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Pharmacokinetics and Clinical Use of Cephalosporin Antibiotics

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Keyphrases □ Cephalosporins—11 antibiotic derivatives, pharmacokinetics, absorption, metabolism, excretion, clinical considerations, review □ Antibiotics—11 cephalosporin derivatives, pharmacokinetics, absorption, metabolism, excretion, clinical considerations, review □ Pharmacokinetics—11 cephalosporin antibiotic derivatives, absorption, metabolism, excretion, clinical considerations, review □ Absorption—11 cephalosporin antibiotic derivatives, pharmacokinetics, clinical considerations, review □ Metabolism—11 cephalosporin antibiotic derivatives, pharmacokinetics, clinical considerations, review □ Excretion—11 cephalosporin antibiotic derivatives, pharmacokinetics, clinical considerations, review

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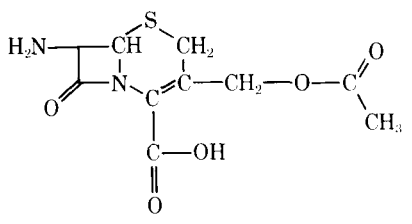
Cephalosporins are a series of compounds containing the 7-aminocephalosporanic acid [7-amino-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid acetate] nucleus (I). Although cephalosporin C was one of the original and active members of the series, being derived from the fermentation products of *Cephalosporium acremonium*, it has not proved to be useful clinically. However, I has been used as the basis for the synthesis of various derivatives (II–XII). An excellent review of the history, isolation, synthesis, analysis, and physicochemical properties of cephalosporins was published (1). The purpose of this work is to review the pharmacokinetics and clinical use of cephalosporin antibiotics.

PHARMACOLOGY AND PHARMACOKINETICS

Cephalexin—Cephalexin, 7-(D-2-amino-2-phenylacetamido) - 3 - methyl - 8 -oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid (II), is an orally active semisynthetic derivative of I with a spectrum of activity against both Gram-positive and Gram-negative bacteria. It has relatively low solubility in water; *i.e.*, 1–2 mg was dissolved in 1 ml of water at 37° (2). At pH 2 and 8, the solubility was increased to approximately 120 and 100 mg/ml, respectively (2). The increase in solubility as a function of pH is due to the zwitterionic nature of the drug. Cephalexin is very unstable at physiological pH (3), showing the presence of decomposition products within 20 min of solution in water. It shows less deterioration at low pH. However, the drug is most stable at pH 4.5, its isoelectric point, and may be kept frozen when dissolved in biological fluids for long periods ($t_{1/2}$ > 90 days) (2).

Studies of the protein binding of cephalexin showed that, in concentrations usually found in therapy, less than 10% of the total drug was bound to human plasma proteins (2). At a total cephalexin concentration of 3.2 μg/ml, 6% of the total drug was in the protein-bound state (2). Cephalexin is removed from the body solely by the processes of glomerular filtration and excretion in the kidney tubules.

Cephalexin is advocated for the treatment of infections of the upper and lower respiratory tract, genitourinary system, skin and soft tissue, and bones and joints and for certain other infections due to susceptible organisms. An excellent review of its antibacterial, pharmacological, and therapeutic properties was presented (4). Blood concentrations of the drug, after the usual therapeutic dose, are high enough to be bactericidal against most susceptible organisms (5).



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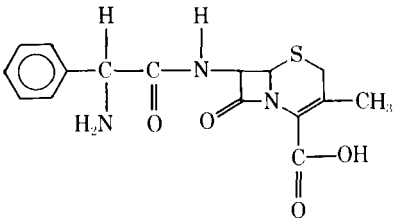


II: cephalexin

Absorption—The oral and intramuscular absorption of cephalexin in normal human subjects has been studied (2, 5–19). After oral administration, absorption was rapid and complete, with peak levels being reached within 1 hr (2, 14). The time to reach peak levels may vary between individuals after administration of the drug in capsule form. This finding can be attributed to a lag time in the absorption process due to dosage form effects. Following a 500-mg dose given as a 5% suspension, cephalexin appeared in the serum in 9 min compared with 38 min when given in capsule form (14).

The peak height is dose dependent, usually reaching a level of 18 μg/ml after a 500-mg dose (14, 20). Single doses of 125, 250, 500, and 1000 mg in 12 fasting subjects produced average peak levels of 4.5, 9, 18, and 32 μg/ml, respectively, at 1 hr (20). Some investigators (6, 10, 17, 19, 21) found peak blood levels that were slightly lower than those reported by others (5, 7, 8, 13, 20, 22). Lower peak values may be related to the time food is ingested.

When cephalexin is administered with food, there is a delay in the onset of absorption, a lower peak, and a prolongation of blood levels (14, 20). A total of 82% of a 500-mg dose was found in the urine when the patients were fasting compared to 73% when the dose was taken with food, indicating that the total amount of drug absorbed was not appreciably altered (20). Similarly, a 1-g dose of cephalexin resulted in a peak serum level of approximately 31 μg/ml in fasted subjects but only 20.9 μg/ml after a standard meal (11). The peak time was increased to 2 hr after administration. Similar results were also reported (23). Apparently, small amounts of food do not significantly affect the absorption process (17, 24).

Absorption and excretion of cephalexin are delayed and peak serum levels are less in newborns and infants in the first 6 months of life. Peak serum levels occurred after 3 hr in these patients, 2 hr in infants 9–12 months in age, and 1 hr in children older than 1 year (25–29). Food, *i.e.*, milk, had the same effect in the infant as did food in the adult; *i.e.*, lower peak levels occurred at later times (26).

The influence of disease on cephalexin absorption is variable. In children (18–20 months) with a malabsorption syndrome, a reduction was reported in the excretion of unchanged cephalexin (28). With a dose of 50 mg/kg, however, effective blood levels were

reached but did not peak until 4 hr postadministration. In another study, absorption was significantly impaired in one of three patients with pernicious anemia and obstructive jaundice (30). Reports of impaired absorption due to infectious diseases are lacking with the exception of the report of decreased plasma levels with a prolonged peak time in patients with severely impaired kidney function (creatinine clearance of 0–2.5 ml/min) (18).

Distribution—Cephalexin is widely distributed in body tissues. The only tissues in which concentrations of the drug were higher than in serum were the kidneys and liver (31, 32). Significant levels of the drug in animals also were demonstrated in other tissues, including lung, spleen, fat, heart muscle, and bone. In humans, levels in the appendix, stomach, gallbladder, omentum, peritoneum, and vein and tumor tissues were lower than in serum following an oral dose of 0.5 or 1.0 g (33). Bile levels were lower than serum levels after a dose of 0.5 or 1.0 g of cephalexin (34, 35). Peak levels of 0.3–32.0 μg/ml were observed at 2–3 hr. Probenecid administration significantly increased biliary levels of the antibiotic, probably due to interference with renal excretion producing higher blood levels. Low tissue levels (<1 μg/ml) were found in the gallbladder wall suspension of two patients.

Low levels of the drug in saliva were reported (36, 37). Detectable levels in the aqueous humor at 1 hr and peak levels of 0.75–2.0 μg/ml at 2–3 hr after an oral dose of 2 g were reported (38). These concentrations occurred whenever the serum level exceeded 10 μg/ml.

Cephalexin does not appear to penetrate into the cerebrospinal fluid in significant amounts in the absence of meningeal inflammation (28, 30, 39).

The appearance of cephalexin in the serum and exudate of normal and leukemic patients was studied (40). After a 500-mg oral dose, peak serum levels (12 μg/ml) were obtained at approximately 1.5 hr. Exudate levels reached a peak of 5 μg/ml within the same period and appeared to decline at a slow rate. After 4 hr, the level declined to approximately 3.5 μg/ml, illustrating that cephalexin rapidly appears in skin exudates, with a half-life of elimination from that fluid of approximately 4 hr.

In leukemic patients, distribution into skin exudate was decreased. The ratio of the mean exudate level, expressed as a percent of the serum level, between normal and leukemic patients was 210, 17, and 3.2 after 1, 2, and 3 hr postadministration, respectively. The data suggest that the volume of distribution of the antibiotic may be changed in the leukemic patient. It is not clear if this result is due to the disease state or to the influence of antineoplastic drug therapy.

Metabolism and Excretion—Cephalexin is not metabolized in the body and is rapidly excreted unchanged, principally by the kidney, although small amounts are also excreted in the bile. Studies with labeled ^{14}C-cephalexin in rats and mice showed that the drug is not metabolized and is eliminated unchanged *via* the kidney (41). In rats, 84% of an orally administered dose appeared in the urine after 24 hr, with 77% appearing in the first 4 hr. Fifteen percent was recovered in the feces and was attributed to biliary excretion. In humans, cephalexin does not undergo enzymatic metabolism (42). Excretion of cephalexin in the urine occurs partly through glomerular filtration (66%) and partly by tubular secretion (33%) (24).

The renal clearance of cephalexin was calculated to be 210 ml/min/1.73 m^2, with 72.2% of the total plasma clearance of the drug being accounted for by renal clearance (43). The ratio between the renal and plasma clearances was 1.69, indicating a significant (28%) nonrenal excretion of cephalexin. Since no metabolite of cephalexin has been found (2), it is difficult to account for the apparent nonrenal excretion. Kirby and Regamey (44) reported values of 252 ± 5 and 248 ± 11 ml/min/1.73 m^2 for renal and serum clearances, respectively. When these values are considered, it can be seen that the entire dose can be accounted for through renal excretion. Other values reported for the plasma clearance of cephalexin are 260 and 376 ml/min (8, 11).

The administration of probenecid shortly before or simultaneously with cephalexin enhances both the peak serum concentration and the duration of activity of the antibiotic in the serum (6, 11, 17, 20). The administration of 500 mg of probenecid with 1 g of cephalexin caused an increase in the mean peak serum level of 79% over the mean peak serum level achieved with a similar dose without probenecid (*i.e.*, an increase from 20.9 to 36.7 μg/ml) (11). Levels at 6 hr were also increased, ranging from 4.5 to 9.7 μg/ml (mean of 7.1 μg/ml). Similar findings also were reported (7, 20, 45).

In subjects with normal renal function, cephalexin had a serum half-life of approximately 0.6–2.1 hr after oral administration (2, 7, 8, 10, 12, 14, 16, 18, 19, 39, 42–47), with a mean and standard deviation of 1.2 ± 0.47 hr. In fasting subjects, the mean serum half-life was 49.5 min, but this value increased to 76.5 min in subjects who received cephalexin with food (11). This latter value probably was due to the half-life being calculated during the time when both absorption and elimination were occurring simultaneously. The serum half-life following oral administration is prolonged in neonates and infants. A half-life of approximately 5 hr in newborn infants and of 2.5 hr in infants 3–12 months of age was demonstrated (27, 29).

Due to its extremely short half-life and long dosing interval (4–6 hr), little accumulation of cephalexin in the serum of patients with normal renal function has been observed (24, 48). Blood level curves and urinary excretion values following doses of 250 or 500 mg of cephalexin every 6 hr were unchanged after 1, 3, and 5 days (20). Similarly, the blood level curves and mean urinary recovery values in six subjects after 1-g doses every 6 hr were not significantly different from those following a single dose (11). Some accumulation was noted by O'Callaghan *et al.* (14), who found that both peak concentration and the length of time the serum levels exceeded 12.5 μg/ml

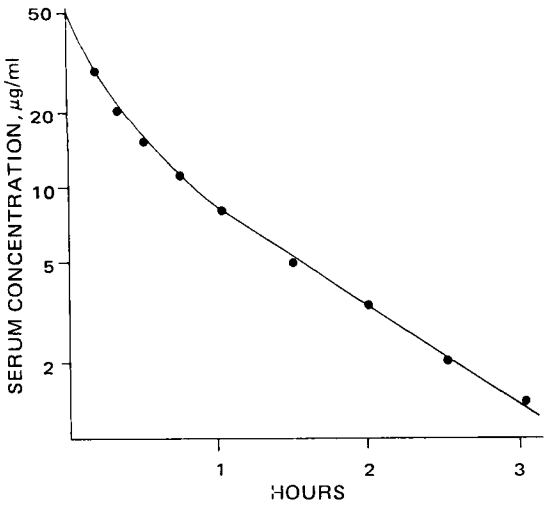


Figure 1—*Serum levels for cephalexin administered intravenously (rate constants for data generation from Table I).*

were significantly increased after the fifth 1-g dose (every 6 hr). These increases did not occur after doses of 500 mg, which is to be expected for a drug with a short half-life and relatively long dosing interval.

Between 82 and 100% of an orally administered dose appeared in the urine after 250- and 500-mg doses of cephalexin (13, 50). However, urinary recoveries of 29–89% were reported in patients with urinary tract infections (49). Urinary levels of the antibiotic are, therefore, high, and peak levels in the urine may be more than 100 times higher than in the serum. Thornhill *et al.* (17) found mean urinary concentrations in a 6-hr period of 830 μg/ml and 1.1 mg/ml after 250 and 500 mg of cephalexin, respectively. Mean urinary concentrations of 2.3 and 5.0 mg/ml were observed in the first 1–2-hr period following administration of 0.5 and 1.0 g of cephalexin, respectively (24). Similar results also were observed (6, 20).

The clearance of cephalexin is prolonged in the presence of renal dysfunction, resulting in higher and more sustained serum levels; *i.e.*, an increase in the serum half-life occurs as renal function decreases (18, 19, 39, 51–55). Serum half-lives of 7.7, 10.8, and 13.9 hr were observed in subjects with creatinine clearances of 13.5, 9.2, and 4 ml/min, respectively (19). No significant increase was found in the serum half-life in patients with creatinine clearances of 45 ml/min; but when kidney function fell below one-fourth of normal, *i.e.*, creatinine clearance of less than 30 ml/min, the half-life increased significantly (55). Similarly, only moderate increases were noted in plasma half-lives when the creatinine clearance was between 10 and 40 ml/min, but a rapid increase was noted thereafter when the value fell below 10 ml/min (52).

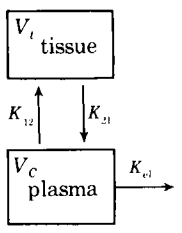
Peak serum levels after single oral doses of 500 mg of cephalexin were reached in 1–2 hr, with appreciable levels still present at 12–24 hr (53). In patients with a creatinine clearance of less than 3 ml/min, however, the peak serum levels occurred at 4–8 hr, and levels of 5 and 6 μg/ml were still present at 48 and 60 hr, respectively. Detectable levels were present for 72–90 hr. A delay in the time to reach the peak serum level occurred in patients with severe renal failure (18, 51). Repeated administration of the drug in patients with renal impairment led to accumulation (18, 19).

Urinary excretion of cephalexin is inversely related to the serum half-life and directly related to the creatinine clearance. Less than 5% of a single dose of cephalexin was excreted within 24 hr in patients with creatinine clearances of less than 2.5 ml/min (18). The urinary excretion of cephalexin at 6, 24, and 48 hr after a 500-mg dose was 7.5, 23, and 37%, respectively (51). Satisfactory antibacterial levels were attained. Satisfactory urine levels were found in patients with creatinine clearances of 3 ml/min (56); however, in another report (19), acceptable levels were not achieved if the creatinine clearance was less than 9 ml/min.

Hemodialysis resulted in a fourfold decrease in serum levels within 7 hr (54). Similarly, a fivefold reduction in half-life was reported when hemodialysis was employed for 12 hr (18, 53). Peritoneal dialysis resulted in a twofold decrease in serum levels after 7 hr (54). Bennett *et al.* (57) described an adjusted dosage regimen as a guide in treating patients with various degrees of renal failure.

Pharmacokinetic Considerations—When the available literature blood level data after intravenous administration of cephalexin are carefully examined (Fig. 1), it appears that the drug follows a two-compartment open model (Scheme I). All investigators analyzed their data using a one-compartment open model. This model may lead to errors in the calculation of the volume of distribution and the elimination and absorption rate constants (58, 59). A reevaluation of selected literature data is shown in Tables I and II. The half-lives reported using a one-compartment open model analysis are equivalent to the half-life of the β-phase. The value of the half-life of the distributive (α) phase was 0.15 hr. Therefore, to describe completely the time course of the drug in plasma, it is necessary to remove at least two or three blood samples within the first 45 min after administration.

