Clinical and In Vitro Evaluation of Cefazolin, a New Cephalosporin Antibiotic

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Cefazolin sodium, a cephalosporin for parenteral use, was evaluated in vitro and in 26 patients. Cefazolin had activity equivalent to cephalothin against Streptococcus pneumoniae, Staphylococcus aureus, group A streptococci, and Proteus mirabilis. Cefazolin was four- to eightfold more active against Escherichia coli and slightly more active against Klebsiella pneumoniae, whereas cephalothin was slightly more active against indole-positive Proteus species. After a 500-mg dose of cefazolin intramuscularly, peak concentrations in the serum were high enough to inhibit all strains of S. pneumoniae, S. aureus, group A streptococci, E. coli, K. pneumoniae, and P. mirabilis, as well as 60% of strains of Proteus species other than P. mirabilis. All of 26 patients (18 with pneumonia, 6 with urinary tract infection, and 2 with skin infections) responded clinically and bacteriologically to cefazolin therapy. There were no major side effects of therapy, and no patient complained of pain at the site of intramuscular injection. Cefazolin is an effective cephalosporin which can be used intramuscularly for therapy of serious bacterial infections. Its major advantages over other cephalosporins are higher, more sustained concentrations in the blood and apparent lack of pain on intramuscular injection.

Cefazolin sodium, a new cephalosporin C antibiotic for parenteral use, is bactericidal against strains of gram-positive and gram-negative bacteria including Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, and Proteus mirabilis. Although cefazolin sodium has a spectrum of activity similar to that of cephalothin, studies in human volunteers have indicated that it gives higher and more sustained concentrations in serum and is less irritating than cephalothin when given by intramuscular or intravenous injection (2).

The present investigation was undertaken to determine the in vitro antibacterial activity of cefazolin sodium and to evaluate it in the treatment of infections in man.

MATERIALS AND METHODS

In vitro susceptibility tests. The following strains of bacteria were isolated from patients: 32 strains of S. aureus, 31 strains each of P. mirabilis and K. pneumoniae, 30 strains of E. coli, 15 strains of Enterobacter species, 12 strains of Streptococcus pneumoniae, 8 strains of indole-positive Proteus species, and 4 strains of group A streptococci.

The susceptibility of the organisms to cefazolin sodium and cephalothin sodium was determined by a dilution method in heart infusion broth at pH 7.4. The antibiotics were diluted in twofold steps in tubes containing 0.5 ml of broth. The bacterial inoculum for each tube was 0.5 ml of a 10^-1 dilution of an 18-hr culture of each strain in heart infusion broth. Studies on S. pneumoniae and group A streptococci were performed in heart infusion broth with 2% sheep red blood cells. The minimal inhibitory concentration was considered to be the lowest concentration of antibiotic that prevented turbidity after 24 hr of incubation at 37 C. At 24 hr, 0.01 ml was removed from each tube without viable growth by use of a sterile platinum loop and streaked on plates of Trypticase soy agar containing sheep red blood cells. After incubation at 37 C for 24 hr, the plates were examined and the lowest concentration of antibiotic that resulted in no growth was taken as the minimal bactericidal concentration.

Determination of antibiotic concentrations in serum and urine. Serum and urine concentrations of cefazolin sodium were determined in patients receiving parenteral cefazolin during the third to the seventh days of therapy. Blood was obtained 0.5, 1, 2, 4, 6, 8, 10, and 12 hr after administration of a dose of cefazolin sodium. Urine specimens were obtained by having the patient void before receiving a dose of cefazolin and collecting urine voided during and at the end of the following 4-hr interval. Serum was sepa-
rated and stored at −20 C until the time of assay. Urine was stored at −20 C. The concentrations of cefazolin in serum and urine were determined by a modification of the agar diffusion method described by Wick, with the use of paper discs (3). A volume of 0.25 ml of Bacillus subtilis spore suspension (Difco 04338-59) was mixed with 100 ml of melted heart infusion agar. Pour plates were made with 10 ml for each plate and were allowed to harden. Sterile paper discs were submerged in known concentrations of cefazolin sodium freshly prepared in pooled human serum and in the sera to be tested. The discs were placed on the pour plates and incubated at 37 C for 24 hr. Each known and unknown serum was plated in quadruplicate. A known serum was plated on each pour plate to measure uniformity of the plates. Zones of inhibition were determined with an antibiotic zone reader, and a standard curve was constructed from the known concentrations of cefazolin sodium. Concentrations of cefazolin sodium in the patients’ sera were determined from this curve. Sera containing more than 15 µg/ml were diluted 1:2, 1:5, or 1:8 in pooled human sera for determination of the concentrations. Urine concentrations of cefazolin sodium were determined in the same manner with two exceptions: (i) the urine specimens were diluted 1:100, 1:200, 1:500, and 1:900 in heart infusion broth before the determinations were performed, and (ii) the standard curve was constructed from known concentrations of antibiotic in heart infusion broth.

