Evaluation of Cefazolin, a New Cephalosporin Antibiotic

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Cefazolin sodium was tested in vitro against 308 isolates of Enterobacteriaceae, Pseudomonas aeruginosa, Neisseria meningitidis, Haemophilus influenzae, Staphylococcus aureus, and enterococcus. Broth and agar dilution and disk diffusion techniques were used with at least two sizes of inocula of organisms. Cefazolin was also studied in the treatment of 85 hospitalized patients with a variety of serious infections. In concentrations of 5 μg or less/ml, cefazolin inhibited and killed more than 90% of isolates of Enterobacteriaceae with the exception of indole-positive Proteus and Enterobacter species. No isolate of P. aeruginosa and only a few of Enterobacter and enterococci were killed by 25 μg of cefazolin/ml, a concentration readily attainable in serum with a 500-mg dose given intramuscularly. Penicillin-susceptible as well as penicillin-resistant isolates of S. aureus were killed by 1 μg or less of cefazolin per ml; however, 25 μg/ml was required to kill 100% of the strains when the inoculum size was increased 100-fold. Cefazolin treatment appeared effective in 82 of 85 patients, including four with endocarditis. Pain was minimal after intramuscular injection, and thrombophlebitis was not observed in those treated intravenously. No patient developed a positive Coombs test, and no evidence of renal toxicity was apparent in clinical studies.

Cefazolin, a semisynthetic derivative of cephalosporin C, is active against a wide variety of pathogenic bacteria (11, 13, 22). Although cefazolin shares the same basic structure with cephaphothlin and cephaloridine, it differs considerably by having both a tetrazolylacetlyl side chain on the amino group and a 5-methyl-thiazidazol-thiethyl group on the 3 position of the 7-aminoccephalsporanic acid (10).

Early studies showed that cefazolin gives sustained antibacterial concentrations in blood after intramuscular or intravenous use, is well tolerated, and has less cross-reactivity with benzylpenicillin in vitro than other commonly used cephalosporins (9, 10, 16). This report describes further the in vitro activity of cefazolin against common bacterial pathogens, its use in 85 hospitalized patients with a variety of severe infections, and the concentrations of cefazolin achieved in body fluids with usual doses in humans.

MATERIALS AND METHODS

Laboratory studies. Minimal inhibitory concentrations (MIC) and minimal bactericidal concentrations (MBC) of cefazolin were determined with 20 to 30 isolates each of Escherichia coli, Proteus mirabilis, indole-positive Proteus, Klebsiella, Enterobacter, Pseudomonas aeruginosa, Salmonella and Shigella, Neisseria meningitidis, penicillin-susceptible and penicillin-resistant Staphylococcus aureus, and enterococci. Both 10⁻¹ and 10⁻⁴ dilutions of an overnight broth culture of each isolate were tested by methods described previously from this laboratory (20). The bactericidal end point (MBC) was defined as the lowest concentration of antibiotic in which fewer than three viable colonies were recovered when about 0.005 ml of broth from each clear tube was subcultured onto agar without antibiotic. The susceptibility of all isolates to cefazolin also was determined in agar by use of the Steers replicator device (19). Inhibitory zones around disks containing 30 μg of cefazolin were measured for isolates of Enterobacteriaceae and P. aeruginosa and were compared with the results of the broth dilution assay as described previously (20, 21).

In addition, the MIC and MBC of cefazolin, cephaloridine, and cephalothin for the 30 isolates of S. aureus were determined with 10⁻¹, 10⁻², and 10⁻⁴ dilutions of an overnight broth culture of bacterial cells. The activity of cefazolin against 28 isolates of Haemophilus influenzae was tested by the agar dilution method (15) with 10⁻² and 10⁻⁴ dilutions of a suspension that contained about 10⁸ organisms/ml.
Colonies of *H. influenzae* grown overnight on chocolate agar were suspended in Tryptase soy broth to give an optical density by visual comparison equivalent to a barium sulfate standard prepared as described elsewhere (2).

The media used were nutrient broth and agar for *Enterobacteriaceae*, *P. aeruginosa*, and *S. aureus*; Mueller-Hinton (MH) broth and agar with 5% sheep blood for enterococci; and heated (chocolatized) MH agar with 5% sheep blood for *H. influenzae*.