Cephalexin, which is only 6% protein bound in the therapeutic range, is distributed widely within plasma water and some extracellular water. The volume of the central compartment using a two-compartment open model analysis is 10.8 liters. In contrast, the volume of distribution of cefazolin (V), another cephalosporin antibiotic, is approximately 4 liters. Cefazolin, being 90% protein bound, is distributed mainly in the plasma water. When the volume of distribution found for cephalexin is compared to that of



Scheme I—Two-compartment open model

Table I—Pharmacokinetic Parameters for Cephalexin Administered Intravenously (Literature Data)[a]

Parameter	Literature Reference 12	14	45	47	Mean ± *SD*
α, hr^{-1}	4.327	4.645	4.382	3.710	4.270 ± 0.400
β, hr^{-1}	0.976	0.773	0.671	0.646	0.766 ± 0.151
K_{12}, hr^{-1}	1.151	1.682	1.546	1.211	1.384 ± 0.238
K_{21}, hr^{-1}	2.369	1.899	1.791	1.846	1.976 ± 0.266
K_{el}, hr^{-1}	1.783	1.889	1.716	1.299	1.671 ± 0.260
$T_{1/2}\alpha$, hr	0.160	0.149	0.159	0.187	0.163 ± 0.016
$T_{1/2}\beta$, hr	0.710	0.897	1.095	1.072	0.943 ± 0.179
V_c, liters	14.544	9.018	8.902	10.681	10.786 ± 2.633
Vd_{ss}, liters	21.612	16.748	17.355	17.687	18.350 ± 2.208
Vd_β, liters	26.568	22.050	23.301	21.462	23.345 ± 2.281
Vd_{ext}, liters	34.997	30.989	33.760	27.271	31.754 ± 3.426
$t_{1/2}$ reported by author, hr	0.7	0.8	1.1	0.61	—

[a] Analysis of data using a two-compartment open model (Scheme I).

cefazolin, the effect of protein binding on the volume of distribution of a drug is evident.

The volume of the tissue compartment into which cephalexin distributes can be found by using Eq. 1:

$$V_t = \frac{K_{12}}{K_{21}} V_c \qquad \text{(Eq. 1)}$$

where K_{12}, K_{21}, V_c, and V_t are defined in Scheme I. The volume of the tissue compartment using this formula is 7.6 liters. This value gives a total volume of distribution within the body of 18.4 liters, a value that is usually reported as Vd_{ss}, the volume of distribution at steady state.

The current literature contains only two references to values of the volume of distribution of cephalexin. A value of 15 ± 2.3 liters was found (43) after a 3-hr intravenous infusion. The formula used was:

$$Vd = \frac{i}{(p)(K_{el} \times 10^3)} \qquad \text{(Eq. 2)}$$

where i is the infusion rate, p is the concentration of cephalexin in the plasma at steady state, and K_{el} is the elimination rate constant for cephalexin. The value of K_{el} was determined by using a log-linear regression on the postdistribution portion of the blood level *versus* time curve after infusion. The value of K_{el} obtained in this manner is analogous to the value of beta obtained from a two-compartment open model analysis. Therefore, the value determined by the use of Eq. 2 is equivalent to the value of Vd_β, the volume that can be determined during the β-phase in a two-compartment open model.

The value of Vd_β shown in Tables I and II when the data were analyzed with a two-compartment open model is approximately 23 liters, which is significantly greater than the reported value of 15 liters (43). The reason for the difference becomes clear when Eq. 2 is examined. If the value of K_{el} were too large, it would cause the value of the volume of distribution calculated by this formula to be too small. One factor that could cause the value of K_{el} to be very large would be the method by which it was obtained. Since it has been shown that cephalexin follows two-compartment open model kinetics, it follows that after infusion is terminated, the resultant curve will have an α- (distributive) phase and a β- (disposition or elimination) phase. Therefore, use of the entire curve after infusion instead of the late postinfusion curve results in an overestimation of the value of K_{el}.

The effect of using this method of analysis of two-compartment open model data is apparent if Fig. 2 is examined. A shortening of the half-life with an increased value of the rate constant is the result of the incorrect analysis of serum level data. deMaine and Kirby (43) reported a relatively short half-life (0.61 hr) for cephalexin. It is difficult, however, to determine if α-phase data were utilized in their determination.

A value of 37 liters (range of 26–53 liters) was reported for cephalexin after intramuscular administration (8). This volume of distribution was determined using:

$$Vd = \frac{\text{dose}}{(AUC)(K_{el})} \qquad \text{(Eq. 3)}$$

where AUC represents the area under the plasma level *versus* time curve from time zero to time infinity. Since the value of K_{el} is analogous to the value of beta used in the two-compartment open model, the volume found by the use of this equation is equal to the value of Vd_β.

The value of 37 liters (8) is much larger than the value of Vd_β determined using the two-compartment open model. The overestimation (8) is attributable to

Table II—Pharmacokinetic Parameters for Cephalexin Administered Orally (Literature Data)[a]

Parameter	Literature Reference 12	13	14	Mean ± *SD*
α, hr^{-1}	3.609	4.247	4.463	4.106 ± 0.444
β, hr^{-1}	0.661	0.989	0.936	0.862 ± 0.176
K_a, hr^{-1}	2.388	1.493	1.889	1.923 ± 0.448
K_{12}, hr^{-1}	1.173	1.000	1.203	1.125 ± 0.110
K_{21}, hr^{-1}	1.652	2.496	2.572	2.240 ± 0.511
K_{el}, hr^{-1}	1.445	1.740	1.624	1.603 ± 0.149
Lag time, hr	0.422	0.280	0.234	0.312 ± 0.098
$T_{1/2}\alpha$, hr	0.192	0.167	0.155	0.171 ± 0.019
$T_{1/2}\beta$, hr	1.048	0.724	0.741	0.837 ± 0.182
V_c, liters	16.800	10.442	9.919	12.387 ± 3.831
Vd_{ss}, liters	28.734	15.213	14.558	19.501 ± 8.002
Vd_β, liters	36.702	19.030	17.211	24.314 ± 10.767
Vd_{ext}, liters	49.989	26.023	21.382	32.464 ± 15.353
$t_{1/2}$ reported by author, hr	1.1	—	0.8	—

[a] Analysis of data using a two-compartment open model (Scheme I).

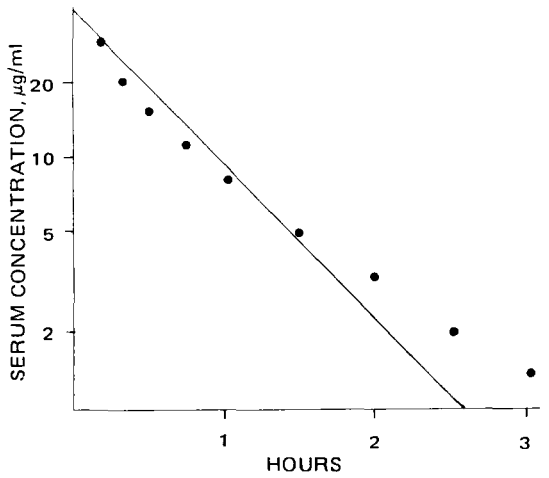
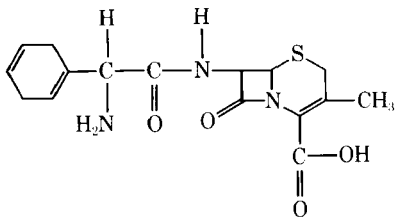


Figure 2—*Log-linear regression on biphasic data.*

an underestimation of the value of K_{el}. It appears that these investigators overestimated the half-life of cephalexin (1.1–2.3 hr) due to the fact that absorption and elimination occurred during the entire sampling time. In studies where the absorptive processes are allowed to vary due to improper fasting or precipitation at the site of muscular injection, the apparent absorption rate constant might be smaller and the $t_{1/2}$ for elimination might appear longer than expected. These phenomena could explain the wide range of elimination half-lives reported in the oral studies.

Use of the one-compartment open model to fit cephalexin data results in errors in the volume of distribution term. Since the therapeutic range of the drug is high, the use of the larger *Vd* (extrapolated) term as a one-compartment open model volume of distribution will not compromise the efficacy of cephalexin therapy since the normal dose results in blood levels that are usually well above the minimum inhibitory concentration (MIC). Since the half-life of cephalexin is short compared to the normal dosing interval (6 hr), drug accumulation is negligible and errors in calculation of the absorption rate constant are not significant. It appears that routine pharmacokinetic analysis of cephalexin could be accomplished using the one-compartment open model treatment without introducing serious error, provided the $t_{1/2}$ was determined correctly from intravenous data, *i.e.*, after the distributive phase and the volume terms are properly interpreted.

Cephradine—Cephradine, 7-[D-2-amino-2-(1,4-cyclohexadien-1-yl)acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monohydrate (III), is a semisynthetic cephalosporin



III: cephradine

used orally, intramuscularly, and intravenously. The structure of cephradine is similar to that of cephalexin, the only difference being in the six-membered ring. Cephalexin has three double bonds forming an aromatic system while cephradine has two double bonds in the same ring. The antibacterial activity of cephradine is similar to that of cephalexin (60).

Cephradine is a white crystalline powder with a molecular weight of 349.4 (61). The synthesis of cephradine has been discussed (62). Cephradine is freely soluble in aqueous solvents. It is a zwitterion, containing both an alkaline amino group and an acidic carboxyl group. In the pH range of 3–7, cephradine exists as an internal salt (63). Cephradine is stable for 24 hr at 25° within the pH range of 2–8. Since it is stable in acidic media, there is little loss of activity in the gastric fluid; losses of less than 7% have been reported (64).

Cephradine is weakly bound to human serum proteins. In one study (63), the drug was less than 20% bound to the serum proteins. At a serum concentration of 10–12 μg/ml, 6% of the total drug was in the protein-bound complex. Another study (65) found that at a total concentration of 10 μg/ml, 28% of the drug was in the protein-bound state; at a total concentration of 100 μg/ml, 30% of the drug was in the protein-bound state. This study also showed that the addition of serum to cephradine decreased antibiotic activity. Another study (61) showed that the protein binding of cephradine varied from 8 to 20%, depending on the concentration of the drug. However, a study by Gadebusch *et al.* (64) found no change in the MIC of cephradine toward either *Staphylococcus aureus* or *Escherichia coli* after the addition of human serum.

Absorption—Cephradine has been administered orally, intramuscularly, and intravenously and is well absorbed using these routes. This large degree of absorption is evidenced by recoveries of approximately 100% of the administered dose in the urine (63, 66–69). In one study (63), tritiated cephradine was administered orally to human subjects in the form of a 250-mg capsule. Urine and feces were collected and assayed for the drug; 92% of the drug was present in the urine at the end of 24 hr, while minimal amounts were present in the feces at the end of 72 hr. These findings are evidence for the claim that cephradine is well absorbed orally and apparently not excreted in the bile.

After oral administration of cephradine, the time of peak serum concentration was at 1 hr with peak concentration in the serum ranging from 6 to 7 μg/ml after a 250-mg capsule (63, 68, 69). After the administration of 500 mg of cephradine in the form of two 250-mg capsules, peak serum levels were in the range of 11–18 μg/ml (60, 63, 66–68). After the administration of 500 mg of cephradine as an oral suspension, a peak serum concentration of 19.5 μg/ml was found at 0.5 hr (68). When human subjects were given 1 g of cephradine, the peak levels ranged from 15 to 24 μg/ml (60, 68).

After the administration of 1 g im, a peak level of 10.4 μg/ml at 2 hr was attained (63). While the peak

concentration of cephradine after intramuscular injection was lower than that after oral administration, the areas under the curve were identical. One advantage of the intramuscular route over the oral route was that the concentration of the antibiotic in the serum was below 1 μg/ml at 4 hr after oral administration while the concentration after intramuscular administration was 6.8 μg/ml (63).

One study (66) found that the rate of absorption after oral administration was influenced by the presence of food but that the extent of absorption was not affected. Serum levels at 30 min after administration were 7.9 μg/ml for nonfasting volunteers and 15.8 μg/ml for fasted volunteers. However, peak levels were not significantly different; values of 19.2 and 18.3 μg/ml were found for nonfasting and fasted volunteers, respectively.

After intravenous administration of cephradine, the peak levels are reached immediately. In one study, a serum concentration of 56 μg/ml at 7 min after injection was attained after administration of 1 g (70). In another study (63), the administration of 1 and 0.5 g of cephradine intravenously gave levels of 86.3 and 46.0 μg/ml, respectively, 5 min after injection. When cephradine was given as an intravenous constant infusion (0.166 g/hr), a steady-state level of 4.8 μg/ml was attained after 3 hr (70).

Distribution—In a study performed with mice (71), cephradine was widely distributed throughout the body. In this study, 50 mg/kg of tritiated cephradine was administered orally to mice and tissue levels were determined as a function of time. The levels in the stomach, small intestine, and kidneys were all above 100 μg/g of tissue. The liver had a level of more than 50 μg/g of tissue at 1 hr after administration. Almost all other body tissues had levels above 1 μg/g of tissue. The levels found in the brain were 0.8–2.2 μg/g of tissue in the 24-hr period of the study.

The tissue levels of cephradine in humans after oral dosing were examined (67). The level in lung tissue 6 hr after administration of 500 mg po was 0.46 μg/g of tissue (serum level was 0.58 μg/ml). Three hours after dosing, adipose tissue levels of 0.46–0.56 μg/g of tissue were found (serum level was 0.31–0.60 μg/ml). Cephradine levels for various other tissues were also given (67). The volume of distribution of cephradine was reported to be 21 liters/1.73 m^2 (72).

Metabolism and Excretion—A study in mice and dogs using paper chromatographic techniques showed that no metabolites of cephradine could be found in the urine (71, 73). A study in humans also could not find any metabolites of cephradine (63).

When 500 mg of cephradine was administered orally to subjects having cholecystolithiasis (67), the levels of cephradine in the bile ranged from 2.2 to 41.0 μg/ml at 3–7.5 hr after administration.

The major route for the elimination of cephradine is renal excretion. Cephradine is removed from the body by the processes of glomerular filtration and tubular secretion (63). A study (61) in which probenecid was coadministered with cephradine resulted in a prolonged half-life and elevated serum levels.

The recovery of unchanged cephradine in the urine ranged from 78.3 to 95.9% (63, 66–68). The urinary concentration of cephradine in the first 2 hr after administration of 500 mg was between 1.1 and 3.2 mg/ml (63, 66, 68).

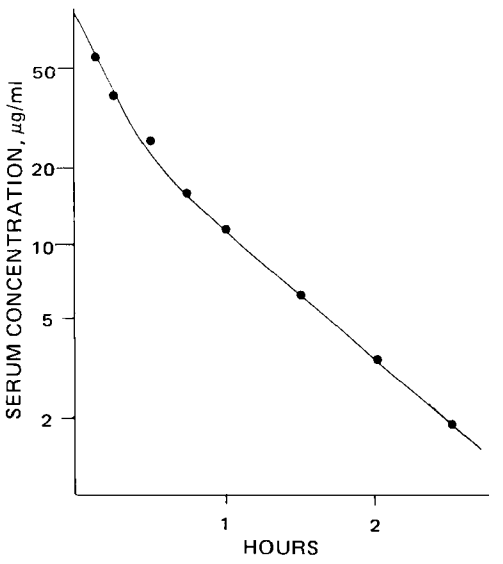


Figure 3—*Serum levels for cephradine administered intravenously (rate constants for data generation from Table III).*

The half-lives of elimination of cephradine were 32 min (70) after intravenous administration, 40–50 min after intramuscular administration (63), and 42 min after oral administration (68). These studies were performed in patients having normal kidney function. During a constant infusion, patients having a creatinine clearance of 125 ml/min had serum and renal clearances of cephradine of 435 and 367 ml/min, respectively (72).

In another study (74), 500 mg of cephradine was administered orally to patients with impaired kidney function. The time required to excrete 90% of the administered cephradine was 24 hr in normal patients. Individuals having impaired kidney function required much longer to excrete a similar amount of the drug.

Pharmacokinetic Considerations—Little work has been performed on the pharmacokinetics of cephradine in subjects with normal and impaired kidney function. Further study is necessary to elucidate these parameters.

A plot of cephradine serum concentration *versus* time (Fig. 3) indicates a biexponential decay. Therefore, fitting of the data for cephradine should be performed using a two-compartment open model. The effects of using a one-compartment open model analysis when a two-compartment open model is indicated were discussed previously.

When the data for intravenous cephradine were fit to a two-compartment open model, the half-life was approximately 45 min. The values of the parameters obtained are listed in Table III.

The volume of distribution was 22 liters, compared to 21 liters/1.73 m^2 reported previously (72). A value of 17 ± 3.9 liters/1.73 m^2 also was reported (61).

The pharmacokinetics of cephradine probably will

Table III—Pharmacokinetic Parameters for Cephradine Administered Intravenously (Literature Data)[a]

Parameter	Literature Reference 63	70	70[b]	Mean ± SD
α, hr^{-1}	5.411	7.369	9.20	6.390 ± 1.385
β, hr^{-1}	0.726	1.262	1.31	0.994 ± 0.379
K_{12}, hr^{-1}	2.167	2.349	3.25	2.258 ± 0.129
K_{21}, hr^{-1}	1.720	3.893	4.69	2.807 ± 1.537
K_{el}, hr^{-1}	2.250	2.389	2.58	2.320 ± 0.098
$T_{1/2}\alpha$, hr	0.130	0.094	0.075	0.112 ± 0.025
$T_{1/2}\beta$, hr	0.969	0.549	0.529	0.759 ± 0.297
V_c, liters	7.906	10.562	9.624	9.234 ± 1.878
Vd_{ss}, liters	17.679	16.936	—	17.308 ± 0.525
Vd_{β}, liters	24.651	19.993	—	22.322 ± 3.294
Vd_{ext}, liters	36.802	24.516	—	30.659 ± 8.678

[a] Analysis of data using a two-compartment open model (Scheme I). [b] Literature values.

