixed with an equal volume of acetonitrile in a polypropylene tube

TABLE 1. Accuracy and precision of high-pressure liquid chromatography assays for the cephalosporins in human plasma

Cephalosporin	% Coefficient of variation (mean ± SD)	% Recovery (mean ± SD)	Level of detection (μg/ml)
Cefoperazone	0.83 ± 0.93	104 ± 8	0.2
Ceftazidime	1.98 ± 1.81	100 ± 13	0.5
Ceftriaxone	0.93 ± 0.61	115 ± 17	0.4
Cefepime	3.10 ± 3.25	101 ± 13	0.5

on a whirlmixer for 30 s. After centrifugation for 5 min at 1,200 × *g*, 400 μl of the supernatant was mixed with 3 ml of dichloromethane for 30 s and centrifuged for 5 min at 1,200 × *g*. A 20-μl volume of the upper aqueous phase containing the analyte was injected into the column, and chromatography was performed at a flow rate of 1 ml/min with a mobile phase consisting of 0.7% (vol/vol) acetonitrile in a 0.005-mol/liter acetate buffer (pH 5.5). Plasma samples containing cefepime were extracted by the method of Barbhaiya et al. (1). Calibration plots were obtained by assaying samples of pooled murine plasma, spiked in the range of 0.5 to 100 μg/ml. The quality controls of the assays for the four drugs are shown in Table 1.

RESULTS

Antibacterial effect in vitro. The growth experiments were performed in triplicate. The growth experiments performed (Fig. 1) were easily reproducible. No antibiotic carryover was observed at low counts of viable *E. coli*. The exponential growth rate (base 10) of *E. coli* in brain heart infusion broth, as determined by linear regression analysis, was 0.93/h, corresponding with a doubling time of 19 min. Both ceftriaxone and cefepime were active at very low concentrations (Fig. 1). A concentration of 0.02 to 0.025 μg of cefepime per ml inhibited growth, and concentrations above 0.03 μg/ml resulted in killing. The $E_{R,max}$ of cefepime on *E. coli* was approached at concentrations above 0.05 μg/ml. For ceftriaxone, a concentration of 0.03 to 0.04 μg/ml inhibited growth, 0.05 μg/ml resulted in killing, and the $E_{R,max}$ was approached at concentrations above 0.08 μg/ml. Ceftazidime was less potent than either cefepime or ceftriaxone: a concentration of 0.1 μg/ml gave inhibition of growth, 0.125 μg/ml resulted in killing, and the $E_{R,max}$ was approached at concentrations above 0.5 μg/ml. The observed $E_{R,max}$s were similar for cefepime, ceftriaxone, and ceftazidime (3.7 to 3.9/h). Cefoperazone was the least potent of the four drugs investigated, giving inhibition of growth in the range of 0.1 to 0.15 μg/ml and killing above 0.2 μg/ml. The $E_{R,max}$ of