**Clinical studies.** Cefazolin sodium was provided in sterile vials containing 0.5 or 1 g of dry powder and was dissolved in 2 or 3 ml of sterile water before parenteral administration. Patients were selected to receive cefazolin on the basis of clinical, roentgenologic, and bacteriological evidence of having an infectious process likely to respond to a cephalosporin type of antibiotic. The response to cefazolin therapy was evaluated by clinical and laboratory criteria. The clinical and bacteriological data were considered adequate for analysis of efficacy, tolerance, and toxicity in 85 hospitalized patients treated with cefazolin. Of the total group of patients, 64 were men and 21 were women; their ages ranged from 18 to 89 years. The most frequently used dosage schedule was 0.5 g given every 8 h intramuscularly for a total of 7 days. However, regimens ranged from 1.5 to 4 g per day injected intramuscularly or intravenously depending upon the severity and type of infection. One patient inadvertently received 6 g of cefazolin/day.

Antibiotic susceptibility testing by the standardized single-disk method (2) was performed on the majority of clinical isolates from patients treated with cefazolin.

Possible toxic effects of cefazolin were detected by determining packed cell volume, total and differential white blood cell counts, total serum bilirubin, serum alkaline phosphatase, serum glutamic oxaloacetic transaminase (SGOT), blood urea nitrogen (BUN), serum creatinine, urinalysis, and a Coombs test for most patients at the onset, during, and after treatment with cefazolin.

Concentrations of cefazolin in body fluids were assayed by a modified agar-well diffusion method (4); cefazolin antibiotic standards were prepared in the same kind of fluid as that being assayed. The following cefazolin assays were done: serum concentrations in seven patients after 1 g of cefazolin given intramuscularly; multiple simultaneous serum and synovial fluid assays in one patient; comparative serum and cerebrospinal fluid concentrations in five patients who required an elective lumbar puncture for neurological diagnostic studies and one patient being treated with penicillin for streptococcal meningitis; and comparative serum, urine, and urine concentrations and clearance during a constant intravenous infusion of cefazolin in a patient with a T-tube in the common bile duct after a cholecystectomy. All patients studied had normal renal function as measured by serum creatinine, BUN, and urinalysis.

**RESULTS**

**Susceptibility of gram-negative pathogens to cefazolin in broth dilution tests.** The activity of cefazolin against isolates of *E. coli*, *P. mirabilis*, *Klebsiella*, and *Enterobacter* is shown in Fig. 1 and 2. At a concentration of 5 μg or less/ml, cefazolin inhibited and killed 100% of isolates of *E. coli* and *P. mirabilis* and more than 90% of isolates of *Klebsiella* when tested with an inoculum of 10^6 bacterial cells/ml. However, an increase in inoculum size from 10^6 to 10^7 bacterial cells/ml resulted in decreased susceptibility of these isolates to cefazolin. For example, 93% of isolates of *E. coli* were inhibited and 63% were killed by 5 μg or less of cefazolin per ml with the 100-fold higher inoculum, whereas 100% were inhibited and killed with the lower inoculum. The effect of the size of the inoculum upon the MBC was most striking for *P. mirabilis*. Cefazolin inhibited 100% of the isolates of *P. mirabilis* at a concentration of 2.5 μg/ml with either inoculum size; 83% of the isolates also were killed with an inoculum of 10^6 organisms/ml, whereas none was killed at 2.5 μg/ml and only 17% were killed by 100 μg of cefazolin/ml when the inoculum was 10^7 organisms/ml (Fig. 1).

As observed previously with other cephalosporin antibiotics, marked differences in susceptibility to cefazolin were found when isolates of *Klebsiella* were compared with those of *Enterobacter* (Fig. 2); 90% of the isolates of *Klebsiella* were inhibited and killed by 10 μg of cefazolin/ml, whereas 10% of the isolates of *Enterobacter* were killed at this concentration when the inoculum was 10^6 organisms per ml. Although not shown, less than 40% of the 29 strains of indole-positive *Proteus* tested were susceptible to 25 μg of cefazolin/ml, a concentration readily obtainable in serum with 0.5 g given intramuscularly. All 22 strains of *P. aeruginosa* studied were resistant to at least 100 μg of cefazolin/ml.