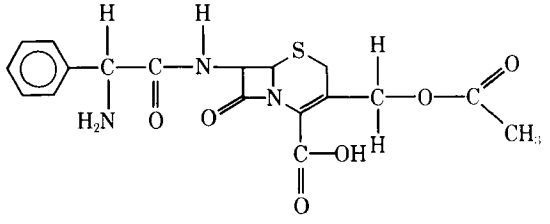
be similar to those found for cephalexin due to the similarity of their structures. The protein binding of these two compounds is not significantly different, so the volume of distributions should be similar, as was found in the reanalysis of literature data (Table III).

Cephaloglycin—Cephaloglycin, 7-(2-amino-2-phenylacetamido)-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, acetate (ester) (IV), is a zwitterion of 7-(D-α-aminophenylacetamido)cephalosporanic acid and exhibits an antibacterial spectrum similar to that of other cephalosporins. It is water soluble [8 mg/ml at 25° (75)] and orally absorbed, and it is indicated for use in treating bacterial infections of the urinary tract (76). The stability of cephaloglycin is dependent on pH, degrading very rapidly in alkaline media and remaining stable under acid conditions (77, 78). The decomposition rate is 6–8%/hr in aqueous solution at pH 7.0, but at pH 4.5 the rate is less than 1%/hr (75).

Cephaloglycin exhibits moderate protein binding. Wick (79) found a decrease of 24% in antibacterial activity when the drug was in the presence of human serum as compared to buffer.

Absorption—Several investigators reported mean peak blood serum activity after a 500-mg dose in the range of 0.9–2.0 μg/ml (48, 80–85). Peak concentrations of 0.6–0.8 μg/ml were reported (83, 86), but in another study no serum levels could be detected (87). A concentration of 2.2–3.0 μg/ml was found after a 500-mg dose (48). The activity in serum is due in part to the parent compound but largely to the deacetylated metabolite (78).

Food was reported not to interfere with cephaloglycin absorption (84); however, another study (6) found decreased peak levels after a meal. Urinary recovery was also decreased. Prolonged serum activity was reported when the drug was administered with



IV: cephaloglycin

food as compared to the fasting state (84). Peak concentrations occurred 2 hr after administration (84, 86). Peak concentrations were found 1 hr after administration to fasting patients and 2 hr after administration to nonfasting individuals (6). Similar results were obtained in children 1–15 years old (88).

Peak heights were compared after oral and intramuscular doses of the drug (48). Only 25% of the orally administered dose was assumed to be absorbed.

Distribution—The antibacterial activity in the bile of rats and mice exceeded that in the circulating blood, but only 0.04–0.23% of a 200-mg/kg dose was recovered in the bile during a 24-hr period. The antibacterial activity in the tissues of mice was determined 4 hr after an oral dose of 200 mg/kg (89). The concentrations of drug in liver and kidney were 1.9 and 3.2 times greater than in the serum, respectively. Other tissues such as lung, spleen, and heart and skeletal muscle had approximately 40% of the activity of the serum. Rat liver levels were similar to blood levels after administration of 100 mg/kg of cephaloglycin, but lung and spleen levels were slightly lower and kidney levels were much higher (90).

Metabolism—Esterases can remove the acetyl group from the C-3 methyl position of I to yield desacetyl cephalosporins (91). Carefully controlled studies, by microbiological assay procedures and chromatographic techniques, showed that 2–10% of the antibiotic activity of serum and urine specimens from humans receiving cephaloglycin is due to the parent compound. The remainder of the biological activity (90–98%) is due to the active metabolite desacetylcephaloglycin (78, 92–94). The metabolite had approximately equal activity against staphylococci but was about fourfold less active against other Gram-positive cocci and Gram-negative bacilli (94).

Excretion—Cephaloglycin and its metabolite are excreted in the urine. A half-life of 2.2 μg/ml/hr was reported (85), but it is not clear how this value was obtained. Other data (6) suggest a half-life for microbiological activity of approximately 1.5 hr.

Several studies (6, 48, 82) found 25% of the orally administered activity in the urine. Stein *et al.* (85) recovered 18% of a 500-mg dose. Most recovered activity was due to the desacetyl metabolite (48, 78, 93, 94). Urine concentrations expressed as antibacterial activity after a 500-mg dose varied from 76 to 330 μg/ml. Somewhat lower (18–255 μg/ml) results were reported (86), as were ranges of 18–750 μg/ml (83) and 70–900 μg/ml (95). It was reported that probenecid increased the serum concentration of the antibacterial activity (6). However, other studies reported no increase in serum concentrations with probenecid, but the duration of assayable activity was prolonged (82, 84).

Disease, except decreasing kidney function, does not appear to affect the pharmacokinetics of this drug. An increase in the half-life of the drug was observed with decreasing renal function (85). Significant prolongation of serum half-life occurred when creatinine clearances fell below 20 ml/min. Adequate urine concentrations in all but anuric patients were observed after a 500-mg dose (85). Hemodialysis did

not appreciably affect the elimination of the drug in anuric patients (85). Peritoneal dialysis caused a 40% decrease in blood levels within 6 hr (83).

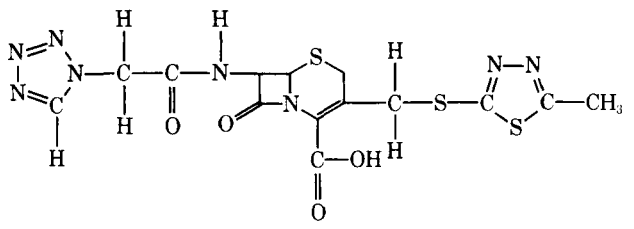
Pharmacokinetic Considerations—The data reported do not allow an accurate estimation of the pharmacokinetic parameters of this drug. Human metabolism of cephaloglycin has not been extensively studied, and blood level data obtained *via* microbiological assay do not yield accurate pharmacokinetic constants; instead, apparent constants are obtained based upon the total activity of the drug and its metabolite.

Since this drug yields poorer blood levels, has a similar spectrum, and does not yield superior urinary levels as compared to cephalexin, no clear advantage for its use is evident. From a pharmacokinetic view, cephaloglycin has many disadvantages compared to cephalexin and should be abandoned in favor of the latter drug. For practical purposes, cephaloglycin is an uninteresting drug, and further pharmacokinetic analysis is not warranted.

Cefazolin—Cefazolin, 3-{[(5-methyl-1,3,4-thiadiazol-2-yl)thio]methyl}-8-oxo-7-[2-(1*H*-tetrazol-1-yl)-acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (V), is a semisynthetic cephalosporin used parenterally. Its synthesis was described previously (96). Cefazolin is a broad spectrum antibiotic, active against most strains of Gram-positive and Gram-negative bacteria (97). It is active against *S. aureus, E. coli, Klebsiella pneumoniae,* and *Proteus mirabilis.*

The free acid form of cefazolin is insoluble in water, becomes more soluble as the pH increases, and reaches a maximum solubility between pH 5 and 6 (98). Cefazolin is available commercially as the sodium salt with a molecular weight of 476.5 (99). In the sodium salt form, cefazolin is highly soluble in aqueous solvents, slightly soluble in methanol, and practically insoluble in acetone, benzene, chloroform, and ethanol (96, 100). The pH of a reconstituted solution and region of maximum stability of cefazolin sodium lies between 4.6 and 6.0 when in an aqueous medium. In a more acidic or alkaline medium, cefazolin is hydrolyzed to products that possess little or no antibacterial activity (98, 99, 101). The pKa of cefazolin in an aqueous solution (23.8 mg of cefazolin sodium in 5.0 ml of water) was 2.3 (99).

The solid lyophilized powder of cefazolin was stable for 1 year when stored at 0–15°, with 92–95% of the original activity remaining when assayed microbiologically (96). The product information brochure (98) states that the lyophilized powder is stable for 2 years at room temperature. Various reports of the



V: cefazolin

stability of the reconstituted aqueous solutions of cefazolin sodium have been published (96, 97, 101, 102). These studies found that the drug is stable at 25° and below, with approximately 90% of the original activity remaining after 72–120 hr (96, 97). Cefazolin is less stable at 37°, and a net loss of 20% of the original activity was found after 72 hr (97). A complete survey of the stability of cefazolin, in which the effects of various diluents and temperatures were studied, is available (101).

Cefazolin is highly bound to human plasma proteins. Investigations using the equilibrium dialysis technique found values of 73% (103), 81% (104), and 84% (105, 106) of the total drug being bound to plasma proteins in normal patients. Values of 74% (107) and 86% (44, 108) were found when the ultrafiltration technique was used to analyze the plasma samples. In one study, the effect of total drug concentration on serum protein binding was studied (105). The binding to serum protein varied from 80 to 90% in the normal therapeutic range of cefazolin. The effect of protein binding on antibiotic activity is unclear, but one study (102) showed that the presence of human serum caused a decrease in antimicrobial activity of 41–48% as compared to a cefazolin solution made in buffer.

Absorption—Cefazolin is not absorbed orally, so it is only administered intramuscularly and intravenously. Cefazolin is well absorbed when administered intramuscularly, as evidenced by urinary recoveries of approximately 100% of the administered dose. The time of peak concentration after intramuscular administration was usually within 45 min to 1 hr after administration (44, 103–126). However, in several cases, the time of peak serum concentration appeared as late as 2 hr after administration (127, 128).

The peak concentration of cefazolin after an intramuscular injection of 250 mg ranged from 12.3 to 30.0 μg/ml (104, 117, 119). After an intramuscular injection of 500 mg, peak levels ranged from 11.0 to 70.0 μg/ml (44, 103, 104, 106–109, 111, 112, 114, 115, 117, 119–121, 124–126, 128, 129); after administration of 1 g of cefazolin, peak levels of 38.8–75.7 μg/ml were found. In one study where 2 g of cefazolin was administered, levels of 111.0 μg/ml were attained; 3 g of cefazolin and 1 g of probenecid resulted in a level of 200.0 μg/ml (123).

Distribution—Rats were injected intramuscularly with ^{14}C-labeled cefazolin, and the tissue concentrations were determined using radioactive and microbiological assays (98, 117, 120, 126, 130, 131). The concentration of cefazolin was very high in the kidneys, lungs, and liver. Peak levels reported (120) for these organs were 68.64, 19.52, and 22.41 μg/g of tissue, respectively. The concentration of cefazolin found in the serum at the time of peak tissue levels was 77.60 μg/ml; levels of 14.42 μg/g of heart tissue, 1.05 μg/g of brain tissue, and 5.10 μg/g of spleen tissue were also found.

In one study where synovial fluid levels of cefazolin were measured in humans (113), the levels of cefazolin found were similar to the levels of cefazolin found in the blood. After an intramuscular injection of 1.0

g, peak serum levels of 65 μg/ml were attained. The synovial fluid level at that time was approximately 75 μg/ml. Cerebrospinal fluid concentrations in human volunteers also were measured (120). In this study, intravenous doses of 10 mg/kg were given and the cerebrospinal fluid and serum levels were determined as a function of time. The serum levels varied from 40 μg/ml at 30 min after injection to 9 μg/ml at 4 hr after injection. However, the cerebrospinal fluid levels remained constant at 4 μg/ml throughout the entire study.

Studies performed on mucous membranes (132) in patients with chronic sinusitus found that the levels of cefazolin were 1.5 and 3.5 μg/g of tissue after a 250- and 500-mg intramuscular dose, respectively. The tissue used was the mucus membrane removed from the maxillary sinus. In other studies performed by these same authors, doses of 250 and 500 mg of cefazolin were administered to patients with tonsillar hypertrophy. The tissue levels attained were 3.4 and 7.6 μg/g of tissue, respectively.

Metabolism and Excretion—The metabolism of cefazolin is a very insignificant process in the elimination of the drug. Various studies using chromatographic separation techniques found that no microbiologically active metabolites were present in the urine of rats or humans (102, 117, 131). In studies where ^{14}C-cefazolin was injected intramuscularly into rats, two metabolites of cefazolin were present in the bile and one metabolite was present in the urine (122). These metabolites accounted for a small fraction of the original dose. Some metabolites were recovered in the urine and the bile (131), but the amounts recovered were very small. Another similar study found no cefazolin metabolites (120).

The bile of normal patients and patients with gallbladder and bile duct impairments was examined for cefazolin content after systemic administration of the drug (113, 121, 133). In one study (113), cefazolin was infused intravenously at a rate of 500 mg/hr for 1 hr and then at a rate of 250 mg/hr for 2 hr. During the steady state, the serum concentration of cefazolin was 50 μg/ml and the concentration of cefazolin in the bile was 12.2 μg/ml. Cefazolin biliary excretion was 0.104 ml/min/1.73 m^2. Other studies performed using patients with normal bile duct and gallbladder function found a biliary concentration twice that of the serum concentration of cefazolin (121); bile levels seven times those found in serum were observed in one study (133).

In diseased patients having a gallbladder or bile duct dysfunction, without obstruction of the bile duct, the levels in the bile were at least twice, and sometimes as high as seven times, those of the serum. These patients had cholelithiasis, cholecystitis, and a nonobstructed cystic duct. The levels found in the gallbladder tissue were similar to those found in the bile. In patients with an obstructed cystic duct, the levels of cefazolin in the bile were below those found in the serum (133).

The recovery of cefazolin in the bile of rats given 20-mg/kg im or sc doses of cefazolin was as high as 20% of the original administered dose (117). Thus, considering the high levels of drug appearing in the bile, cefazolin may be effectively used to treat infections in the bile duct or gallbladder.

Cefazolin is eliminated from the body mainly through renal excretion. Urinary recovery studies (44, 70, 98, 99, 104–109, 111, 113–118, 121, 127, 134) showed that essentially 100% of the administered dose can be accounted for as unchanged drug in the urine. The serum and renal clearances for cefazolin were reported to be 62 ± 6 and 64 ± 6 ml/min, respectively (44). Since these values are not significantly different, it can be concluded that the renal route of elimination is responsible for removal of a major percentage of the drug.

The mechanisms responsible for the elimination of cefazolin are glomerular filtration and tubular secretion. This elimination was first postulated by Regamey *et al.* (108) by comparing the creatinine clearance, a measure of glomerular filtration, to the clearance of cefazolin. The mechanisms involved in the elimination of cefazolin were further elucidated when probenecid was administered concurrently with the antibiotic (44, 114, 123). In all of these studies, a prolonged half-life and elevated serum levels characteristic of the competitive inhibition of the tubular secretion of cefazolin were found.

Numerous pharmacokinetic studies have been performed using patients with normal kidney function (44, 70, 98, 99, 103–122, 127, 128, 134, 135) and impaired kidney function (98, 99, 103, 105, 106, 109, 111, 114, 122, 128, 136). The range of half-lives reported for cefazolin after intravenous administration is 69–108 min (44, 70, 99, 108, 127, 134), with an average of 88 min. After intramuscular administration, the values of the reported half-lives range from 96 to 153 min (44, 99, 104, 105, 109, 114, 127, 134), with an average of 121 min.

In one study where multiple dosing of cefazolin was investigated, a half-life of 124 min was found after the first dose and a value of 88 min was found after a series of multiple doses (106). The reason for this change of half-life after a series of intramuscular multiple doses is unclear, but the explanation reported was that cefazolin-metabolizing enzymes were produced (106). However, since cefazolin has not been shown to be appreciably metabolized, this explanation does not seem plausible.

The renal and total body clearances of cefazolin have been studied (44, 70, 105, 106, 108, 113, 114, 128, 130). The plasma clearance found in one study was 61.5 ± 6.1 ml/min and the renal clearance was 64.6 ± 6.0 ml/min after either intravenous or intramuscular administration (44). Values of 50 ml/min (106, 128), 61.2 ml/min (105), 78.0 ml/min (130), 81.8 ml/min (113), and 83.6 ml/min (70) have been reported for renal clearance.

