Evaluation of a New Cephalosporin Antibiotic, Cephapirin

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Cephapirin sodium, a parenterally administered derivative of cephalosporanic acid, was tested in vitro against 150 stock cultures of Enterobacteriaceae and 30 stock cultures each of Pseudomonas aeruginosa and Staphylococcus aureus. Both broth- and agar-dilution techniques were employed with two sizes of inocula of organisms. At a concentration of 7.5 μg or less/ml, cephapirin inhibited and killed 100% of strains of Escherichia coli and Proteus mirabilis and more than 80% of Klebsiella species when tested against an inoculum of 10^8 bacterial cells/ml. However, even at 100 μg/ml, only a few isolates of other Enterobacteriaceae and Pseudomonas were inhibited. A 100-fold increase in the inoculum resulted in decreased susceptibility of organisms. All penicillin-susceptible as well as penicillin-resistant S. aureus isolates were inhibited and killed by 5 μg or less of cephapirin/ml when tested with an inoculum of either 10^4 or 10^6 organisms/ml. The drug also was studied in various doses in the treatment of 77 patients with diverse infections. Cephapirin was effective in the treatment of 27 of 32 patients with pulmonary infection, as well as in 6 of 7 patients with staphylococcal or streptococcal soft tissue infection. Of 25 patients with urinary-tract infections, 19 developed a negative culture during therapy. A single 4-g intramuscular dose of cephapirin was effective in only 2 of 11 patients with gonococcal urethritis or endocervicitis. Two patients with gonococcal urethritis treated with multiple injections were cured. The drug was well tolerated except for pain at the site of injection in 14 patients and phlebitis in 4 patients. No abnormalities in renal or hepatic function could be attributed to cephapirin. In addition, no abnormalities were found in the renal tubules of rabbits challenged with 500 mg of cephapirin/kg. If further studies document that cephapirin is well tolerated by the parenteral route, it may have advantages over cephalothin or cephaloridine.

MATERIALS AND METHODS

Laboratory studies. Minimal inhibitory concentrations (MIC) and minimal bactericidal concentrations (MBC) of cephapirin were determined by a dilution technique in Nutrient Broth with 30 isolates each of Escherichia coli, Proteus mirabilis, indole-producing strains of Proteus, Pseudomonas aeruginosa, Klebsiella, Enterobacter, and Staphylococcus aureus. The bactericidal end point (MBC) was defined as the lowest concentration of antibiotic in which fewer than three viable colonies were recovered when approximately 0.005 ml of broth from each clear tube was subcultured onto antibiotic-free agar. Each isolate was tested with both 10^-2 and 10^-4 dilutions of an overnight broth culture of bacterial cells by methods described previously from this laboratory (6, 9, 10). The susceptibility of these same isolates to cephapirin also was determined in Nutrient Agar by use of the Steers replicator device (8). In addition, inhibitory zones about discs containing 30 μg of cephapirin were measured for 102 isolates and were compared with the results of broth-dilution studies (11). Finally, to delineate the site and morphology of potential nephrotoxicity of cephapirin, four rabbits were...
given cepahpirin (500 mg/kg), and their kidneys were studied by light and electron microscopy by use of techniques described in detail in a previous report (7). Briefly, a single dose of 500 mg of cepahpirin/kg was administered intramuscularly to four rabbits. Animals were killed 24 hr after treatment, the time at which peak destruction of tubular elements had been observed in rabbits treated with 200 mg of cephaloridine/kg. Fixation was accomplished by intravascular infusion, and tissue which included representative areas from all parts of the nephron was obtained for light and electron microscopy.

Clinical studies. There were adequate clinical and bacteriological data for analysis from 77 patients treated with cepahpirin. Of the total group of patients, 57 were men and 20 were women; their ages ranged from 19 to 90 years. The criteria employed for selection of patients with urinary-tract infections, collection and quantitation of bacteriological specimens, and performance of serological typing have been described in previous publications (4, 5). Other patients were selected to receive cepahpirin on the basis of clinical, radiographic, and bacteriological evidence that an infectious process likely to respond to a cephalosporin type of antibiotic was present, and response to cepahpirin therapy was assessed on clinical and laboratory parameters. However, no attempt was made to compare the response to cepahpirin in these patients with the response in a comparable group of patients treated with other cephalosporin-type antibiotics. Susceptibility to cepahpirin in vitro was determined for each of the isolates recovered from patients in this study.

The dosage of antibiotic was predicated on the severity and type of infection, and daily doses ranged from 2.0 to 8.0 g. The most frequent dosage schedule was 0.5 or 1.0 g administered every 6 hr intramuscularly for a total of 7 to 10 days.