All 30 isolates of *Salmonella* and *Shigella*, including five strains of *S. typhi*, were inhibited and killed by 10 μg of cefazolin/ml with both the high and low inocula (Fig. 3). Cefazolin showed good bactericidal activity against these enteric pathogens; there was little discrepancy between the MIC and MBC with either inoculum size. All 30 strains of *N. meningitidis* were inhibited and killed by 0.5 μg or less of cefazolin per ml regardless of the size of the inoculum and by both the broth and agar dilution techniques.

**Comparison of data from single-disk and broth dilution tests.** Figure 4 depicts the zone diameters for 82 isolates of *Enterobacteriaceae* and *Pseudomonas* tested with 30-μg cefazolin disks by a standard method (2) and the relation between zone of inhibition and MIC as determined by the broth dilution technique.
FIG. 1. Cumulative percentage of 30 strains each of *E. coli* and *P. mirabilis* inhibited (MIC) or killed (MBC) by increasing concentrations of cefazolin tested in broth medium with two different sizes of bacterial inocula.

**Fig. 2.** Cumulative percentage of isolates of *Klebsiella* (28) and *Enterobacter* (23) inhibited (MIC) or killed (MBC) by increasing concentrations of cefazolin tested in broth medium with bacterial inocula of two different sizes.
distinct separation into susceptible and resistant populations was observed; isolates inhibited by 10 μg or less of cefazolin per ml had zones of inhibition 16 mm or greater in diameter. Similar comparisons of single-disk and broth dilution susceptibility tests were made for 15 isolates of *S. aureus* and *Diplococcus pneumoniae* recovered from patients in this study. The MIC by broth dilution was 0.5 μg or less of cefazolin per ml for these clinical isolates, and all had zones of inhibition around the 30-μg cefazolin disk of 23 to 47 mm. Comparison of zones of inhibition produced by 30-μg cephalothin and 30-μg cefazolin disks showed close agreement in the limited number of clinical isolates studied.

**Susceptibility of S. aureus to cefazolin in broth dilution tests.** The cumulative percentage of 30 isolates of *S. aureus* susceptible to increasing concentrations of cefazolin is shown in Fig. 5. With the inoculum of 10⁴ organisms per ml, all isolates of *S. aureus*, regardless of penicillin susceptibility or resistance, were inhibited and killed by 1 μg or less of cefazolin per ml. Although the higher inoculum of 10⁵ organisms per ml resulted in a higher MBC, all isolates of *S. aureus* were still killed by 25 μg of cefazolin/ml, a concentration readily obtainable in serum with 0.5 g given intramuscularly.

Since cephaloridine, unlike cephalothin, has been reported to be less active against penicillin-resistant staphylococci when tested with a high inoculum because of its relative susceptibility to staphylococcal β-lactamase (3, 21), a comparative study of the bactericidal activity of cefazolin, cephaloridine, and cephalothin under the same testing conditions was performed with three different sizes of inocula. As shown in Fig. 6, cephaloridine was the most active cephalosporin against penicillin-susceptible *S. aureus* and the least active against

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**FIG. 3.** Cumulative percentage of 30 isolates of Salmonella and Shigella, including *S. typhi*, inhibited (MIC) or killed (MBC) by increasing concentrations of cefazolin tested in broth medium with bacterial inocula of two different sizes.

**FIG. 4.** Comparison of antibiotic-disk (30-μg content) and broth dilution tests of susceptibility of Enterobacteriaceae and Pseudomonas isolates to cefazolin tested against an inoculum of approximately 10⁵ organisms/ml.
penicillin-resistant *S. aureus* at the highest inoculum, $10^9$ staphylococci/ml. The activity of cefazolin and that of cephalothin were very similar against *S. aureus* isolates, regardless of their penicillin resistance, with the highest inoculum. At a concentration of 25 µg of antibiotic/ml and an inoculum of $10^9$ staphylococci/ml, 95 to 100% of the penicillin-susceptible isolates of *S. aureus* were killed by all three cephalosporins, whereas 81, 75, and 50% of penicillin-resistant strains of *S. aureus* were killed by cefazolin, cephalothin, and cephaloridine, respectively.