When probenecid was administered concurrently with cefazolin, higher levels and a prolonged half-life were found as compared to the administration of cefazolin without probenecid (123). Cefazolin was administered at a dose of 2 g intramuscularly to human volunteers. When cefazolin was administered with probenecid, peak levels of about 140 μg/ml were at-

tained. When cefazolin was administered alone, the peak level attained was about 110 μg/ml. There was a significant difference in the serum levels attained at the end of 12 hr when the two levels were compared. At that time, the cefazolin serum levels were less than 40 μg/ml with, and 10 μg/ml without, the coadministration of probenecid. Therefore, concurrent administration of cefazolin and probenecid resulted in levels above the MIC of many susceptible bacterial organisms for a prolonged period. In this study, equal cefazolin serum levels were attained when 3 g of the drug was administered concurrently with probenecid compared to the administration of 2 g of cefazolin and 1 g of probenecid. Increased serum levels and prolonged half-lives were obtained in other studies (44, 114).

Since cefazolin is eliminated from the body primarily by renal excretion, a longer half-life and a higher serum level result in a patient with impaired kidney function. The effect of kidney function on the pharmacokinetics of cefazolin has been investigated (98, 99, 103, 105, 106, 109, 111, 114, 122, 128, 136). In one study (114), normal volunteers and patients with varying degrees of renal impairment (creatinine clearance of 0–47 ml/min) were given 500-mg intramuscular doses of cefazolin. The peak levels achieved in the patients with normal kidney function ranged from 44.0 to 70.0 μg/ml at 30–60 min after injection. The peak levels attained in the patients with kidney failure ranged from 42.0 to 81.5 μg/ml at 30–120 min after drug administration. The half-life of cefazolin in the normal patients ranged from 1.37 to 1.96 hr, with a mean value of 1.60 hr. In the patients with renal impairment, the half-life ranged from 4.84 hr in a patient with a renal clearance of 47.2 ml/min to 69.2 hr in an anuric patient.

A similar study (128) found that as creatinine clearance decreased, the half-life increased. Czerwinski *et al.* (128) stated that: "in patients with serum creatinine concentrations less than 2.5 mg/dl or creatinine clearances greater than 25 ml/min modification of cefazolin dosage is not necessary since urinary excretion is rapid and exponentially related to plasma concentration. In patients with more severe renal impairment, modification of dosage is necessary to prevent accumulation." This observation was based on the fact that the plasma half-life of cefazolin does not significantly change until the creatinine clearance falls below 25 ml/min. Below 25 ml/min, the half-life of cefazolin increased rapidly (128).

In this study (128), the effect of renal function on the volume of distribution, total serum protein, and serum albumin was examined. No significant differences in total serum protein existed in normal patients as compared to patients with varying degrees of renal dysfunction. However, the volume of distribution in normal patients was much less than that of patients having severe renal impairment. In patients having normal kidney function, the volume of distribution was 13.52 ± 3.70% of body weight. Values of 13.62 ± 4.06 and 16.53 ± 2.62% of body weight were found in patients with moderate kidney function and severe impairment, respectively.

In a study in which cefazolin was administered to patients with varying degrees of renal dysfunction, patients with lower creatinine clearances generally bound cefazolin to plasma proteins to a lower extent than patients with higher creatinine clearance (105). Since there is a lower degree of protein binding in the patients with poor kidney function, this increase in the volume of distribution is expected.

In patients with renal impairment, the reported urinary recovery of cefazolin was less than that of normal patients. Patients with normal kidney function excreted 81.47 ± 6.80% of the dose in 24 hr, with almost 55% of the dose excreted in the first 6 hr (128). In patients with moderate impairment (creatinine clearance of 47–69 ml/min), 36% was excreted in the first 6 hr, with a total 24-hr cumulative excretion of 68.14 ± 6.08% of the original dose. In patients with severe renal impairment (creatinine clearance of 5–21 ml/min), 5.9% of the dose was excreted in the first 6 hr, with a total of 22.08 ± 14.13% of the dose excreted in 24 hr. Urinary concentrations remained relatively high in patients having normal kidney function and only moderate impairment; urinary concentrations of 698 ± 216 and 638 ± 245 μg/ml were reported for the first 6 hr, respectively. However, in patients with severe impairment, the urinary concentration was 58 ± 85 μg/ml in the first 6 hr.

In another study (109), levels in the urine somewhat higher than those previously reported (128) were found. In patients having normal kidney function, levels of 1.5 ± 0.2 mg/ml were attained in the first 4 hr. In patients having moderately impaired kidney function (creatinine clearance of 56–80 ml/min), levels of 1.9 ± 0.6 mg/ml were reached. In patients with severe kidney impairment, a mean value of 368 ± 199 μg/ml was attained. However, even in patients having severely impaired kidney function, the urinary concentrations were above the MIC for many organisms. Cefazolin is known to be an effective antibiotic for the treatment of urinary infections (129).

The effect of hemodialysis on the pharmacokinetics of cefazolin has been investigated (105, 109, 122, 128, 136). Four patients received 500 mg of cefazolin intramuscularly about 2 hr before undergoing hemodialysis (128). The half-life of cefazolin during dialysis was 9.3 ± 2.5 hr, which represents a 33% decrease in the half-life (39.14 ± 18.07 hr) between dialysis periods.

In another study (122), 1 g of cefazolin was injected intravenously before dialysis was started. Between dialyses, the serum cefazolin levels were 89.8 ± 28.5 μg/ml at 15 min after administration and 61.6 ± 25.3 μg/ml after 8 hr. The half-life was 32.7 ± 9.3 hr. During dialysis, the serum concentration of cefazolin was 84.3 ± 20.7 μg/ml at 15 min after administration and fell to 31.6 ± 6.0 μg/ml at 8 hr. The half-life was reduced to 6.9 ± 2.3 hr during the dialysis period. The hemodialysis extraction percentage was 23% (122).

During dialysis, little difference existed between the concentration of cefazolin in the arterial plasma and venous plasma (136). In one study where the effect of peritoneal dialysis was investigated (109), it

Table IV—Pharmacokinetic Parameters for Cefazolin Administered Intravenously (Literature Data)[a]

Parameter	Literature Reference								Mean ± *SD*
	44	70	70[b]	110	118	122	127	139[b]	
α, hr^{-1}	3.604	8.743	7.80	4.766	1.494	1.487	2.873	4.832	3.971 ± 2.510
β, hr^{-1}	0.346	0.447	0.44	0.433	0.419	0.299	0.315	0.573	0.404 ± 0.095
K_{12}, hr^{-1}	1.687	4.660	2.41	1.817	0.265	0.447	1.279	1.961	1.730 ± 1.452
K_{21}, hr^{-1}	0.946	3.370	4.46	2.583	1.054	0.735	0.889	2.148	1.674 ± 1.028
K_{el}, hr^{-1}	1.317	1.160	1.44	0.799	0.594	0.605	1.020	1.299	0.970 ± 0.309
$T_{1/2}\alpha$, hr	0.192	0.080	0.08	0.145	0.464	0.466	0.241	0.167	0.240 ± 0.169
$T_{1/2}\beta$, hr	2.005	1.550	1.56	1.600	1.652	2.321	2.197	1.248	1.796 ± 0.387
V_c, liters	2.371	4.269	1.091	4.308	5.461	6.881	4.330	3.482	4.442 ± 1.429
Vd_{ss}, liters	6.598	10.171	—	7.338	6.831	11.065	10.566	6.791	8.479 ± 2.013
Vd_{β}, liters	9.003	11.074	—	7.948	7.736	13.930	13.999	8.145	10.266 ± 2.763
Vd_{ext}, liters	12.869	12.115	—	8.681	9.240	18.756	19.323	10.133	13.013 ± 4.378

[a] Analysis of data using a two-compartment open model (Scheme I). [b] Literature values.

was found that this procedure had a less dramatic effect on decreasing the half-life of cefazolin. The half-life of the drug before the dialysis was not given, but the half-lives found after dialysis were 20.3 and 46 hr.

Use in Children and Infants—The use of cefazolin in pediatrics has been discussed (110, 124, 135, 137, 138). In one study (124) in which 25 mg/kg of cefazolin was injected into a neonate, peak levels of 35 μg/ml were attained in the serum. At the end of 12 hr, the serum level was 10.7 μg/ml. It was reported that 41.5% of the dose was excreted in the urine within the first 24 hr.

After a 6.25-mg/kg dose of cefazolin in children (ages not given), the concentration of cefazolin in the urine was 850 μg/ml (135). After a dose of 10.0–12.5 mg/kg, the concentration in the urine was 1425 μg/ml. Another study (137) found similar results with newborn babies; however, in premature infants, the 7-hr urinary recovery was 61.5% as compared to the 7-hr urinary recovery of 41.4% in newborn babies.

The concentration of cefazolin in the mothers' milk was reported to be very low (124, 275). The levels in the umbilical cord after an injection of 500 mg into the mother before delivery was between 5 and 7 μg/ml 15 min after injection (124). Levels in newborns were not reported.

Pharmacokinetic Considerations—All studies of the pharmacokinetics of cefazolin, except two (70, 139), were performed using a one-compartment open model. As can be seen in Fig. 4, the resultant plot appears to be biexponential and the two-compartment open model analysis (70, 139) appears to describe more appropriately the pharmacokinetics of this drug than do other published studies. Use of the two-compartment open model analysis of cephalosporin data was discussed in the section on cephalexin.

The pharmacokinetic parameters obtained when the literature data were analyzed using a two-compartment open model appear in Table IV. Other reported values (70, 139) also appear in this table for comparison.

The half-life of cefazolin when analyzed by a two-compartment open model is approximately 1.8 hr. This value is not significantly different from the reported values of 1.5 and 1.95 hr for cefazolin after intravenous and intramuscular administration, respectively.

Cefazolin, being over 80% bound at therapeutic concentrations, has a relatively small volume of distribution. The volume of the central compartment, found when literature data were analyzed using a two-compartment open model, was 4.4 liters. This value approximates the volume of the plasma water. In one report (70), the volume of distribution (15 liters) was found by using a constant-infusion one-compartment open model. This volume represents a Vd_{β} of a two-compartment open model, and its significance was discussed under *Cephalexin*.

A volume of distribution of 10 liters after an intravenous infusion was found by using Eq. 3 and is analogous to Vd_{β} (44). It is not significantly different from the term shown in Table IV.

The volume of distribution after intramuscular administration of cefazolin was approximately 12.2% of body weight (105); thus the volume of distribution would be 8.5 liters in a 70-kg human. This value was calculated by fitting the blood levels of cefazolin to a one-compartment open model. Therefore, the volume found in this analysis is analogous to the two-compartment Vd_{ext}. This number is not appreciably different from the two-compartment Vd_{ext} (Table IV).

A value of 13.2% of body weight was reported for

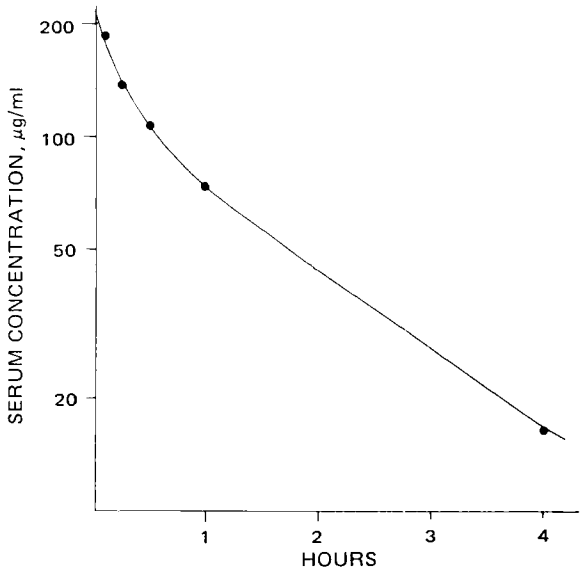


Figure 4—*Serum levels for cefazolin administered intravenously (rate constants for data generation from Table IV).*

the volume of distribution of cefazolin after intramuscular administration (128). The method used was to extrapolate the log-linear portion of the serum level curve to the y axis. The y intercept would erroneously be called $C_p{}^0$, and the volume of distribution is then dose/$C_p{}^0$. However, this intercept is actually $(C_p{}^0k_a)/(k_a - K)$, where K and k_a are the overall one-compartment open model elimination and absorption rate constants, respectively. Therefore, the value of this intercept was not correctly evaluated, and the volume obtained is incorrect.

The value for the renal clearance of cefazolin when analyzed by a two-compartment open model is 71.8 ml/min. This value is similar to the values reported with a one-compartment open model analysis. Reported values range from 61.5 to 81.8 ml/min (108, 113).

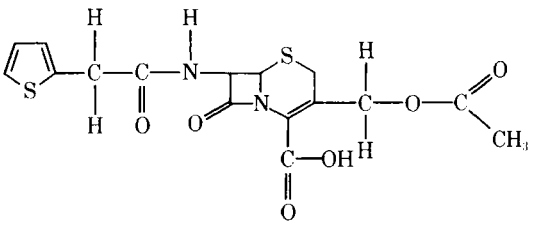
The normal dosage for patients with normal kidney function is 0.5–1.0 g every 12 hr (99). Since 12 hr is approximately six half-lives, over 98% of the drug has left the body. Since cefazolin has a wide therapeutic range and since accumulation does not take place due to the short half-life and long dosing interval, the use of one-compartment open model kinetics for this drug as well as for cephalexin will not seriously affect data analysis.

Cephalothin—Cephalothin, 3-(hydroxymethyl)-8-oxo-7- [2-(2-thienyl)acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate acetate (ester) (VI), is a semisynthetic cephalosporin and is available as the sodium salt for intravenous or intramuscular administration. The molecular weight of cephalothin sodium is 418.4. The synthesis of cephalothin has been discussed (139). It is moderately soluble in aqueous media, *i.e.*, up to 300 mg of cephalothin sodium may be dissolved in 1 ml of water. The pH of an aqueous solution of cephalothin sodium is 5.2; however, the activity of cephalothin is not altered by a variation of pH from 4 to 7.5 (153). It is active against both Gram-negative and Gram-positive bacteria, including such strains as *Diplococcus pneumoniae, S. aureus,* and *E. coli* (140).

In one study of the stability of cephalothin (141), the drug was stable for 12 days when stored at −15° in either serum or pH 6 phosphate buffer. When stored at 4°, 10% of the original activity was lost in 48 hr and 40% was lost by the end of the 12th day. When cephalothin was stored in serum at room temperature, only 13% of the original activity remained after 2 days. However, the drug in the phosphate buffer lost only 15% of its original activity after 12 days when stored at room temperature. Other studies of cephalothin stability have been reported (142, 143).

With the ultrafiltration technique, cephalothin was found to be 65% protein bound to human serum proteins (44, 105, 108, 144). In one study (141), cephalothin was about 60% less active against a test organism when in serum as compared to phosphate buffer.

Absorption—Cephalothin is not absorbed when administered orally (140). When 500 mg of cephalothin was administered orally, there was no detectable antibacterial activity in the serum between 1 and 4 hr (140). The recovery of cephalothin in the urine



VI: cephalothin

ranged from 4.3 to 11.3% of the administered dose. These results were confirmed in another study (145).

Cephalothin is well absorbed following intramuscular administration. After an intramuscular dose of 500 mg, peak levels of 6.3–8.0 μg/ml were attained. When the dose was increased to 1 g, peak levels of 15.0–20.0 μg/ml were attained (140, 141, 145–148). Peak levels were obtained approximately 0.5–1 hr after administration. When probenecid was administered concurrently with intramuscular cephalothin, peak levels of 20.2 and 33.0 μg/ml were attained after 500-mg and 1.0-g doses, respectively.

Peak levels after intravenous administration of 1 g of cephalothin as a single intravenous dose ranged from 30 to 60 μg/ml at 15 min after injection (149–153). After an intravenous infusion of 1 g over 15 min, levels of 10.22 μg/ml were attained (149). When cephalothin was administered intraperitoneally, a serum level of 4.45 μg/ml was attained 1 hr after dosing (149).

Sheng *et al.* (160) studied the serum concentrations of cephalothin after intramuscular administration of 12.5 mg/kg to infants and children. In newborn infants (1.5 hr–8 days old), peak levels of 25 μg/ml were attained 30 min after injection. In older infants and children, levels of 14.72 μg/ml were attained 0.5 hr after injection.

Distribution—When cephalothin was administered on a dosage schedule of 2 g every 4 hr intramuscularly, the levels of cephalothin were high in the heart, liver, and kidneys. A concentration of 640 μg/ml was found in the heart blood, with a corresponding level of 201 μg/g of tissue in the myocardium of the heart (153). The level of the drug in the kidneys was 548 μg/g of tissue in the renal cortex, and it was 63 μg/g of tissue in the liver (153). Brain cortex levels were reported to be 11 μg/g of tissue.

In a study of the penetration of cephalothin into the spinal fluid, levels of 0.16 and 0.31 μg/ml were attained at 30–60 min after an intravenous injection of 2 g to patients with meningitis or nervous system inflammation (155). In patients not having meningitis, the concentrations of cephalothin were below the limits of the assay (0.16 μg/ml) and could not be detected. A spinal fluid level of 11.7 μg/ml (serum concentration of 15.9 μg/ml) was found 2 hr after administration of 1 g intramuscularly (140).