A survey for possible hematologic, renal, and hepatic toxicity was made by determination of the hematocrit, total and differential white blood cell counts, urinalysis, blood urea nitrogen (BUN), alkaline phosphatase, and serum glutamic oxalacetic transaminase (SGOT) at the onset, during, and after treatment with cepahpirin in most patients.

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**Fig. 1. Cumulative percentage of 30 isolates of penicillin-susceptible and penicillin-resistant S. aureus inhibited (MIC) or killed (MBC) by increasing concentrations of cepahpirin tested in broth medium with bacterial inocula of two different sizes.**
RESULTS OF LABORATORY STUDIES

Susceptibility of staphylococci to cephapirin. The cumulative percentage of 30 isolates of S. aureus susceptible to increasing concentrations of cephapirin is shown in Fig. 1, which also summarizes the effects of inoculum size on the antibacterial activity of this antibiotic. When tested with an inoculum of either $10^4$ or $10^5$ organisms/ml, all penicillin-susceptible as well as penicillin-resistant isolates were inhibited and killed by 5 μg or less of cephapirin/ml. Although the bactericidal activity of cephapirin against penicillin-resistant S. aureus was diminished when the higher inoculum of bacterial cells was employed, this may be of little significance because a concentration in serum of 10 μg/ml is readily attainable with a 1-g intramuscular dose (3). Although not shown in Fig. 1, staphylococcal isolates appeared equally susceptible to cephapirin in agar and broth, and all 30 isolates were similarly inhibited when tested in Nutrient Agar by use of the Steers replicator device.

Susceptibility of gram-negative pathogens to cephapirin. The antibacterial activity of cephapirin against 30 isolates each of E. coli, P. mirabilis, Klebsiella, and Enterobacter is depicted in Fig. 2 and 3, which also show the effect of inoculum size on determination of both the MIC and the MBC. At a concentration of 7.5 μg or less/ml, cephapirin inhibited and killed 100% of strains of E. coli and P. mirabilis and more than 80% of strains of Klebsiella when tested against an inoculum of $10^3$ bacterial cells/ml. However, increasing the inoculum size 100-fold from $10^4$ to $10^5$ bacterial cells/ml resulted in a diminution in the susceptibility of these isolates to cephapirin. For example, with the $10^3$ inoculum, more than 90% of the E. coli isolates were both inhibited and killed by 5 μg or less of cephapirin per ml, whereas with the higher inoculum 63% were inhibited and only 33% were killed. The effect of the size of the inoculum upon the MIC for susceptible P. mirabilis and Klebsiella was less marked than that observed with E. coli. However, the bactericidal activity of cephapirin against P. mirabilis and Klebsiella was diminished when the higher inoculum of bacterial cells was employed. For example, with the $10^3$ inoculum, all

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**Fig. 2.** Cumulative percentage of 30 isolates each of E. coli and P. mirabilis inhibited (MIC) or killed (MBC) by increasing concentrations of cephapirin tested in broth medium with bacterial inocula of two different sizes.
Fig. 3. Cumulative percentage of 30 isolates each of Klebsiella and Enterobacter inhibited (MIC) or killed (MBC) by increasing concentrations of cephapirin tested in broth medium with bacterial inocula of two different sizes.

of the *P. mirabilis* isolates and more than 80% of the strains of *Klebsiella* were killed by 10 μg of cephapirin per ml, whereas with the higher inoculum only 70% of the *P. mirabilis* and 40% of the *Klebsiella* isolates were killed.

Figure 3 also depicts the importance of separating *Klebsiella* from *Enterobacter* when determining susceptibility to the cephalosporin antibiotics. As has been demonstrated previously with other cephalosporin antibiotics, most isolates of *Enterobacter* were resistant to at least 100 μg of cephapirin per ml.

Although not shown in Fig. 2 and 3, cephapirin exerted negligible activity against indole-positive strains of *Proteus* and strains of *Pseudomonas aeruginosa*, regardless of the size of the inoculum. In addition, isolates of *Enterobacteriaceae* appeared slightly more susceptible to cephapirin when tested in agar than when tested in broth.

Comparison of data from single-disc and broth-dilution tests. The zones of growth inhibition about discs containing 30 μg of cephapirin were measured with 77 gram-negative isolates including strains of *Enterobacteriaceae* recovered from patients in this study, and the results were compared with those obtained in broth-dilution studies (Fig. 4). In general, separation into susceptible and resistant populations was attained by use of the 30-μg disc, and strains inhibited by 10 μg or less of cephapirin per ml had zones of inhibition 16 mm or greater in diameter. In only 8 of the 77 isolates was there disagreement between the results of the two types of tests; four of the eight discrepancies were seen among indole-positive strains of *Proteus*.