**Comparison of results from broth dilution and agar dilution tests.** Determinations of the MIC of cefazolin for all isolates of *E. coli*, *P. mirabilis*, *Klebsiella*, *P. aeruginosa*, *Salmonella* and *Shigella*, *N. meningitidis*, and 19 of 23 strains of *Enterobacter* by both the broth and agar dilution techniques were in close agreement and usually were identical. Of 23 strains of *Enterobacter*, four showed a greater than 10-fold increase in MIC by broth dilution as compared with results in agar. Results of agar dilution tests with indole-positive *Proteus* isolates were difficult to interpret because of the swarming phenomenon, which persisted despite inclusion of an inhibitor in the medium. Isolates of *S. aureus*, both penicillin-susceptible and -resistant, appeared more susceptible to inhibition by cefazolin on agar when compared with broth dilution results. The magnitude of the apparent difference was consistently one to two dilutions less in agar. Figure 7 shows the cumulative percentage of 28 isolates of enterococci which were inhibited or killed by increasing concentrations of cefazolin when tested by broth and agar dilution techniques. Enterococci were quite resistant, and none of the isolates was inhibited below 15 µg of cefazolin/ml; a 100-fold increase in inoculum size resulted in a marked decrease in bactericidal activity. Agar dilution testing yielded lower MIC values of cefazolin for enterococci than did broth dilution tests. For example, at 25 µg of cefazolin/ml, 100% of the isolates of enterococci were inhibited on agar versus 36% in broth with an inoculum of $10^4$ organisms/ml.
EVALUATION OF CEFAZOLIN

Susceptibility of H. influenzae to cefazolin in agar dilution tests. Figure 8 illustrates the activity of cefazolin against 28 isolates of H. influenzae tested by the agar dilution technique. The effect of inoculum size was marked; 79% of these isolates of H. influenza were inhibited by 10 μg of cefazolin/ml with the standard inoculum (10^4 organisms/ml), whereas only 18% were inhibited when the higher inoculum was used. At 25 μg of cefazo-
lin/ml, 82 to 100% of isolates of *H. influenza* was inhibited, depending upon the size of the inoculum used in the agar dilution test.

**Gram-negative infections.** Thirty-two patients with gram-negative infections were treated with cefazolin (Table 1). During treatment, 12 patients with urinary tract infection improved and had sterile urine during therapy, but four of six patients with *E. coli* infection relapsed with the same strain in their urine 2 weeks after cessation of therapy. Cefazolin was effective in the treatment of five of six patients with pneumonia due to *H. influenzae*, including one patient with bacteremia. All five patients with purulent arthritis and/or tenosynovitis due to disseminated infection with *Neisseria gonorrhoeae* were cured with cefazolin therapy.

**Gram-positive infections.** The results of cefazolin therapy in 53 patients with staphylococcal, pneumococcal, streptococcal, and *Bacillus subtilis* infections are shown in Table 2. The four patients with endocarditis were intravenous drug abusers; nonetheless, all three patients with staphylococcal endocarditis and the patient with *B. subtilis* endocarditis had sterile blood culture 1 to 6 months after cessation of cefazolin therapy. Patients with other types of streptococcal and staphylococcal infections also responded well to cefazolin treatment. All 40 patients with pneumococcal pneumonia as diagnosed by Gram stain morphology and/or bacteriological culture, including three with bacteremia and one each with empyema and septic arthritis, improved with cefazolin therapy. The only death among 85 patients treated with cefazolin in this study occurred in an elderly man whose pneumococcal pneumonia had cleared by clinical criteria before he succumbed to undifferentiated squamous cell carcinomatosis.

**Tolerance and toxicity.** Nine of 85 patients complained of pain after intramuscular administration of cefazolin when asked specifically about this complication; in five instances the pain was mild and transient, in two cases it was of moderate severity, and two patients refused further intramuscular injections because of pain and preferred the intravenous route. Eleven patients received 1.5 to 4 g of cefazolin intravenously for 3 or more days, and one patient was given 112 g of cefazolin over a 28-day period; none of these patients developed local thrombophlebitis.