At 1 hr after injection of 1 g of cephalothin intravenously, the level of cephalothin in pleural fluid was 70.6 μg/ml; at 2 hr, the level was 40.8 μg/ml (140). A level of 12.6 μg/ml in synovial fluid 20 min after injection of 1 g of cephalothin intravenously also was reported (150). Distribution of the drug into the

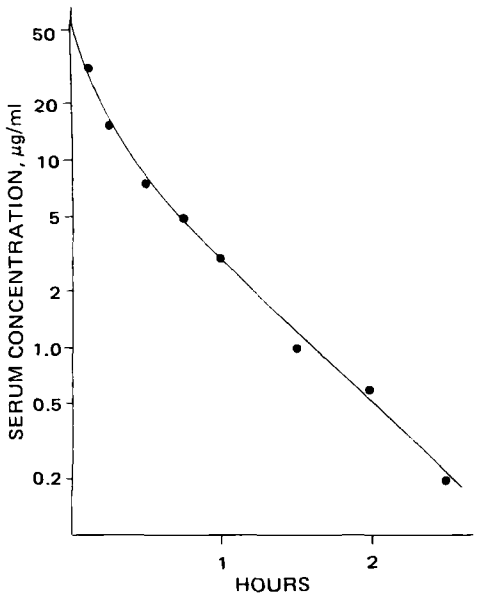


Figure 5—*Serum levels for cephalothin administered intravenously (rate constants for data generation from Table V).*

aqueous humor of the eye was reported (152). In this study, 1 g of cephalothin was administered intravenously and an aqueous humor level of 0.48 μg/ml 0.5 hr after administration was found. Ascitic fluid levels of 2.6–4.0 μg/ml after intravenous administration of 1 g of cephalothin were reported (149).

Many studies have appeared concerning the placental transfer of cephalothin (156–160, 275). Cephalothin is transferred rapidly from the maternal blood supply to the fetus (156, 157, 275). Concentrations of 30.2 and 12.5 μg/ml were found in the mother and fetus after an intravenous injection of cephalothin (156). The drug appeared in the amniotic fluid within 15 min after administration. The concentration of cephalothin in the mother's milk was reported to be very low (275).

Metabolism—Cephalothin is rapidly metabolized in the body to desacetylcephalothin. The site of the desacetylation of cephalothin is speculated to be within the liver and kidneys (161). It is possible to separate the unchanged drug from its metabolite by use of chromatographic techniques (162). One study found that 33% of the recovered urinary antibiotic activity is due to the metabolite (161).

Wick (163) studied the antibacterial activity of desacetylcephalothin against various strains of bacteria. He found that while the metabolite was active against many forms of bacteria, it was less effective than the unchanged drug. The levels of the metabolite in the urine of mice were almost twice those of the unchanged drug.

The time course of desacetylcephalothin appearance was studied in a patient with chronic renal failure after a 1-g iv dose (42). Appreciable metabolite production did not occur until approximately 2 hr after dosing. A differential microbiological assay was apparently used, but the procedure was not discussed in detail. Examination of the data indicates that the metabolite was assayed in the presence of greater than 100 times the concentration of the parent compound. Due to the lack of experimental detail and the technical difficulties of such an analysis, it is not possible to assess the meaning of these findings.

Excretion—The biliary excretion of cephalothin was studied in humans by injecting 1 g of cephalothin intravenously and collecting bile and serum (164). The peak levels of cephalothin in the bile ranged from 0.4 to 42.0 μg/ml. The time of the peak concentration was between 1 and 3 hr. In the first 3 hr after administration, the levels in the bile were generally above 1 μg/ml. In duodenal juice collected by intubation from patients with normal kidney function, the levels of cephalothin ranged from 4.6 to 6.5 μg/ml. In patients with renal insufficiency, the levels in duodenal juice were slightly elevated, with maximum levels between 10 and 16 μg/ml. This increase in biliary levels was due to the elevated serum concentration attributed to poor kidney function. Therapeutic levels were found in only 2.4% of the subjects in one study (276).

The half-life of cephalothin in patients with normal kidney function was reported to be between 0.47 and 0.85 hr (44, 105, 108, 141, 165–167). After an intramuscular dose of 1 g, levels of 800 and 2500 μg/ml were found in the urine (48, 140, 145, 168).

Cephalothin is excreted through the processes of tubular secretion and glomerular filtration, as is apparent by the increase in plasma levels after the coadministration of probenecid (140, 146). Serum levels of 33.0 μg/ml, almost double those in individuals not given probenecid, were reported after administration of 1.0 g of cephalothin and probenecid (140). The reported renal clearance was 274 ml/min, and the total body clearance of cephalothin was 472 ml/min (108). Therefore, 58% was removed from the body by renal processes. The rest was removed by metabolism.

Since cephalothin is metabolized *in vivo*, the total recovery of unchanged drug does not equal the amount of administered drug. In one study (131), approximately 52% of the initial dose was recovered in the urine after 24 hr; other recoveries ranged from 50 to 70% (140, 141).

The half-life of cephalothin is increased in patients with impaired renal function (169). The half-life of cephalothin increased to 18 hr in patients with creatinine clearance less than 5 ml/min (165). The half-life of cephalothin increased from 0.5 hr in a normal patient to 2.9 hr in a patient with a creatinine clearance of 5 ml/min (166). The serum half-life of cephalothin only increased moderately even in a patient with severe kidney dysfunction (103). In another study (42), a uremic patient was given 1 g of cephalothin intravenously. The half-life of cephalothin was about 2 hr. The levels of the metabolite, desacetylcephalothin, increased over the first 12 hr and then declined, with the half-life of the metabolite being about 8 hr.

Cephalothin is removed from the body during both hemodialysis and peritoneal dialysis (148, 170). The half-life of cephalothin was reported to be 3.3 hr during dialysis (170). The half-life of cephalothin during the nondialysis periods was not given. Perkins *et al.* (148) found that 24% of cephalothin was removed

Table V—"Apparent" Pharmacokinetic Parameters for Cephalothin Administered Intravenously (Literature Data)[a]

Parameter	Literature Reference					Mean ± *SD*
	70	70[b]	98	164	246	
α, hr^{-1}	10.850	6.4	6.620	4.550	7.090	7.277 ± 2.625
β, hr^{-1}	1.750	1.53	1.740	0.610	2.140	1.560 ± 0.660
K_{12}, hr^{-1}	3.680	1.45	1.390	1.520	1.430	2.005 ± 1.118
K_{21}, hr^{-1}	3.520	2.37	2.680	1.080	3.650	2.732 ± 1.183
K_{el}, hr^{-1}	5.400	4.20	4.280	2.550	4.140	4.092 ± 1.173
$T_{1/2}\alpha$, hr	0.063	1.08	0.105	0.152	0.098	0.104 ± 0.037
$T_{1/2}\beta$, hr	0.396	0.45	0.399	1.139	0.324	0.564 ± 0.385
V_C, liters	11.637	—	4.681	5.660	9.081	7.764 ± 3.198
Vd_{ss}, liters	23.818	—	7.101	13.598	12.628	14.286 ± 6.969
Vd_β, liters	35.890	—	11.549	23.738	17.622	22.199 ± 10.395
Vd_{ext}, liters	59.927	—	24.168	46.831	29.650	40.144 ± 16.345

[a] Analysis of data using a two-compartment open model (Scheme I). [b] Literature values.

from the body during peritoneal dialysis.

Pharmacokinetic Considerations—If the serum levels of cephalothin after intravenous administration are plotted on a semilogarithmic axis (Fig. 5), the resultant plot appears to be biexponential. However, since cephalothin is metabolized, it is possible that the two-compartment open model is not appropriate and the kinetics should be described by a model with a provision for a saturable metabolic process.

A complicating factor in the analysis of cephalothin is that the reported serum concentrations of the drug do not represent actual concentrations of cephalothin but the total combined antibiotic activities of cephalothin and desacetylcephalothin. In addition, the standard curves used in microbiological analysis are constructed using pure drug and a particular microorganism. The sensitivity of these microorganisms to the parent compound and the metabolite are dissimilar.

As drug blood levels decline, a change in the proportion of free drug to metabolite occurs as a function of time. The measured zone sizes, therefore, do not represent a simple log-linear relationship with concentration since the sensitivity of the microorganism to the combined "antimicrobial agents" is apparently changing as a consequence of an altered parent compound to metabolite ratio. In addition, if one uses a different microorganism with different sensitivity to these drugs, one would expect the assay results to yield somewhat altered "apparent concentrations."

It is, therefore, not possible to analyze the published data pharmacokinetically, since the calculated rate constants are artifactual. Since this drug is widely used and considerable blood level data have been published and widely quoted, a two-compartment open model analysis of literature data is provided in Table V for the sake of completeness and comparison. These data should not be interpreted to represent actual pharmacokinetic parameters.

Cephaloridine—Cephaloridine, 1-[[2-carboxy-8-oxo-7-[2-(2-thienyl)acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]pyridinium hydroxide inner salt (VII), has a qualitative spectrum of antibacterial activity almost identical to that described for cephalothin, although there are differences in the degree of activity against specific bacterial genera (103, 116, 144, 167, 171–182).

When the acetoxy group of cephalothin is replaced with pyridine, the resulting compound, cephaloridine, is more stable both *in vitro* and *in vivo* (77, 142, 143, 183, 184).

Cephaloridine was reported to be 15% (79) and 8–31% (185) protein bound in human serum. Other reports give protein binding values within this range; however, most values appear to be less than 20% (42, 167, 186).

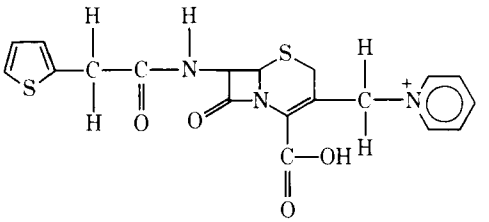
Absorption—Cephaloridine is readily absorbed after intramuscular injection and poorly absorbed from the GI tract (86, 173). A 250-mg intramuscular dose gave a peak serum concentration of about 15 μg/ml (103, 187), while 500-mg and 1-g doses gave peak blood levels of approximately 30 and 40 μg/ml, respectively (103, 188). Slightly lower levels also were reported (48, 108, 116, 126, 173, 179, 186, 189).

After intramuscular administration to children 2 months to 14 years of age, peak serum concentrations (approximately 45 min after administration) were 7, 16, and 32 μg/ml after a 50-, 100-, and 200-mg/kg dose, respectively (190). Similar results were reported in another study (275).

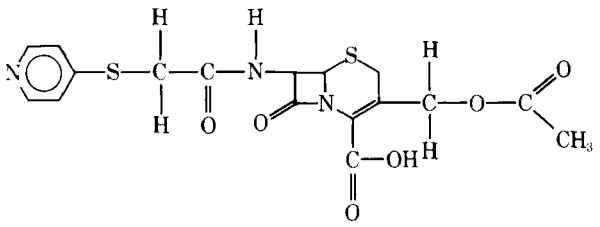
Distribution—Biliary excretion was found to be a minor pathway of elimination. A biliary concentration of 10 μg/ml was found when the serum concentration was 24 μg/ml (189, 191).

Cephaloridine concentrations in the spinal fluid of patients with uninfected meninges were 6–12% of those in the blood and serum (188, 189, 192, 193). However, poor penetration of the drug into the cerebrospinal fluid was reported (194).

Cephaloridine concentrations of about 12 μg/ml were found in fresh wounds 1 hr after a 15-mg/kg intravenous dose (185). The antibiotic levels decreased as the wound age increased.



VII: cephaloridine



VIII: cephapirin

Cephaloridine was found to diffuse into peritoneal and pleural fluids (193, 195). The drug distributed well into the liver, spleen, stomach wall, and lung but was found in a much smaller amount in the cerebral cortex (189).

Cephaloridine injected subconjunctivally was found to penetrate aqueous humor and subretinal fluid effectively (196, 197). Low but effective subretinal levels were reported (198).

Records (199) was unable to detect antibacterial activity in the aqueous humor after a 1-g dose of cephaloridine. However, levels of 7–28 μg/ml were found in the secondary aqueous humor which refills the eye following aspiration of the primary fluid.

Prakash *et al.* (200) injected 1 g of cephaloridine intramuscularly every 12 hr for two doses to 60 women undergoing amniotomy for induction of labor to study the absorption and transfer of the antibiotic to the fetus as protection against intrapartum infections. The drug provided inhibitory concentrations in maternal serum, amniotic fluid, and umbilical cord blood. Similar results were found in another study (275).

Metabolism and Excretion—Urine specimens, both animal and human, which were examined by chromatographic and bioautographic techniques, showed that no other microbiologically active metabolites were present and that cephaloridine was excreted unchanged in the urine (183, 201).

Renal excretion of this drug is considered to be largely the result of glomerular filtration, but a 1.2-fold increase in cephaloridine serum concentration was found after probenecid administration (173, 179, 202, 203) and appears to indicate some tubular secretion. Excretion was found to be pH dependent, *i.e.*, increasing with decreasing pH (277).

Kidney disease resulting in impaired kidney function results in increased serum half-lives up to 23 hr (54, 105, 167, 189, 192, 203–207). The relationship between renal function and biological half-life was discussed (192).

Hemodialysis reduced the serum half-life in uremic patients to 3–5 hr (105, 167, 189, 204). An extraction ratio of 0.23–0.35 was reported (148, 192). Peritoneal dialysis resulted in a daily loss of 125–500 mg of drug from the body.

Urinary concentrations of 150 μg/ml or greater after a 0.5- or 1-g dose were maintained in all but anuric patients (192).

Urinary recovery after intramuscular and intravenous dosing was 60–80% (44, 116, 126, 172, 173, 179, 186, 187). Several investigations found 85% of a 500-mg dose in the urine (44, 105, 108).

Renal clearances were reported to be 146–280 ml/min (108, 173). A plasma clearance of 167 ml/min/1.73 m^2 and a renal clearance of 125 ml/min/1.73 m^2 were reported, indicating that approximately 75% of the drug was removed from the body by the kidneys (44, 108).

A serum half-life of approximately 1.1–1.5 hr was reported for cephaloridine (108, 126, 166, 167, 192, 205); however, a value of 48 min also was found (173). The volume of distribution was 16 liters (108).

Pharmacokinetic Considerations—Extensive pharmacokinetic analysis of literature data is not possible for this drug, since appropriate intravenous data have not been published. Most studies performed with cephaloridine involved intramuscular administration and were not designed for pharmacokinetic analysis. This drug is primarily administered *via* the intramuscular route.

Since its physicochemical properties are not significantly different from the other cephalosporins, the pharmacokinetics of this drug should be similar to those of the other cephalosporins; *i.e.*, its time course in the body is biexponential. Like the other cephalosporins, its half-life (1 hr) is short in relation to the normal dosing interval (6 hr), so the pharmacokinetics of this drug can be described adequately by a one-compartment open model.

Cephapirin—Cephapirin, 3-(hydroxymethyl)-8-oxo-7-[2-(4-pyridylthio)acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate acetate (ester) (VIII), is a semisynthetic cephalosporin for parenteral use. It is derived from 7-aminocephalosporanic acid. Cephapirin has a spectrum of antimicrobial activity similar to that of cephalothin (208). Cephapirin is effective against Gram-positive bacteria. Except for two strains of *Staphylococcus epidermidis* and *S. aureus*, cephapirin is effective at concentrations of 3.1 μg/ml or less against all susceptible strains of Gram-positive bacteria. Gram-negative bacteria were found to be less sensitive to the effects of the drug (208).

The sodium salt of cephapirin is extremely soluble in water; at 25°, the solubility is greater than 500 mg/ml (209). The pH of a reconstituted solution of cephapirin (sodium salt) is between 5.7 and 7.3 (209). Cephapirin is stable at 25° when reconstituted in most commonly used parenteral solutions. When reconstituted in sterile water, only 6% of the initial activity of the drug is lost in a 24-hr period. A complete study of the stability of cephapirin has been published (209).

Cephapirin is 44–50% bound to human plasma proteins (210). The addition of cephapirin to serum had little effect in lowering the MIC of this drug to *S. aureus* (208).

Absorption—Since cephapirin is not absorbed orally, it is only administered through the intramuscular and intravenous routes. Cephapirin seems to be relatively well absorbed after intramuscular injection. In one study in which 1 g of cephapirin was administered intramuscularly, peak levels in the serum of 24.2 μg/ml were attained at 0.5 hr after injection (211). Peak levels of cephapirin after intramuscular

administration of 0.5- and 1.0-g doses were 8 and 15 μg/ml, respectively (210). Peak levels were attained between 0.5 and 1 hr after administration.