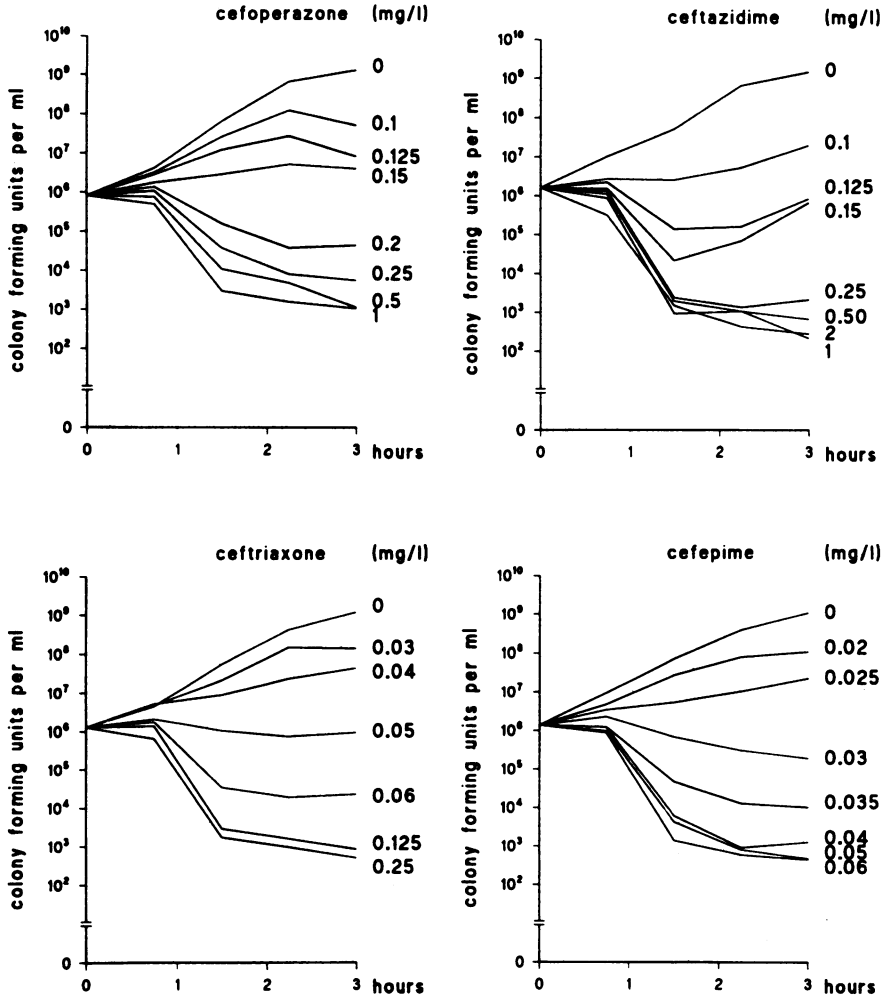

FIG. 1. In vitro growth of *E. coli* in the presence of various concentrations of the cephalosporins.

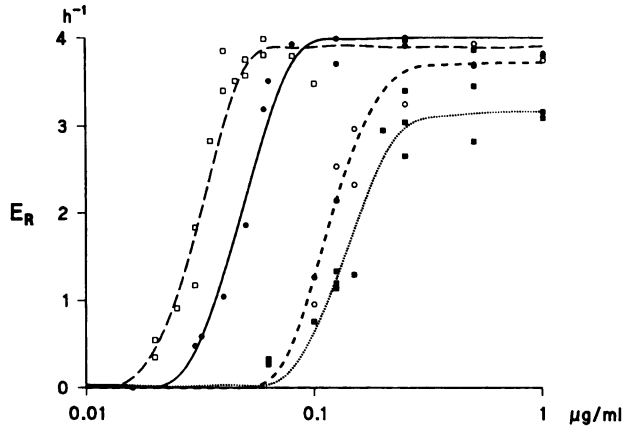

FIG. 2. Concentration-effect relationship of the four cephalosporins against *E. coli* in vitro, as determined in short-term growth experiments and established by using the Hill equation. Symbols: ●, ceftriaxone; □, cefepime; ○, ceftazidime; ■, cefoperazone.

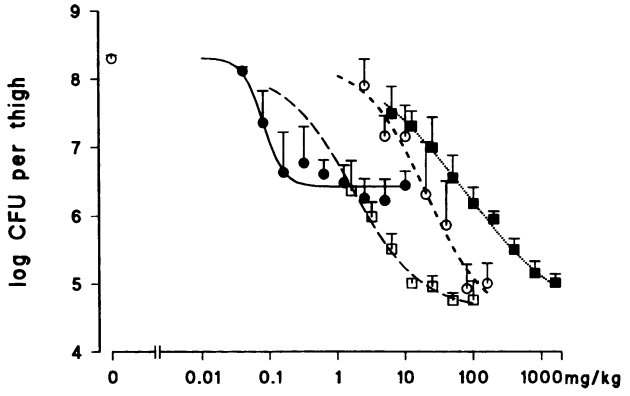

FIG. 3. Effect of the four cephalosporins in vivo on the number of CFU of *E. coli* in a thigh muscle. Each symbol on the curve represents the geometric mean and standard deviation of at least four mice. The dose-effect relationships were established for the four cephalosporins by using the Hill equation. Symbols: ●, ceftriaxone; □, cefepime; ○, ceftazidime; ■, cefoperazone.

cefoperazone was approached at concentrations above 0.5 μg/ml. The observed $E_{R,max}$ was 3.1/h, which was slightly lower than the $E_{R,max}$s of the other cephalosporins.

The mathematical concentration-effect relationships of the four cephalosporins, determined by using equation 2, are shown in Fig. 2. The actual values of the parameters of the Hill equation are given in Table 2. The EC_{50}s for cefepime, ceftriaxone, ceftazidime, and cefoperazone were 0.031, 0.048, 0.117, and 0.139 μg/ml, respectively.