Of all the tests of hematological, renal, and liver function obtained at the onset, during, and after treatment with cefazolin, the only sustained abnormalities were elevations of serum alkaline phosphatase in 4 of 85 patients. The serum bilirubin remained normal in all of these four; one had been started concurrently on isoniazid therapy, one had a recent fracture of his femur, and the other two patients had elevations of alkaline phosphatase less than twice the normal value.

None of the 85 patients studied developed a rash during or after treatment with cefazolin. A direct and indirect Coombs test was done during and/or after cefazolin therapy in 38 patients; none developed a positive Coombs test during the periods of observation.

**Distribution of cefazolin in body fluids.** The serum concentrations of cefazolin achieved with 1 g given intramuscularly to seven pa-

### Table 1. Gram-negative infections treated with cefazolin

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of patients</th>
<th>No. improved</th>
</tr>
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<tr>
<td>Urinary tract infection</td>
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<td></td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td><em>K. pneumoniae</em></td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td><em>P. mirabilis</em></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonia</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td><em>K. pneumoniae</em></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Mixed gram-negative flora</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Empyema (Bacteroides-Pepto-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>streptococcus)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lung abscesses (mixed coliforms)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Disseminated gonococcal syndrome</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Totals</td>
<td>32</td>
<td>29</td>
</tr>
</tbody>
</table>

### Table 2. Gram-positive infections treated with cefazolin

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of patients</th>
<th>No. improved</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacteremia</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cholangitis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><em>Diplococcus pneumoniae</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Pneumonia and bacteremia</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Pneumonia and empyema</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonia, bacteremia and septic arthritis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Group A streptococcus (cellulis-tis)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><em>Bacillus subtilis</em> (endocarditis)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Totals</td>
<td>53</td>
<td>53</td>
</tr>
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</table>
Patients with normal renal function are shown in Fig. 9. The mean serum concentrations of 73 and 28 μg of cefazolin/ml at 1 and 5 h, respectively, after a 1-g intramuscular injection are two to four times those expected from equivalent doses of cephaloridine or cephalothin.

Cefazolin readily crosses an inflamed synovial membrane; the results of simultaneous serum and joint fluid assays for cefazolin in a patient with purulent arthritis of the knee due to D. pneumoniae also are shown in Fig. 9. The concentration of cefazolin achieved in the joint space was comparable to levels measured in serum, and, although there appeared to be a slight delay in entrance, the synovial fluid levels actually exceeded those in serum by 2 h after an intramuscular injection.

In contrast, no cefazolin was detectable (lower limit of assay, 0.5 μg/ml) in the cerebrospinal fluid of five patients with noninflamed meninges 1 and 2 h after a single 1-g intramuscular injection of cefazolin. Cerebrospinal fluid obtained from a patient receiving penicillin treatment intravenously during the early convalescent period of acute streptococcal meningitis was found to have 1 μg of cefazolin activity/ml with a simultaneous serum concentration of 27 μg/ml at 2 h, after 1 g of cefazolin was given intravenously. The penicillin was totally inactivated by 1 million units of penicillinase (Difco) per 100 ml of agar in the modified agar-well diffusion assay (4), whereas the cefazolin standards and controls were not affected.

The urinary and biliary excretion of cefazolin was studied in an otherwise healthy young woman 2 weeks after treatment of a staphylococcal biliary tract infection that followed a cholecystectomy. A constant-infusion pump was used to deliver 500 mg of cefazolin intravenously during the first hour and 250 mg per h for a total dose of 1 g. During the steady state, the serum concentration of cefazolin was maintained at 50 μg/ml; simultaneous urine and bile concentrations of cefazolin were 4,500 and 12.2 μg/ml, respectively. The clearance of cefazolin in the urine was 81.8 ml per min per 1.73 m² (body surface area) or 79.8% of the simultaneous creatinine clearance; clearance of cefazolin in the bile was 0.104 ml per min per 1.73 m² or 0.1% of the urinary creatinine clearance. Essentially 100% of the total 1-g dose of cefazolin was recovered in the urine by 24 h, as measured in the modified agar-well diffusion assay (4). No change in activity of cefazolin was found by this assay after storage at 4 or 37 C for 18 h in nutrient broth.