Similar comparisons of single-disc and broth-dilution techniques for testing susceptibility were made for 25 isolates of staphylococci, pneumococci, or group A streptococci recovered from patients in this study. The MIC by broth dilution was less than 0.25 μg of cephapirin per ml for all isolates, and these results correlated with a zone of inhibition around the 30-μg disc of greater than 23 mm.

Histopathology of renal tissue of rabbits. Light and electron microscopic study of kidneys removed from four rabbits treated intramuscularly with 500 mg of cephapirin/kg and sacrificed 24 hr after treatment failed to demonstrate any pathological lesions in the renal tubules.

RESULTS OF CLINICAL STUDIES

Genitourinary-tract infection. Cephapirin was evaluated in 25 patients with gram-negative bacteriuria and in 13 patients with gonococcal
infection. Treatment of one patient with acute uncomplicated pyelonephritis due to *E. coli* resulted in a satisfactory clinical and bacteriological response. Seventeen courses of treatment were administered to 15 patients for chronic *E. coli* bacteriuria, and, although the urine was rendered sterile during treatment in 14 of 17 episodes of infection, only 1 of 9 patients studied at 6 weeks after cessation of therapy remained free from bacteriuria. In one patient, the original strain of *E. coli*, which was initially susceptible to cepiparin, was replaced by a resistant strain of the same serogroup during therapy. In seven patients who relapsed with bacteriuria due to the same serotype, no emergence of resistance was noted. One patient with metastatic breast carcinoma and probable uretero-pelvic obstruction died during cepiparin therapy prescribed for bacteriuria and bacteremia due to a sensitive strain of *E. coli*. Although an autopsy could not be obtained, the bacteremia was thought to be secondary to necrotizing papillitis and multiple renal abscesses, and bacteremia persisted during the fourth day of treatment despite intravenous administration of 1 g of cepiparin every 6 hr.

Five of eight patients with *Klebsiella* bacteriuria had sterile urine specimens during antibiotic therapy; the initial isolates from the remaining three patients were resistant to cepiparin in vitro testing prior to initiation of treatment. Although the urine remained sterile in only one of the four patients studied 6 weeks after completion of therapy, emergence of a *Klebsiella* isolate resistant to cepiparin was not noted.

One patient with mixed *Proteus mirabilis* and *E. coli* infection cleared her bacteriuria during two separate courses of cepiparin therapy and improved clinically, but bacteriuria recurred with the same organisms shortly after cessation of each course of therapy.

Twelve males with acute gonococcal urethritis were treated with either a single intramuscular dose of 4 g of cepiparin (10 patients) or 1 g of cepiparin parenterally every 6 hr for 8 days. Response with the single-dose regimen was unsatisfactory, and 8 of 10 patients had persistent gonococcal infection; the two patients who received multiple doses were cured. In addition, a single injection of 4 g of cepiparin was ineffective in the treatment of a woman with gonococcal endocervicitis.
**Pulmonary infections.** The results of cephapirin therapy were evaluated in 30 patients with pulmonary infections due to gram-positive organisms. Of 15 patients with pneumococcal pneumonia treated with cephapirin, 14 improved. The effectiveness of cephapirin therapy was difficult to evaluate in the one remaining patient with pneumococcal pneumonia. He was an alcoholic patient with pneumococcal bacteremia and leukopenia whose pneumonia and temperature were slow to respond, and kanamycin was added during the fourth day of treatment because of suspected gram-negative superinfection. He gradually became afibrile and the pulmonary infiltrates resolved.

Cephapirin was also effective in five of six patients with *S. aureus* infections of the lung. Among the patients with staphylococcal pneumonia who improved during cephapirin treatment were three with life-threatening infection (one with pneumonia and bacteremia, one with a lung abscess, and one with empyema). The one patient who did not improve was a chronic alcoholic male with a large lung abscess due to a penicillin-resistant strain of *S. aureus*. The MIC and MBC of cephapirin for this isolate were 0.25 and 0.50 μg/ml, respectively. The lung abscess progressed during the 10-day course of cephapirin (1 g administered every 6 hr parenterally), and the sputum remained positive for *S. aureus*. Therapy was changed to methicillin, and the patient improved but the sputum remained positive for *S. aureus*.

One patient with aspiration pneumonitis associated with the isolation of a microaerophilic streptococcus, superimposed on chronic bronchiectatic lung disease, had a good response to cephapirin therapy with lysis of fever and clearing of pulmonary infiltrate. Eight patients with pneumonia of unproven etiology (probably pneumococcal on the basis of clinical presentation and Gram stain of sputum or transtracheal aspirate) received cephapirin therapy, and seven improved.