After intravenous administration, a level of 72.6 μg/ml was reported at 0.5 hr after injection (211). These levels fell to 6.06 μg/ml at 1 hr after administration. Another study (210) found much lower levels after intravenous administration of 1.0 g of cephapirin. A peak level of about 15 μg/ml was attained.

Excretion and Metabolism—Cephapirin is metabolized to desacetylcephapirin *in vivo* (212). Approximately 41% of the recovered antibiotic is in the desacetylcephapirin form. Desacetylcephapirin was approximately 54% as potent as the unchanged drug against *S. lutea* (212).

Cephapirin is eliminated from the body largely through renal processes. Less than 1% of the original dose was recovered in the bile (210).

After an intravenous dose of 1 g, urinary levels of 2560 ± 503 μg/ml were found. Recoveries after 1-g intravenous and intramuscular doses were 72 ± 7.5 and 54 ± 18.6%, respectively (211).

The reported half-lives of cephapirin after intravenous and intramuscular administrations to normal volunteers were 21 and 47 min, respectively (211).

Since the elimination of cephapirin is largely due to renal excretion, the half-life of cephapirin is extended in patients with renal dysfunction. A study using azotemic patients found that the serum half-life of cephapirin was 95.9 min (212). These patients were not undergoing any form of dialysis treatment during the study. The average creatinine clearance was 12.6 ml/min. These patients excreted 19.5% of the initial dose in the urine.

The effect of dialysis on the half-life of cephapirin was studied, and the half-life in patients undergoing dialysis was about 107 min (212). Dialysis removed 22.8% of the dose.

A review of the use of cephapirin in children was prepared (213). Intramuscular injections of 20 mg/kg produced peak levels of 14.5 μg/ml, and injections of 12.5 mg/kg produced peak levels of 7.6 μg/ml. The antibiotic concentration in the urine after an intramuscular dose of 20.0 mg/kg was 1600 μg/ml. This recovery was 53% of the initial dose.

Pharmacokinetic Considerations—A very limited number of studies report serum levels of cephapirin (211, 214). Due to the paucity of information, plus the fact that the drug is metabolized and assayed microbiologically, it is difficult to discuss the pharmacokinetics of cephapirin. Only one study (211) described the pharmacokinetics of this drug. The reported half-life was 21 min after intravenous injection. This value was probably calculated by a log-linear regression using all points. Graphical estimation of the terminal portion of the curve, however, results in a half-life of approximately 42 min.

These data (211) are shown in Fig. 6. It can be seen that the curve appears to be biexponential. For the sake of completeness, the data were fitted to a two-compartment open model (Table VI). The half-life of the β-phase is about 45 min, almost twice that reported but identical to that obtained from the terminal portion of Fig. 6. The rate constants in Table VI should be considered to be apparent due to the fact that the drug is metabolized to a less active compound and assayed *via* a microbiological procedure. A more detailed discussion appears in the *Cephalothin* section.

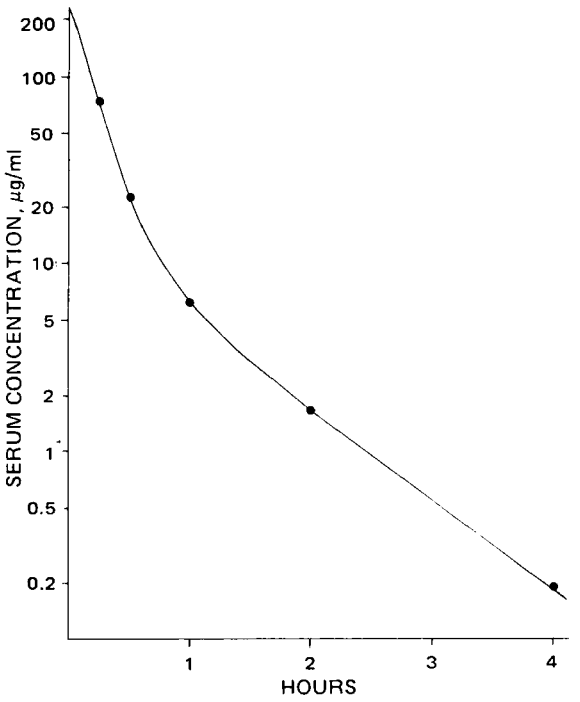


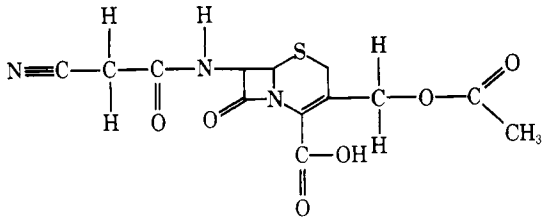
Figure 6—*Serum levels for cephapirin administered intravenously (rate constants for data generation from Table VI).*

Cephacetrile—Cephacetrile, 7-(2-cyanoacetamido) - 3 -(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylate acetate (ester) (IX), is a bactericidal drug whose mode of action is similar to the β-lactam antibiotics (215). It is less active than cephaloridine against penicillin-susceptible strains of *S. aureus* but is more active than cephaloridine or cephalexin against β-lactamase-producing strains. Cephalothin is more active in this regard than cephacetrile. Cephacetrile was reported to be relatively stable to β-lactamase degradation (180). It is also less active than cephaloridine and more active than ceph-

Table VI—Pharmacokinetic Parameters for Cephapirin Administered Intravenously (Literature Data)[a]

Parameter	Literature Reference 211	214	Mean ± *SD*
α, hr^{-1}	5.353	5.290	5.321 ± 0.045
β, hr^{-1}	0.926	1.082	1.004 ± 0.110
K_{12}, hr^{-1}	0.890	1.090	0.990 ± 0.141
K_{21}, hr^{-1}	1.177	1.570	1.374 ± 0.278
K_{el}, hr^{-1}	4.213	3.710	3.960 ± 0.360
$T_{1/2}\alpha$, hr	0.129	0.132	0.131 ± 0.002
$T_{1/2}\beta$, hr	0.749	0.669	0.709 ± 0.057
V_c, liters	6.166	12.379	9.273 ± 4.393
Vd_{ss}, liters	10.830	20.916	15.873 ± 7.132
Vd_β, liters	28.055	41.829	34.942 ± 9.739
Vd_{ext}, liters	108.888	118.517	113.703 ± 6.809

[a] Analysis of data using a two-compartment open model (Scheme I).



IX: cephacetrile

alothin against certain Gram-negative organisms (215). Similar results were reported in other studies (216–219). Cephacetrile was 33–36% bound to serum (215, 220). A binding range of 23–34% also was reported (221). Metabolism of the drug appears to be negligible based on chromatographic work (215, 220). It also appears to be less nephrotoxic than cephaloridine (222–224).

Absorption—Cephacetrile is absorbed after intramuscular injection. In one study, peak serum concentrations of 22.7 μg/ml were achieved 1 hr after administration of a 1-g dose and declined to an average of 1.65 μg/ml 4 hr after dosing (225). Similar results were reported (226), but some lower peak levels also have been found (221, 227, 228). Peak levels of 17.1 μg/ml at 30 min after injection were reported (229).

Dvoracek *et al.* (228) used a one-compartment open model to fit their data and found an intramuscular absorption half-life of 0.3 hr. This value was one-fifth the elimination half-life of 1.4 hr. This drug apparently is rapidly absorbed without a significant lag time (221, 228). Patients with decreased renal function exhibited prolonged peak times (229).

Distribution—Distribution to duodenal juice was low after a 1-g intramuscular injection (227). The maximal concentrations ranged from 1.0 to 3.1 μg/ml and were attained at the 1st and 2nd hr after administration. Higher levels (2.9–7.0 μg/ml) were reported in patients with renal failure (227).

Cephacetrile was administered to healthy pregnant women during labor by intravenous infusion and multiple bolus dosing (230). Maternal serum and amniotic fluid concentrations were determined as a function of time, and cord serum concentrations were determined after delivery. In the maternal serum, a mean steady state of 30 μg/ml was obtained. Cord serum and amniotic fluid concentrations reached 14 and 8–9 μg/ml, respectively, after intravenous administration and 19 and 22–25 μg/ml, respectively, after intramuscular administration. Maurice *et al.* (221) reported cerebrospinal fluid, fetal cord, amniotic fluid, bone, and prostatic tissue levels.

Excretion—Peak bile levels were observed between 1 and 4 hr after a 1-g intramuscular dose of the drug in cholecystectomized subjects (227, 231). The biliary concentration was low, with the peak concentration ranging from 1.0 to 6.8 μg/ml. In normal patients, the 1-hr peak concentrations were 14.7–19.4 μg/ml (227, 231).

Cephacetrile was reported to be 60–100% excreted in the urine (215, 220–222, 225, 226, 228, 229, 232–234).

The renal and plasma clearances of this drug were found to be approximately 230–240 ml/min (228). A plasma and renal clearance of 361 ml/min/1.73 m^2 was reported (226), which is further evidence that the drug is not significantly metabolized (228, 233, 235).

The serum half-life was reported to range between 0.5 and 1.5 hr (215, 220, 221, 226, 227, 229, 235, 236).

The pharmacokinetics of this drug were analyzed using a two-compartment open model (228). A β-phase half-life of 1.2 hr was found after intravenous injection. The rate constants are shown in Table VII. The intramuscular data were analyzed *via* a one-compartment open model, and a half-life of 1.4 hr was found.

Altered renal function was accompanied by a drop in the urinary elimination of the drug (219, 221, 222, 226–228, 231, 233–235, 237). In patients with renal failure, the serum concentrations of the antibiotic rose significantly (40.6 ± 8.1 μg/ml) 1 hr after injection (227). An increase in the half-life from 2.2 to 30 hr was noted (221, 226, 227, 229, 231, 233–238), depending on the severity of the renal function.

The relationships between renal function and the drug's half-life of elimination from the body have been studied (221, 231, 233–237, 239). Suggested doses in the case of renal insufficiency have been recommended (221, 229, 234, 240).

Hemodialysis in one study reduced the serum half-life by a factor of eight, with a mean extraction ratio of 32% (236). Fillastre *et al.* (229) found a twofold de-

Table VII—Pharmacokinetic Parameters for Cephacetrile Administered Intravenously (Literature Data)[a]

	Literature Reference				
Parameter	221	228 241	228[b] 241	232 236 242	Mean ± *SD*
α, hr^{-1}	2.410	3.880	4.44	2.470	2.920 ± 0.830
β, hr^{-1}	0.536	0.530	0.57	0.550	0.540 ± 0.010
K_{12}, hr^{-1}	0.658	1.540	1.80	0.680	0.960 ± 0.500
K_{21}, hr^{-1}	1.010	1.370	1.66	1.050	1.140 ± 0.200
K_{el}, hr^{-1}	1.280	1.510	1.55	1.290	1.360 ± 0.130
$T_{1/2\alpha}$, hr	0.287	0.180	0.16	0.280	0.250 ± 0.060
$T_{1/2\beta}$, hr	1.294	1.300	1.24	1.270	1.290 ± 0.020
V_C, liters	11.239	8.967	9.221	11.169	10.458 ± 1.292
Vd_{ss}, liters	18.578	19.005	—	18.444	18.676 ± 0.293
Vd_{β}, liters	26.921	25.380	—	26.376	26.226 ± 0.780
Vd_{ext}, liters	44.747	35.805	—	42.952	41.168 ± 4.730

[a] Analysis of data using a two-compartment open model (Scheme I). [b] Literature values.

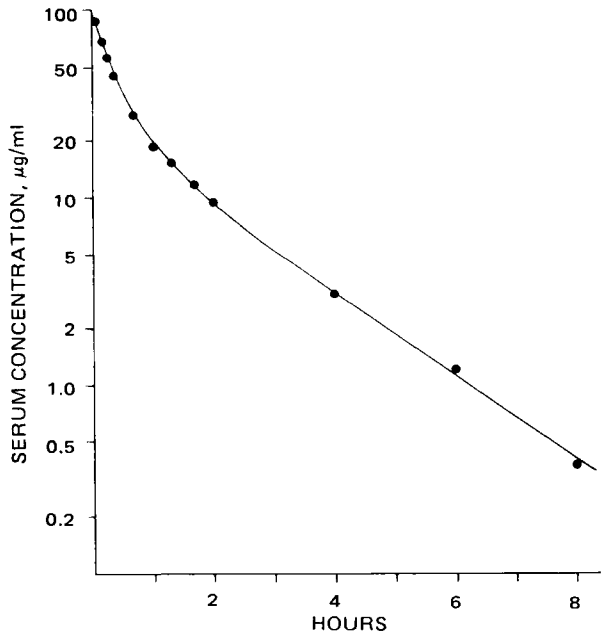


Figure 7—*Serum levels for cephacetrile administered intravenously (rate constants for data generation from Table VII).*

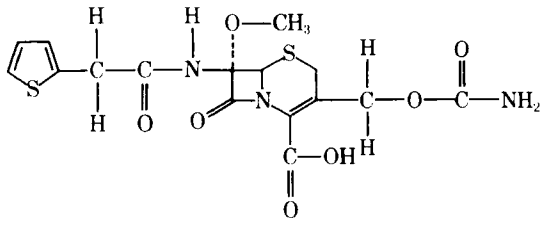
crease in serum levels compared to controls, with an extraction percentage of 27–33%. Similar results also were reported (226).

Evidence was presented that cephacetrile is actively secreted by the kidney and that probenecid can compete for the secretory route (233).

Pharmacokinetic Considerations—As with other cephalosporins, cephacetrile appears to follow two-compartment open model kinetics (Fig. 7). Investigators, with one exception (228), analyzed their data *via* a one-compartment open model. Shown in Table VII are the pharmacokinetic parameters obtained by analyzing literature data according to a two-compartment open model (220, 221, 228, 232, 236, 241). The analysis by Dvoracek *et al.* (228) is included for comparison and is similar to the other studies shown in Table VII. The half-life of the β-phase is within the range of reported values. Dvoracek *et al.* (228) reported a value of 9542 ml as the volume of the tissue compartment. The sum of $V_c + V_t$ is Vd_{ss} and is equal to 18,763 ml, in agreement with the Vd_{ss} values calculated using data from other studies (Table VII). The only other volume of distribution term reported was 0.3–0.5 liter/kg or 21,000–35,000 ml (221). The method of calculation was not clear, but the graphical data suggest that the reported value was actually Vd_{ext}.

In spite of the good fits of cephacetrile data using a two-compartment open model, little practical advantage is gained with this type of analysis for the reasons stated in the *Cephalexin* section.

Cefoxitin—Cefoxitin, 3-(hydroxymethyl)-7-methoxy-8-oxo-7-[2-(2-thienyl)acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid carbamate (ester) (X), is a semisynthetic cephamycin antibiotic (243). The 7-methoxylated cephalosporins possess marked resistance to the action of β-lactamases from Gram-positive and Gram-negative organisms (244). Of the Gram-negative microorganisms generally susceptible to cephalothin, *i.e.*, *E. coli*, *P. mirabilis*, and *Klebsiella*, cefoxitin was significantly more active than cephalothin (243, 245). The Gram-positive microorganisms, on the other hand, were less susceptible to cefoxitin than to cephalothin (243, 245).



X: cefoxitin

Cefoxitin does not appear to be orally absorbed; however, the drug appears rapidly in the blood after intramuscular injection (246). After 0.5- and 1.0-g doses, approximately 90% was recovered in the urine. After a 2-g iv dose, 99% was recovered in the urine, indicating that no extrarenal excretion occurred. Probenecid was found to affect the elimination of cefoxitin in mice (245), suggesting that this drug is eliminated *via* glomerular filtration as well as tubular secretion. This finding was also reported in humans (247). The drug was also found to be widely distributed in soft tissue (245).

The biological half-life of cefoxitin was calculated to be 45 min (246) compared to 25 min for cephalothin. The serum concentration *versus* time curve (Fig. 8) for this drug, as well as other cephalosporins, appears to exhibit biphasic decay. Analysis of the data of Kosmidis *et al.* (246) *via* a two-compartment open model analysis is shown in Table VIII. Since a paucity of published data exists concerning this antibiotic, it is not possible to draw further conclusions relative to its pharmacokinetic characteristics. The main advantage of this drug seems to be its resistance to degradation by β-lactamases.