**DISCUSSION**

Cefazolin is a new member of the group of semisynthetic derivatives of cephalosporin C (11-13, 22). As is the case with both cephalothin and cephaloridine, cefazolin is effective in man only when administered by the parenteral route. However, there are some differences in activity, tolerance, toxicity, and pharmacology when studies with cefazolin are compared with results obtained previously with cephalothin and cephaloridine in this laboratory (20, 21) and elsewhere (9-13, 16, 22).

In vitro studies of cefazolin showed it to be similar to cephalothin and cephaloridine in its activity against E. coli, Klebsiella, and P. mirabilis, except for the reduction in its bactericidal activity against P. mirabilis when tested against a large inoculum of organisms. Like other cephalosporins, cefazolin showed little activity against most isolates of indole-positive Proteus, Enterobacter, and enterococci. Similarly, strains of P. aeruginosa were absolutely resistant to cefazolin, as they have been to
other cephalosporins. In addition, cefazolin was as active as cephalothin against all isolates of S. aureus tested and was more active than cephaloridine against penicillinase-producing strains of S. aureus. The relative susceptibility of cephaloridine to penicillinase by hydrolysis of the β-lactam ring has been attributed to the pyridine ring substitution on the cephalosporanic acid nucleus of cephaloridine (3). Clinically, the effectiveness of cefazolin as an antistaphylococcal drug was demonstrated in the present study by the successful treatment of three patients with endocarditis due to S. aureus, a situation in which sustained bactericidal concentrations are required for cure (5).

Like cephaloridine, cefazolin appeared to cause less pain upon intramuscular injection than does cephalothin. Furthermore, cefazolin did not cause thrombophlebitis despite extended intravenous use in 11 patients. If this finding holds true for many patients, it would be an important practical advantage for this cephalosporin over cephalothin.

The development of a positive direct Coombs test in association with cephalothin therapy is well recognized (7,8); however, cephalothin has rarely been implicated as a cause of hemolytic anemia (8). The incidence of a positive direct Coombs test occurring with cephaloridine was reported to be 8% in one study as compared with a higher incidence with cephalothin (7,8). On the other hand, none of the 38 patients tested who were treated with cefazolin in this study developed a positive Coombs test. These findings are in accord with in vitro studies which have shown that, when compared with cephalothin and cephaloridine, cefazolin has less cross-reactivity with benzylpenicillin and the least capacity to cause injury to the red cell membrane (10).

A major disadvantage of cephaloridine is its potential nephrotoxicity, which necessitates a dose limitation of 4 g/day even in adults with normal renal function (18,20). Cephalothin has rarely been reported to cause renal tubular damage in high doses in man (18). Silverblatt et al. (17) were able to produce acute proximal tubular necrosis in rabbits with 200 mg or less of cephaloridine/kg. In contrast, less abnormalities of the proximal renal tubules were observed in rabbits after administration of 500 mg of cefazolin per kg (F. Silverblatt, personal communication).

Serum concentrations of cefazolin after comparable doses administered intramuscularly are about twice those reached with cephaloridine and four times those achieved with cephalothin (9,20,21). Like cephalothin (6), cefazolin enters joint fluid very readily and synovial concentrations are equivalent to those in serum. In contrast, in the present study, cefazolin entered the cerebrospinal fluid (CSF) very poorly in six patients, only one of whom, however, had inflamed meninges; similar results have been obtained by others (9). An inverse correlation between CSF antibiotic concentrations and serum protein binding has been noted with certain antibiotics (14). On the basis of relative protein binding, poor penetration of cefazolin into CSF might be predicated from its reported protein binding of 74% compared with values of 56 to 66% for cephalothin and 21 to 24% for cephaloridine (14,16), and cefazolin cannot be recommended for the treatment of pyogenic infections of the central nervous system. The relatively low concentrations of cefazolin achieved in bile and the proportion of a 1-g dose excreted in bile, about 0.1%, are similar to those reported with the same amount of cephaloridine (1).

In conclusion, cefazolin yields higher concentrations in serum and may have other advantages with regard to tolerance and toxicity when compared with cephalothin and cephaloridine.

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