Two other patients were treated with cephapirin for pulmonary infections. During therapy with cephapirin, one of these patients developed an empyema from which a cephapirin-resistant *Haemophilus influenza* organism was isolated. This patient improved with chest tube drainage and institution of ampicillin therapy. The second patient developed an abscess in the right upper lobe behind an obstructing carcinoma. When *Bacteroides* species were isolated from the patient’s sputum and transtracheal aspirate, cephapirin was discontinued and treatment with chloramphenicol was instituted. No evaluation of this patient’s response to cephapirin therapy was possible.

During and shortly after cephapirin therapy, the sputum examination revealed colonization with organisms resistant to cephapirin in 5 of 32 patients treated for pulmonary infection. In no case was clinical superinfection with an organism causing disease encountered.

**Miscellaneous infections.** Six of seven patients with soft tissue infection (five with group A beta-hemolytic streptococcus and two with *S. aureus*) were successfully treated with cephapirin. A group A beta-hemolytic streptococcus was eradicated for a large decubitus ulcer in a paraplegic patient. However, this organism was then replaced by *Pseudomonas*. The patient had persistent fever spikes which may have been due to the *Pseudomonas* superinfection or osteomyelitis underlying the ulcer.

**Tolerance and toxicity.** Eight of 66 patients complained of pain after intramuscular administration of cephapirin in doses of 0.5 to 1.0 g every 6 hr, but all completed the prescribed course of the drug. In addition, 6 of 10 patients who received 4 g of cephapirin as a single dose complained of severe pain at the site of injection. Four of 24 patients developed phlebitis after receiving intravenous cephapirin for 2 days.

Data from 64 of the 77 patients could be analyzed for possible toxic effects because adequate hematologic and chemical surveys were obtained before, during, and after treatment with cephapirin. The only hematologic alteration was a transient eosinophilia in five patients who were also receiving other medications. One patient developed fever, arthralgia, and slight eosinophilia toward the end of the course of cephapirin. These symptoms subsided promptly the day after cessation of therapy. There was one other patient with fever which possibly was related to cephapirin therapy. Although elevations of SGOT and alkaline phosphatase were observed in three patients, and two developed elevations of BUN, in each patient there was concomitant illness that provided an explanation for these alterations. No patients developed a rash during or shortly after cephapirin therapy.

**DISCUSSION**

The family of cephalosporins possess a broad spectrum of antimicrobial activity, and their discovery, synthesis, and clinical application represent a major development in drug therapy. All clinically available cephalosporin drugs share similar structural relationships and antibacterial activity, but, at the same time, differ in several important respects (2, 6, 9, 10).
EVALUATION OF CEPHAPIRIN

To begin with, intramuscular administration of cephaloridine is tolerated considerably better and is associated with less pain and tissue reaction than is the case with cephalothin. Second, cephalothin, cephaloridine, and cephapirin are not sufficiently well absorbed after oral administration; in this regard, cephalaxin and cephaloglycin offer an advantage over the other cephalosporins. Even so, because of low concentrations in serum, cephaloglycin should not be given to patients with infections located outside the urinary tract. Third, parenteral treatment with cephaloridine is associated with higher and more sustained levels than are seen with either cephalothin or cephapirin.

Cephaloridine has some drawbacks apparently not shared by cephalothin or cephapirin. First, cephaloridine is more susceptible to inactivation by staphylococcal penicillinase, and, for this reason, should probably not be used as a first-line drug in suspected or proven staphylococcal sepsis (10). Second, renal functional impairment has been reported in some patients treated with cephaloridine, and administration of 100 mg of cephaloridine/kg has resulted in acute injury and necrosis of the middle portion of the proximal tubule of rabbits (7). In contrast, in the present study, no abnormalities of the proximal renal tubules were observed in rabbits after administration of 500 mg of cephapirin/kg.

The relatively large number of treatment failures in patients with bacteriuria in this study after cessation of cephapirin is not surprising. Most of these patients had previously received antimicrobial therapy with various agents, but infection had persisted or recurred. Although the majority did not have structural abnormalities, three had renal calculi and 10 had upper urinary-tract infection substantiated by urethral catheterization. Previous studies reported from our laboratory have demonstrated that renal bacteriuria is more refractory to drug therapy than is infection confined to the bladder. An effective antimicrobial agent must do no less than render the urine sterile during therapy, and persistence of the initial pathogen, even in low numbers, is invariably associated with recrudescence of significant bacteriuria after cessation of treatment. In this regard, cephapirin performed as well as other cephalosporin-type antibiotics.

It is apparent that cephapirin has an antimicrobial spectrum comparable, if not identical, to that of cephalothin. If further studies, including controlled observations, document that cephapirin is well tolerated by the parenteral route, this may be its sole advantage over cephalothin.

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LITERATURE CITED