Cephanone—Cephanone, 3-(5-methyl-1,3,4-thiadiazol-2-ylthiomethyl)-7-[2-(3-sydnone)acetamido]-

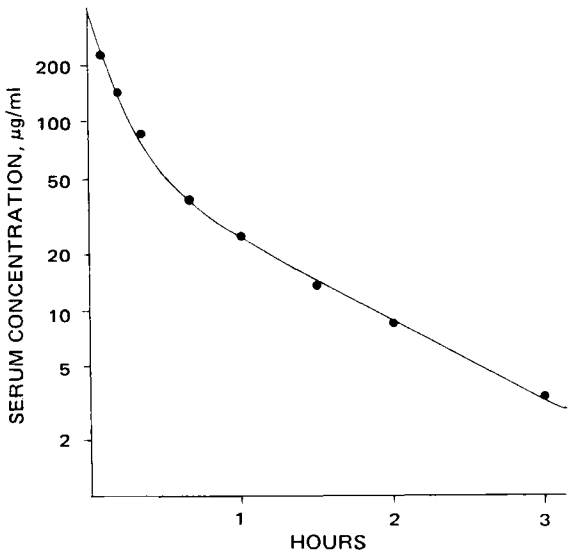


Figure 8—*Serum levels for cefoxitin administered intravenously (rate constants for data generation from Table VIII).*

Table VIII—Pharmacokinetic Parameters for Cefoxitin Administered Intravenously (Literature Data)[a]

Parameter	Literature Reference, 246
α, hr^{-1}	6.316
β, hr^{-1}	1.041
K_{12}, hr^{-1}	2.191
K_{21}, hr^{-1}	2.274
K_{el}, hr^{-1}	2.892
$T_{1/2\alpha}$, hr	0.110
$T_{1/2\beta}$, hr	0.666
V_c, liters	6.883
Vd_{ss}, liters	13.516
Vd_β, liters	19.120
Vd_{ext}, liters	29.463

[a] Analysis of data using a two-compartment open model (Scheme I).

Table IX—Pharmacokinetic Parameters for Cephanone Administered Intravenously (Literature Data)[a]

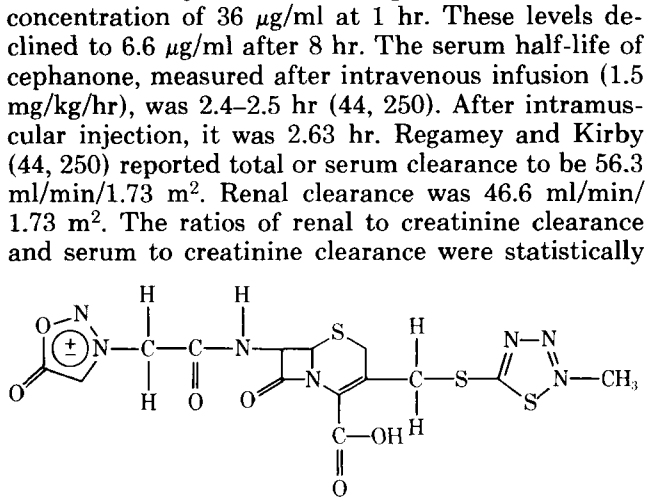
	Literature Reference		
Parameter	249	250	Mean ± *SD*
α, hr^{-1}	2.100	0.641	1.370 ± 1.032
β, hr^{-1}	0.282	0.224	0.252 ± 0.041
K_{12}, hr^{-1}	0.377	0.106	0.241 ± 0.191
K_{21}, hr^{-1}	1.645	0.360	1.002 ± 0.909
K_{el}, hr^{-1}	0.360	0.398	0.379 ± 0.027
$T_{1/2\alpha}$, hr	0.330	1.080	0.705 ± 0.532
$T_{1/2\beta}$, hr	2.457	3.097	2.776 ± 0.453
V_c, liters	10.400	5.184	7.792 ± 3.688
Vd_{ss}, liters	12.782	6.713	9.747 ± 4.291
Vd_β, liters	13.275	9.226	11.250 ± 2.863
Vd_{ext}, liters	13.870	15.867	14.868 ± 1.412

[a] Analysis of data using a two-compartment open model (Scheme I).

3-cephem-4-carboxylic acid (XI), is a semisynthetic cephalosporin derivative with an antibacterial spectrum similar to that of cephalothin (44, 248, 249). This drug was withdrawn from clinical trials due to suspected carcinogenicity, but it is included in this review for the sake of completeness. The drug is 86–88% protein bound (44, 250) and is relatively stable to β-lactamase degradation (180).

The average drug concentration in serum 0.5 hr after intramuscular administration of 1 g of cephanone was reported to be 38 μg/ml (249). Peak concentrations were attained at 1 hr. After 6 hr, the blood level declined to 22.1 μg/ml; after 12 hr, the blood level was still relatively high: 5.3 μg/ml. This level exceeds the MIC for most susceptible organisms (249). The half-life was 174 min; however, after intravenous administration, the half-life was 126 min, indicating that intramuscular administration does not provide, as with cefazolin and cephalexin, a pure elimination phase. After a 1-g iv injection, the blood levels ranged from 81.2 to 8 μg/ml after 8 hr. At 12 hr postadministration, drug levels were not detectable (249).

Regamey and Kirby (250), however, found higher blood levels after both intramuscular and intravenous injections. After intravenous administration of 250 mg of cephanone, a peak serum concentration of 31.9 μg/ml was present at the end of the 1st hr. An intramuscular injection of 500 mg resulted in a peak concentration of 36 μg/ml at 1 hr. These levels declined to 6.6 μg/ml after 8 hr. The serum half-life of cephanone, measured after intravenous infusion (1.5 mg/kg/hr), was 2.4–2.5 hr (44, 250). After intramuscular injection, it was 2.63 hr. Regamey and Kirby (44, 250) reported total or serum clearance to be 56.3 ml/min/1.73 m^2. Renal clearance was 46.6 ml/min/1.73 m^2. The ratios of renal to creatinine clearance and serum to creatinine clearance were statistically



XI: cephanone

identical, *i.e.*, 0.40–0.47. These ratios suggest that cephanone leaves the body chiefly through the kidneys.

The volume of distribution was reported to be 12 liters/1.73 m^2 (44) and 13.6 liters (250). These values were obtained after constant infusion and are analogous to the Vd_β of a two-compartment open model analysis.

Urinary excretion of cephanone appears to be high; however, variable results were reported (249). During a 24-hr period, all of a 1-g intravenous dose was excreted, but only 38% was found in the urine after a 500-mg injection. Intramuscular injection resulted in 50% of the administered (1-g) dose being excreted in the urine. Urinary drug concentrations were high. After administration of 1 g intramuscularly or intravenously, urine concentrations were 1.7 and 5.0 mg/ml, respectively, after 8 hr.

Regamey and Kirby (250) found 92% of a 500-mg im dose excreted in the urine. Similar results were obtained after intravenous infusion. Urine concentrations of cephanone were 900, 200, and 20 μg/ml in collections 0–4, 4–8, and 8–24 hr after administration, respectively.

After intravenous administration, the decline in cephanone serum levels appears to be biexponential (Fig. 9). It was possible to fit these data using a two-compartment open model analysis (Table IX). It can be seen that the half-life of the β-phase is in reasonable agreement with the literature using a one-compartment open model analysis. The volume of distribution terms are relatively low, probably due to the high degree (86–88%) of protein binding. This partially contributes to the relatively high blood levels seen with this drug. The large degree of protein binding probably results in the high and prolonged serum levels of cephanone.

Cefamandole—Cefamandole, 7-D-mandelamido-3-[[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl]-8-oxo-5-thio-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (XII), is a semisynthetic cephalosporin intended for parenteral use. The sodium salt has a molecular weight of 484.5. The spectrum of antibacterial activity is similar to that of other cephalosporins (251).

Since cefamandole is one of the newest cephalosporins, no pharmacokinetic studies have appeared.

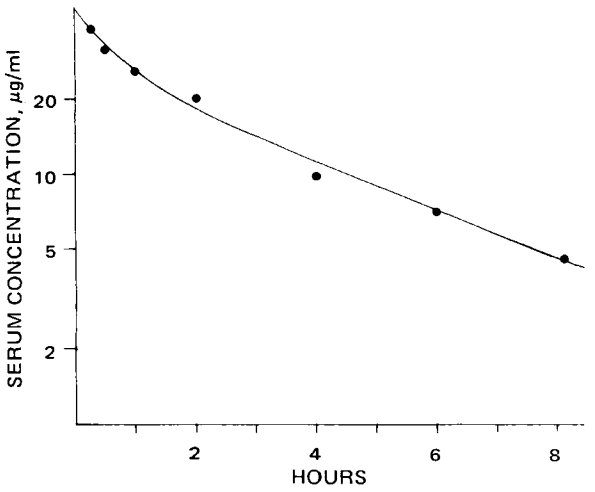
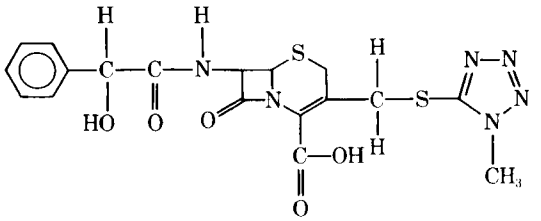


Figure 9—*Serum levels for cephanone administered intravenously (rate constants for data generation from Table IX).*

CLINICAL USE

Appropriate antibiotic usage requires an accurate knowledge of the antimicrobial susceptibility pattern of the drug to be given, sound clinical reasoning as to why the drug is being given, and knowledge of whether it will reach the site of the pathogen in adequate concentrations without producing serious side effects. This portion of the review is an attempt to provide an overview of the appropriate clinical use of cephalosporin antibiotics from the standpoint of an infectious disease physician.

General Considerations for Cephalosporin Administration—Cephalosporins are usually effective for infection from Gram-positive bacteria such as staphylococci (*S. aureus* and *S. epidermidis*), group A *Streptococcus*, anaerobic streptococci, and *Streptococcus pneumoniae* ("pneumococcus") and from Gram-negative organisms such as *E. coli*, *P. mirabilis*, *Hemophilus* species, and *K. pneumoniae*. However, once one of these bacteria has been identified as the causative organism of an infectious disease process, usually other antibiotic agents are preferable, either because of a greater degree of microbiological activity or because of a smaller likelihood of producing a suprainfection. For instance, the antibiotic of choice for group A *Streptococcus*, the "pneumococcus," nonpenicillinase-producing staphylococci, and anaerobic streptococci is penicillin G; ampicillin is the preferred antibiotic for *Hemophilus* infection and often has equal or greater activity toward *E. coli* and *P. mirabilis*; and oxacillin is a more logical choice for penicillinase-producing *S. aureus*. Cephalosporins have a greater degree of activity against *S. epidermidis* (about 80–85% sensitive to oxacillin, almost all sensitive to cephalosporins); but if a strain is sensitive to oxacillin, it is a better drug to give because of its narrower spectrum as compared to a cephalosporin.



XII: cefamandole

It is only with respect to *Klebsiella* that cephalosporins are clearly more active than ampicillin, penicillin G, or oxacillin. Although more strains of *Klebsiella* are sensitive to aminoglycosides, such as gentamicin and kanamycin, one usually prefers a cephalosporin in a situation where an isolate is sensitive to both classes of antibiotics due to the greater potential toxicity of the aminoglycosides.

The enterococci, indole-positive *Proteus*, *Enterobacter* species, *Serratia*, *Pseudomonas*, *Herellea*, and *Citrobacter* are usually resistant to cephalosporins.

The cephalosporin popularity stems mainly from their reasonably broad antimicrobial coverage, their relatively low incidence of serious adverse drug reactions, the small frequency of cross-reaction in patients with a history of penicillin hypersensitivity, and their common usage to prevent the development of infection following surgical procedures involving the insertion of prosthetic devices such as vascular grafts, artificial heart valves, and orthopedic hardware.

Appropriate Use of Cephalosporins by Parenteral Route—*Prevention of Infection on Prosthetic Devices*—Few subjects create more lively debate than the use of antibiotics for prophylactic purposes. As seen by Jawetz (252), there is no place for prophylactic antibiotics unless the prophylaxis is directed against one particular or small group of microorganisms.

All other attempts at more general prophylaxis with antibiotics usually have been unsuccessful. Chemoprophylaxis has never proven significant in reducing the likelihood of a patient developing an infection in clinical situations where multiple organisms may invade, as is the case in most GI surgical procedures, pancreatitis, or the insertion of an in-dwelling bladder catheter. In fact, general prophylaxis has often been detrimental by favoring colonization and infection by microbes resistant to the antibiotic given. Since most compromised hosts, such as patients with leukemia or lymphoma, develop infection from organisms on their skin or from their genitourinary tract, and since it is impossible to sterilize the entire patient, antibiotic prophylaxis has also been of no value in these cases.

In view of these comments, it would be logical to administer a cephalosporin antibiotic only in clinical situations where one can predict the likely pathogen with a high degree of certainty and the particular pathogen is easily eradicated by this type of antibiotic. The administration of a cephalosporin to prevent infection following the insertion of artificial material (*e.g.*, prosthetic heart valves, Dacron or Teflon artificial grafts, and orthopedic hardware) follows this dictum, since after the placement of these foreign bodies about 90% of the infections develop from a single group of organisms, namely staphylococci, either coagulase negative (*S. epidermidis*) or coagulase pos-

itive (*S. aureus*). As already mentioned, cephalosporin antibiotics are usually active against all types of staphylococci whereas the isoxazole antibiotics, such as oxacillin, are usually ineffective against 15–20% of coagulase-negative staphylococci. Because of this situation, cephalosporins have emerged as the most appropriate agents to use in the prevention of infections on prosthetic material.

Some clinical situations represent "gray zones" in prophylactic antibiotic usage because more than one organism, but usually not more than five, may produce the infection. An open comminuted fracture represents a situation where infection commonly occurs from a relatively small number of microbes. Traumatic wound infections above the waist are often from skin bacteria, such as *S. aureus* or group A *Streptococcus*, while those below the waist are usually caused not only by these common skin microbes but also by *E. coli* and *P. mirabilis* (indole-negative *Proteus*), probably derived from bacterial "fallout" from the GI tract. As a result, oxacillin, which exhibits its activity against these Gram-positive bacteria, and cephalosporins, which are bactericidal toward both these Gram-positive and Gram-negative organisms, are the logical choices for prophylaxis against wound infection above and below the waist, respectively.

Two major problems have developed with the use of cephalosporins for prophylaxis. One is that they are often administered too long, even in appropriate situations, and the other is that they are often given illogically in clinical problems such as bowel surgery where they can be detrimental by the replacement of susceptible organisms with resistant ones.

Various investigators have demonstrated clearly that maximum protection from infection from a surgical procedure occurs only if adequate tissue levels are present at the time of the surgical procedure (253) and that the continuation of antibiotics beyond the operative period has no value. This situation was nicely illustrated in a study where a single dose of cephalothin administered immediately prior to the insertion of prosthetic heart valves was as effective in the prevention of infection as was the use of additional dosages after the operation (254).

The tendency of physicians to be reluctant to discontinue completely antibiotics by the intravenous route after they no longer are necessary has been a traditional problem with all antibiotics, particularly with the use of cephalosporins for prophylaxis. For instance, it is quite common for a surgeon to administer a cephalosporin in a ritualistic sequence: first intravenously, then intramuscularly, and finally orally for 1 to many weeks following an operative procedure. In fact, one often wonders why the physician does not go next to the intradermal or intraocular route! Unfortunately, this gradual weaning process has been a major reason for the increase in cost for this class of antibiotics, because it not only increases the amount of antibiotic administered but also enhances the chances of toxic drug reactions or superinfection, resulting in greater morbidity and prolonged hospital stay.

Therapy of Lung Infections Acquired in the Community—If the sepsis appears to be from a pulmonary infection produced by bacteria acquired from outside the hospital, and especially if the patient has a history of chronic lung or other debilitating disease, a cephalosporin antibiotic seems to be the wisest choice. The usual pathogens in this setting are *K. pneumoniae*, *Strep. pneumoniae*, *Hemophilus influenzae*, *S. aureus*, and group A *Streptococcus* organisms and are almost always sensitive to this antimicrobial agent if given in adequate dosage. There is some hesitancy about relying on ampicillin or penicillin alone, since most *Klebsiella* organisms and many staphylococci are resistant to both penicillin and ampicillin (about 80% of the *S. aureus* acquired outside the hospital now produces penicillinase).

It usually is possible to use penicillin or ampicillin as the sole antibiotic only in healthy patients with mild respiratory infections, since the physician can usually exclude the *Staphylococcus* or *Klebsiella* organism in such a clinical setting because these organisms almost always produce very serious disease.

Therapy of Lung Infections Acquired in Hospitals—Pulmonary infection acquired in a hospital setting is a difficult clinical problem because of the rapid colonization of the upper respiratory tract by common as well as bizarre bacteria. In a recent epidemiological survey (255) (Table X), 10.7 and 15.3% of the hospital-acquired pneumonias were produced by *Pseudomonas aeruginosa* and *K. pneumoniae*, respectively, followed in decreasing frequency by *E. coli* (10.6%), *Strep. pneumoniae* (9.5%), *Enterobacter* species (8.0%), and *S. aureus* (6.6%). Thus, in patients who develop hospital-acquired pneumonias, a combination of a cephalosporin and gentamicin appears to make sense, since it affords a more clinically proven coverage against *S. aureus* and *Klebsiella* than may be obtained with gentamicin and ampicillin. Moreover, the *Bacteroides* species usually involved in hospital-acquired pneumonias come from the upper respiratory tract where they are usually sensitive to cephalosporins.