Antibacterial effect in vivo. In irradiated, untreated control mice, the number of *E. coli* per thigh increased exponentially from 10^7 at 1 h after infection to 10^8 at 5 h. All four cephalosporins caused a marked reduction of the number of viable *E. coli* per thigh (Fig. 3). Ceftriaxone was the most potent of the four, and was antibacterially effective in doses above 0.04 mg/kg. The $E_{N,max}$ was reached at a dose of 1.25 mg/kg; at this dose the number of viable *E. coli* in the thigh decreased from 1×10^7 at 1 h after infection to 2×10^6 at 5 h. This corresponds with an $E_{N,max}$ of 1.9. The ED_{50} of ceftriaxone was 0.116 mg/kg. Cefepime was less potent than ceftriaxone (ED_{50} = 1.78 mg/kg), but its $E_{N,max}$ was higher. A single dose of cefepime reduced the number of viable *E. coli* in the thigh to approximately 8×10^4, which corresponds to an $E_{N,max}$ of 3.5. The values of $E_{N,max}$ for ceftazidime and cefoperazone were similar (3.9 to 4.1) to that of cefepime, but the potency of ceftazidime and cefoperazone was lower (ED_{50} = 20.6 and 74 mg/kg, respectively). The actual values of the parameters of the Hill equation are shown in Table 2. The relationship between log dose and effect was approximately linear in the dose ranges of 0.05 to 0.5 mg/kg for ceftriaxone, 0.5 to 10 mg/kg for cefepime, 2.5 to 80 mg/kg for ceftazidime, and 10 to 1,600 mg/kg for cefoperazone.

Pharmacokinetics. The pharmacokinetics of the four cephalosporins in the plasma of mice are shown in Table 3 and Fig. 4. Cefepime, ceftazidime, and cefoperazone were rapidly cleared from the plasma (apparent elimination half-lives, between 12 and 22 min), whereas the clearance of ceftriaxone was much slower (apparent elimination half-life, almost 45 min). Ceftazidime and cefepime showed virtually no binding to murine plasma protein (less than 5%), binding of cefoperazone amounted to 5 to 10%, and binding of ceftriaxone amounted to 60%. From these data, the length of time that the free drug concentration exceeded the MIC (with the MIC determined in the presence of 10% murine plasma) was calculated (Table 3).

DISCUSSION

The results of the present study show that the in vivo pharmacodynamics of the four cephalosporins against *E. coli* generally reflect their in vitro pharmacodynamics. Cefepime, ceftazidime, and cefoperazone had approximately the same maximum effects in vivo and in vitro. Furthermore, the order of potency of these three drugs was the same in vitro and in vivo: cefepime was the most potent, ceftazidime had an intermediate potency, and cefoperazone was the least potent. This similarity between the in vitro and in vivo orders of potency is probably a result of the pharmacokinetics of these three drugs: neither their half-lives in plasma nor their protein bindings differed greatly. However, ceftriaxone exhibited rather unexpected in vivo pharmacodynamics: its maximum in vitro effect was similar to those of cefepime and ceftazidime (Table 2), but its maximum in vivo antibacterial effect was much lower than those of cefepime and ceftazi-

TABLE 2. In vitro and in vivo pharmacodynamic parameters of the four cephalosporins[a]

Cephalosporin	In vitro			In vivo		
	$E_{R,max}$/h	*s*	EC_{50} (μg/ml)	$E_{N,max}$	*s*	ED_{50} (mg/kg)
Cefepime	3.8 (3.6–4.0)	6.5 (4.3–8.8)	0.031 (0.029–0.032)	3.5 (3.2–3.8)	0.9 (0.6–1.1)	1.7 (1.3–2.1)
Cefoperazone	3.1 (2.8–3.4)	4.6 (1.8–7.4)	0.139 (0.120–0.158)	4.1 (3.4–4.8)	0.5 (0.4–0.7)	74 (22–126)
Ceftriaxone	3.9 (3.7–4.1)	5.8 (4.2–7.3)	0.048 (0.045–0.050)	1.9 (1.5–2.2)	2.9 (1.0–4.8)	0.08 (0.06–0.10)
Ceftazidime	3.7 (3.5–4.0)	4.6 (2.5–6.7)	0.117 (0.108–0.127)	3.9 (2.5–5.3)	1.0 (0.4–1.5)	20.6 (3.7–37.5)

[a] The 95% confidence intervals are given in parentheses. *s* is a parameter reflecting the slope of the concentration-effect relationship or dose-effect relationship, EC_{50} is the concentration that establishes 50% of the in vitro maximum effect, and ED_{50} is the dose that establishes 50% of the in vivo maximum effect.

TABLE 3. Pharmacokinetics of cephalosporins in plasma of mice[a]

Cephalosporin	Dose (mg/kg)	AUC_{0-4} (μg · h/ml)	$t_{1/2}$ (min)	C_{max} (μg/ml)	% Unbound drug	Time above MIC (h)
Cefoperazone	1,600	896.0	22.1	955.8	90–95	4.7
Ceftazidime	160	98.2	12.2	131.6	95–100	3.8
Ceftriaxone	5	21.5	44.7	19.9	40	5.2
Cefepime	100	69.5	13.5	138.0	95–100	2.4

[a] AUC_{0-4} is the area under the concentration-time curve in plasma, $t_{1/2}$ is the apparent elimination half-life, and C_{max} is the peak concentration in plasma. The MIC was determined in the presence of 10% murine plasma.

dime. In fact, ceftriaxone was slightly more bacteriostatic in vivo (reduction from 1×10^7 to 2×10^6 CFU per thigh), whereas a maximally effective single dose of any of the other three cephalosporins reduced the number of bacteria in the thigh substantially, namely to approximately 8×10^4 CFU per thigh. A satisfactory explanation for this comparatively low maximum in vivo effect of ceftriaxone cannot be offered. Although the pharmacokinetics of ceftriaxone in plasma of mice differ from those of the other three cephalosporins, this cannot explain the divergent pharmacodynamic characteristics of ceftriaxone observed in vivo, because the apparent elimination half-life of ceftriaxone was much longer (44 min) than those of the other cephalosporins (12 to 22 min). A long elimination half-life of beta-lactam antibiotics in plasma is advantageous for the treatment of an experimental infection (11). It appears that ceftriaxone is more potent at low dosages than cefepime (Fig. 3), although it should be noted that the dose-effect curve of cefepime at dosages below 1.6 mg/kg was obtained by extrapolation. The higher in vivo potency of ceftriaxone can be explained by its relatively long apparent elimination half-life. The higher protein binding of ceftriaxone relative to the other cephalosporins (60% versus less than 10% for the other cephalosporins) also does not explain its comparatively low maximum in vivo effect. It is generally assumed that only unbound drug is antimicrobially active and available for diffusion into the interstitial space (13). If the high degree of protein binding of ceftriaxone (60%) is taken into account, a calculation shows that in mice even a dose of 5 mg of ceftriaxone per kg gives plasma concentrations of unbound drug that exceed the MIC for this