Although most strains of *S. aureus* are susceptible to gentamicin *in vitro*, there is extremely little clinical experience for the use of this antibiotic in patients with overwhelming staphylococcal disease. Moreover, the enterococcus is rarely, if ever, involved

Table X—Major Organisms Associated with Suspected Hospital-Acquired Pneumonia from October 1970 to October 1973

Organism	Number	Percent
Klebsiella pneumoniae	138	15.3
Pseudomonas aeruginosa	97	10.7
Escherichia coli	96	10.6
Streptococcus pneumoniae	86	9.5
Enterobacter species	73	8.0
Staphylococcus aureus	60	6.6
Proteus species	45	4.9
Serratia species	17	1.9
Candida	17	1.9
Herellea	14	1.5
Citrobacter	3	0.3
Enterococcus	1	0.1
Other organisms	256	28.3
Total	903	100.0

in producing pneumonia; hence, the absence of coverage for this organism with the combination of a cephalosporin and gentamicin is of no great concern. For instance, in a review of hospital-acquired pneumonias at Hartford Hospital (255), from 1970 to 1973 there was only a single equivocal case of pulmonary infection caused by the enterococcus (Table X).

Inappropriate Use of Cephalosporins by Parenteral Route—*Treatment of Central Nervous System Infections*—Although cephalothin is often an effective antibiotic in many types of infection, especially pulmonary infections, its poor penetration into the cerebrospinal fluid is often not appreciated. In humans without meningitis, no detectable levels of this antibiotic were achieved after the intravenous administration of cephalothin, whereas even in patients with meningitis, low levels of 0.16–0.31 μg/ml were obtained (155). After the rapid intravenous infusion of 2–4 g of cephalothin in 14 patients, either as a single dose or at 4–6-hr intervals for several days and, in one case, for 3 weeks, Lerner (256) found cerebrospinal cephalothin levels of 0.155–25 μg/ml only in patients with cerebrospinal fluid protein content in excess of 50 mg/100 ml. When the protein concentration was less than 50 mg/100 ml, no measurable drug activity could be found in the cerebrospinal fluid.

Brown *et al.* (257) treated 12 patients with meningococcal meningitis with intravenous cephalothin at a dosage of 100–200 mg/kg/day. Clinical results were variable, and they concluded that this antibiotic could not be recommended as an effective alternative to penicillin or ampicillin. Mangi *et al.* (258) recently summarized eight cases of meningitis that developed during cephalothin therapy from organisms sensitive to this antibiotic, indicating dramatically its poor penetration into the cerebrospinal fluid.

Empirical Therapy of Infections from the Genitourinary or GI Tract—Since infection derived from the genitourinary and GI tracts are also usually from Gram-negative organisms with a wide variety of antimicrobial susceptibility patterns, the antibiotic "coverage" must be very broad. Combination of ampicillin and gentamicin meets this requirement better than a cephalosporin with gentamicin. Gentamicin sulfate is an aminoglycoside which has *in vitro* activity against practically all important Gram-negative and Gram-positive bacteria including *Ps. aeruginosa*, *Serratia marcescens*, and *S. aureus*. This antibiotic, however, is usually not effective against *Strep. pneumoniae*, group D *Streptococcus* (enterococcus), and anaerobes such as *Bacteroides* species. By adding ampicillin, protection also is created against the group D *Streptococcus* and *Strep. pneumoniae*, but there is only moderate defense against *Bacteroides*.

There is usually no need for antibiotic coverage of anaerobes, *Strep. pneumoniae*, group A *Streptococcus*, and *S. aureus* in the urinary tract, since these organisms are essentially of no clinical importance in this area. Thus, since cephalosporins have little activity against group D *Streptococcus*, and since ampicillin has a high degree of activity against this organism, the latter antibiotic seems to be the more appropriate drug to combine with gentamicin, especially when the suspected source of the bacteremia is from the urinary tract, an area where the enterococcus commonly resides.

Table XI—Organisms Isolated from Blood in Patients with Bacteremia *Definitely* Related to Urinary Tract Instrumentation

Organism	Number of Cases	Cephalosporin Activity[a]
Escherichia coli	9	±
Enterococcus	4	—
Enterobacter species	3	—
Proteus mirabilis	3	+
Proteus vulgaris	2	—
Citrobacter freundii	2	—
Proteus morganii	1	—
Klebsiella species	1	+
Serratia marcescens	1	—
Pseudomonas aeruginosa	1	—
Total	27	

[a] + = high degree of activity, ± = moderate activity, and — = no activity.

Table XI records the organisms that were definitely involved in bacteremia following urinary tract manipulation from 1970 to 1973 (255). Until these epidemiological data were shown to physicians, particularly to urologists, it was customary to administer a cephalosporin as a sole antibiotic in patients who suddenly became septic following instrumentation of the urinary tract. As can be seen from this table, over half of the organisms were not covered by this antibiotic; a combination of gentamicin and ampicillin would have provided appropriate protection against all of these pathogens.

Table XII (255) shows the 10 most common organisms producing bacteremias on a general surgical service during the same period. It is again apparent that over half of the organisms would not have been covered if a cephalosporin was used as the only antibiotic.

Additional Therapeutic and Economic Considerations in Selection of Cephalosporins for Parenteral Administration—From an inspection of Table XIII and Fig. 10, it is apparent that cephalothin and cephapirin are very similar from a pharmacokinetic standpoint. After the administration of 1 g of either antibiotic, results from sequential determinations of blood levels are very similar. Moreover,

Table XII—"Top Ten" Bacteremias in General Surgery (1970–1973)

Organism	Number of Isolates	Cephalosporin Activity[a]
Escherichia coli	23	±
Pseudomonas	12	—
Bacteroides	12	—
Klebsiella	11	+
Staphylococcus aureus	8	+
Enterococcus	7	—
Proteus indole +	6	—
Proteus indole —	5	+
Enterobacter	4	—
Serratia	3	—
Total	91	

[a] + = high degree of activity, ± = moderate activity, and — = no activity.

Table XIII—Comparison of Pharmacokinetic Parameters of Cephalosporin Antibiotics

Parameter	Cephalexin[a]	Cephradine	Cephaloglycin[a]	Cefazolin	Cephalothin	Cephaloridine	Cephapirin	Cephacetrile	Cefoxitin	Cephanone
Serum clearance, ml/min	248 ± 11	435	—	62 ± 6	472	167	—	230—240	—	56.3
Renal clearance, ml/min	252 ± 5	367	—	64 ± 6	274	125	—	230—240	—	46.6
Renal excretion (24 hr), %	80—100	79—96	18—25	100	52	75	41	60—100	90—100	92
Half-life, hr	0.9	0.8	1.5	1.8	0.6	0.6—1.5	0.7	1.3	0.67	2.8
Half-life after hemodialysis, hr	—	—	—	6.9—9.3	3.3	3—5	1.8	—	—	—
Percent protein bound	6—10	8—20	24	73—86	65	8—31	44—50	23—36	—	86—88
Peak serum levels (0.5 g), μg/ml	18	46	0.9—2.0	11—70	6—8	30	8	—	10.9	36.0
Peak serum levels (1.0 g), μg/ml	32	86	—	38—75	15—20	40	15	17—22	22.5	81.2
Vd_{β}, liters	23	22	—	10	22	—	35	26	19	11
Vd_{ext}, liters	32	31	—	13	40	—	113	41	29	15

[a] Oral administration.

cephapirin shares essentially the same antibacterial spectrum (208) as cephalothin with similar therapeutic results from infections such as pneumoniae (259, 260), septicemia, empyema, osteomyelitis, soft tissue infections, and urinary tract infections (148, 213, 261, 262). Adding even further to the similarities is the conversion of both antibiotics to a desacetyl metabolite, which results in appreciable loss of antibiotic activity (263).

A double-blind study (264) comparing the phlebitis produced by cephapirin and cephalothin showed that neither the incidence nor the degree of phlebitis was significantly different with the two drugs. Although cephalothin and cephapirin are not generic equivalents, there appears to be no reason why these antibiotics cannot be considered equivalent, making it acceptable and safe for a patient receiving 1 g of cephalothin to be given 1 g of cephapirin in its place or vice versa.

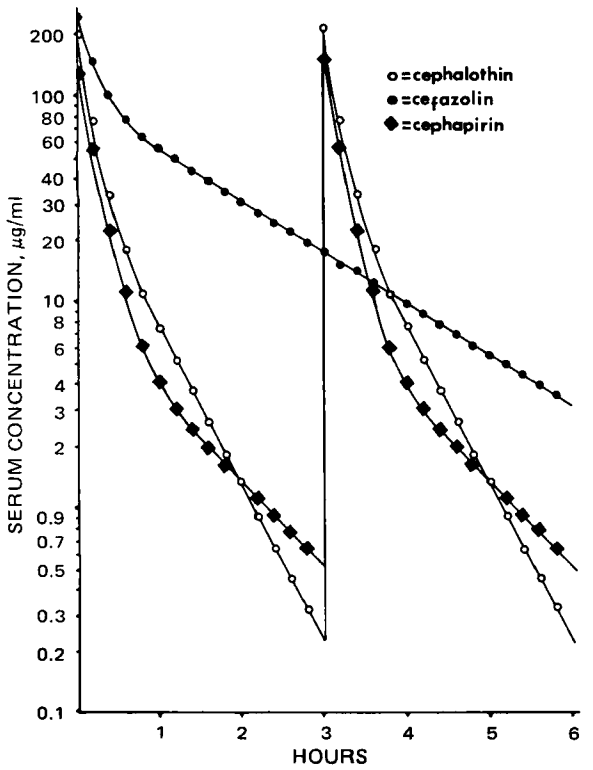


Figure 10—*Comparison of serum levels after intravenous administration of a single 1-g dose of cefazolin* versus *1 g of cephalothin or cephapirin every 3 hr (rate constants for data generation reported in Tables IV–VI).*

Cephaloridine has little justification for use in clinical medicine any longer since it is the only parenteral cephalosporin associated with significant nephrotoxicity (265–268) in humans and has no greater therapeutic effectiveness than any of the other three available cephalosporins for use by the parenteral route. With the recent availability of cefazolin, the logic for the continued usage of cephaloridine has been reduced even further.

Of the cephalosporins presently available for administration by the parenteral route, cefazolin is the preferred agent on both a therapeutic and economic basis. This impression is based on the following reasoning:

1. Cefazolin provides serum levels two to three times as high as cephalothin or cephapirin (see pharmacological and pharmacokinetic sections) (Table XIII and Fig. 10).

2. Biliary tract excretion of cephalosporins in humans is highest with cefazolin (approximately 17, 7, and 1 μg/ml for cefazolin, cephaloridine, and cephalothin, respectively) (269).

3. Cefazolin can be given comfortably and safely by either the intravenous or intramuscular route. In a dosage greater than 0.5 g, cephalothin is poorly tolerated.

4. Unlike cephalothin or cephapirin, cefazolin is not metabolized into a less active compound (see sections on pharmacology and pharmacokinetics).

5. Clinical studies demonstrated that cefazolin has therapeutic effectiveness at least as adequate as cephalothin and cephapirin (44).

6. Toxicology studies in animals and clinical experience with cefazolin in humans indicate that it is as safe as cephapirin and cephalothin (110, 274).

7. Cefazolin has the longest half-life of all cephalosporins (cephalothin, 0.6 hr; cephapirin, 0.7 hr; cephaloridine, 0.6–1.5 hr; and cefazolin, 1.8 hr). As a result, it can be administered less frequently (Table XIII).

8. Since cefazolin can be given less frequently and in a smaller total daily dosage (approximately half as frequently and/or half the number of grams), appreciable reduction in pharmacy cost can be predicted.

9. The microbiological activity of cefazolin is essentially similar to that of cephalothin and cephapirin except for its slightly greater activity against *E. coli* and *Enterobacter* species (111, 270).

10. To increase the economic savings for both the hospital and the patient, advantage should be taken of cefazolin's ability to be administered without appreciable discomfort by the intramuscular route. Such administration will reduce the cost of intravenous administration and lessen the demands on the intravenous therapist. The levels achieved by 1 g of cefazolin by the intramuscular route are high; peak levels in 1 hr are about 70 μg/ml, with appreciable levels (8–10 μg/ml) still present at 8 hr. These levels are certainly adequate since most Gram-positive bacteria such as *S. epidermidis, S. aureus,* the pneumococcus, and group A *Streptococcus* require less than 2–3 μg/ml, and the average MIC of cefazolin for Gram-negative bacteria such as *E. coli, P. mirabilis, Salmonella* species, *K. pneumoniae, H. influenzae,* and *Shigella* species are 1.6, 6.2, 4.0, 2.0, 4.0, and 8.0 μg/ml, respectively (104).

11. More frequent use of intramuscular medication will reduce the incidence of hospital deaths associated with bacteremia from prolonged in-dwelling intravenous polyethylene catheters.

12. Cefazolin is manufactured by two different pharmaceutical companies, allowing for competitive bidding.

In brief, cefazolin appears to combine the best features of cephalothin, cephapirin, and cephaloridine.

Cephalosporins for Oral Administration—Cephalexin, cephradine, and cephaloglycin are semisynthetic analogs of cephalosporin C that can be administered by the oral route. Their antibacterial spectrum *in vitro* is very similar to the parenteral cephalosporins; as expected, the enterococci, indole-positive *Proteus, Enterobacter, Serratia,* and *Pseudomonas* organisms are usually resistant. These oral agents often have less activity against staphylococci than any of the parenteral cephalosporins or the penicillinase-resistant penicillins. Cephalexin and cephradine have become the favorite oral cephalosporins since, in contrast to cephaloglycin which is relatively poorly absorbed from the GI tract and produces effective concentrations only in the urine (271), they are well absorbed and result in adequate antibiotic levels throughout most of the body (68, 79, 272).

Although cephalexin and cephradine have been used successfully in many infections of the respiratory tract, soft tissue, and urinary tract (63, 273), there is no evidence that their results are any better in the treatment of these illnesses from organisms that are sensitive to much cheaper oral drugs such as penicillin, ampicillin, oxacillin, dicloxacillin, or erythromycin. Their main use probably should be in the followup management of patients who are initially treated with parenteral cephalosporins or in the initial treatment of patients who have infections of the urinary tract from organisms (usually *Klebsiella)* resistant to other oral antibiotics or of patients with a history of penicillin hypersensitivity.

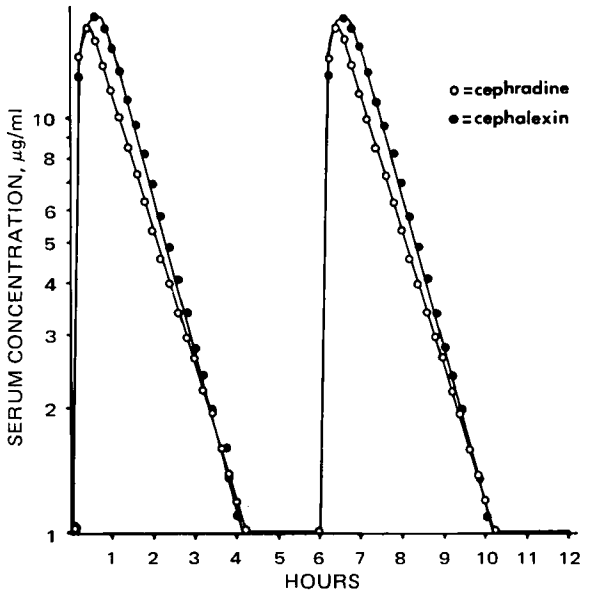


Figure 11—*Serum concentration of cephradine and cephalexin after 500 mg of each drug by the oral route (rate constants for data generation reported in Tables II and III).*

Cephalexin and cephradine, although different drugs, can also be considered similar in terms of pharmacokinetics and therapeutic equivalence (66) and can be interchanged in a fashion analogous to cephalothin and cephapirin. Figure 11 depicts the almost identical serum levels of cephradine and cephalexin following the administration of 500 mg of each drug. Moreover, inasmuch as cephradine and cephalexin are produced by different pharmaceutical companies, competitive bidding should result in a significant reduction in cost for the hospital and patient.

Conclusion—In brief, an explosion in the number of commercially available cephalosporins has occurred as the potential market for the sale of this class of antimicrobial agents has grown appreciably. To prevent excessively high hospital pharmacy cost with the resultant increase in the cost of a patient's hospital stay, the present cephalosporins and each new one that appears—which will be numerous—must not be automatically looked upon as "unique" antibiotics, even though they are not exact generic equivalents. The important issue is whether they are equivalent from pharmacokinetic and therapeutic standpoints, since the former determines the mode of administration and the likelihood of an adverse drug reaction, while the latter decides whether a patient will survive an infectious disease process.

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