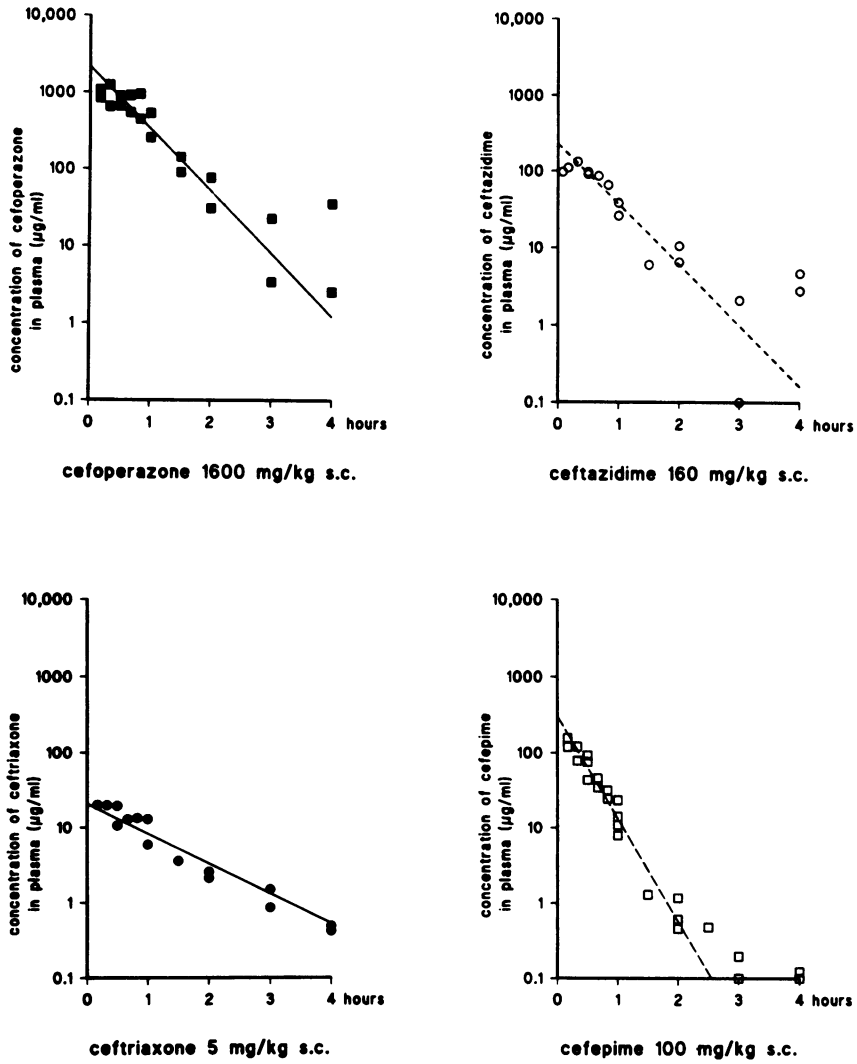

FIG. 4. Pharmacokinetics of the four cephalosporins in plasma. The drugs were administered subcutaneously at the following doses: cefoperazone, 1,600 mg/kg; ceftazidime, 160 mg/kg; ceftriaxone, 5 mg/kg; and cefepime, 100 mg/kg.

E. coli over a period of 5.2 h, compared with only 2.4 h for a dose of 100 mg of cefepime per kg.

One may argue that the high protein binding of ceftriaxone causes a delay in the buildup of free drug in the interstitium. This, coupled with the relatively fast elimination of the four cephalosporins under study in mice and the short observation period used in this study, could bias the observations in favor of cefepime, ceftazidime, and cefoperazone. However, the low molecular weight of the four cephalosporins cannot account for a delay of more than a few minutes before the actual equilibrium is achieved. Furthermore, one expects that the results would be biased in favor of ceftriaxone if the elimination half-life plays a pivotal role in attaining a maximum effect.

With respect to the potency of the cephalosporins, our results concerning the in vivo effect of ceftriaxone are consistent with those of Frimodt-Møller et al. (3), who found that ceftriaxone was the most potent of 14 cephalosporins studied in an experimental pneumococcal infection model in mice. However, their conclusion that ceftriaxone had a superior in vivo antibacterial effect differs from ours. Their infection model (the mouse protection test) fundamentally differs from the thigh muscle infection model we employed, since they did not use granulocytopenic mice and did not try to establish a maximum effect. In their model, no attempt was made to quantify bacterial numbers, and this led to a less precise estimate of the antibacterial effect. The use of granulocytopenic mice in our experimental infection model has the added advantage of increasing the precision of the estimate of the antibacterial effect of the antimicrobial agent because of the absence of any synergistic antibacterial effect of granulocytes (9). Furthermore, to exclude possible interference by the humoral immune system, we used an *E. coli* strain that is resistant to murine serum.

In current clinical practice, dosage schedules of beta-lactam antibiotics are intended to keep the free plasma concentration of the drug above the MIC for as long as possible (2). Theoretically, one would expect frequent administration of low doses to be more efficacious than less frequent administration of high doses. If it is assumed that a maximum therapeutic effect can be obtained by the implementation of these dosage schedules, it is important to know which drug provides the highest maximum in vivo effect. However, most of the reports on studies comparing antimicrobial agents in vitro and in vivo are concerned with potency, and it is implicitly assumed that the most potent antimicrobial agent is also the most efficacious. Although the present study is limited in the sense that it includes just one test strain, a relatively short observation period, and only single-dose regimens, the results show that a clear distinction should be made between antibacterial potency and maximum antibacterial effect. This finding may be especially relevant for immunocompromised patients, who are entirely dependent on antimicrobial therapy for recovery from infection. For this group of patients, the antimicrobial agent with the highest maximum in vivo effect must be the agent of choice.

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