Clinical studies with cefazolin sodium

Twenty-six patients were studied and treated with cefazolin sodium at the Hospital of the Medical College of Pennsylvania from December 1971 to May 1972. The criteria for inclusion in the study were the presence of bacterial infection and no previous antibiotic treatment. Specimens for bacterial cultures were obtained before therapy was started and were processed immediately.

Cefazolin was administered intramuscularly in a dosage of 1 to 3 g per day in divided doses every 6, 8, or 12 hr. For intramuscular injection, 1 g of the drug was dissolved in 2 ml of sterile water. The following determinations were performed in patients before and after therapy: urinalysis, white blood cell count and differential, hemoglobin, hematocrit, blood urea nitrogen (BUN) serum creatinine, serum alkaline phosphatase, serum bilirubin, serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase (SGPT), and direct and indirect Coombs’ Tests.

RESULTS

In vitro antibacterial activity of cefazolin sodium and comparison with cephalothin sodium. Cefazolin sodium and cephalothin sodium had equivalent in vitro activity against S. pneumoniae, S. aureus, group A streptococci, and P. mirabilis. Both antibiotics inhibited all strains of S. pneumoniae and group A strepto-

Fig. 1. Comparison of susceptibility of 12 strains of Staphylococcus pneumoniae and 22 strains of Staphylococcus aureus to cefazolin and cephalothin.

Fig. 2. Comparison of susceptibility of 31 strains of Proteus mirabilis to cefazolin and cephalothin.
all strains of *Pseudomonas* were resistant to 50 μg of cephalothin and cefazolin/ml. The minimal bactericidal concentrations of both antibiotics for gram-positive cocci and gram-negative bacilli were usually the same as or twice the minimal inhibitory concentrations.

**Cefazolin sodium concentrations in serum and urine.** As shown in Table 1, mean serum concentrations of cefazolin after a 500-mg intramuscular dose in patients with normal serum creatinine concentration were 34.4 μg/ml (20.5 to 47 μg/ml) at 0.5 hr, 36.4 μg/ml (17.8 to 56 μg/ml) at 1 hr, 25.6 μg/ml (16.5 to 45 μg/ml) at 2 hr, and 16.1 μg/ml (8.8 to 21 μg/ml) at 4 hr. In two patients, levels of drug were still measurable in the serum at 12 hr. In patients with abnormal renal function (serum creatinine greater than 1.2 mg/100 ml), the serum concentrations of cefazolin were more sustained.

During the 4 hr after administration of 500 mg of cefazolin intramuscularly, concentrations in the urine ranged from 380 to 3,600 μg/ml. During this 4-hr collection, approximately 43 to 81% of injected cefazolin activity was recovered in the urine in patients with normal renal function, and 22 to 43% of the injected activity was recovered in patients with abnormal renal function (excluding one patient who received a 1-g dose).

**Clinical studies with cefazolin sodium.** The clinical data are summarized in Table 2. The ages of the 26 patients ranged from 30 to 88 years with a mean of 60 years, and 18 of them were males.

**Patients with pneumonia.** In 14 of the 18 patients with pneumonia, the infecting organism was *S. pneumoniae* (patients 1–14). Response to therapy was prompt in the 14 patients, and all...
were cured. One died of cardiac causes on the
day therapy was stopped. Two patients had
pneumonia caused by anaerobic streptococci,
one diagnosed by transtracheal aspiration and
one diagnosed by percutaneous needle aspiration
of the lung. One of these two patients (no. 15)
responded slowly and received cefazolin for a
total of 22 days. The second patient responded
rapidly and received the drug for only 7 days.
The causative organisms isolated by transtracheal
aspiration in the other two patients (no. 17
and 18) were *Haemophilus parainfluenzae*
and *H. influenzae*. They responded rapidly to
cefazolin therapy.

**Patients with urinary tract infection.** Six
patients had urinary tract infection, and five of
these had symptoms of pyelonephritis (i.e., fever
and flank pain). Two patients (no. 20 and 22)
had bacteremia. All responded to cefazolin. Pa-
tients 23 and 24 were cured (i.e., no bacteriuria 1
month after discontinuing cefazolin). Three pa-
tients relapsed after therapy; patient 20 had a
relapse of both bacteriuria and bacteremia, and
no. 21 and 22 had a relapse of bacteriuria alone.
Patient 20 was retreated with cefazolin for an-
other 14 days during which a transurethral re-
section for prostatic hypertrophy was performed.
After the cefazolin was discontinued the second
time, he was treated with cephalixin for 2 weeks
and was then lost to follow-up with sterile urine
cultures. During cefazolin therapy, patient 19,
who was critically ill, developed bacteremia
caused by an *Enterobacter* strain resistant to 50
µg of cefazolin/ml.

**Patients with miscellaneous infections.** Two
patients had infections caused by group A
streptococci; patient 25 had cellulitis of the leg
and patient 26 had multiple abscesses secondary
to “skin popping” of heroin. Both patients
responded well to cefazolin therapy.

**Side effects of therapy.** Patient 25 de-
veloped a drug fever which rapidly disappeared
after therapy was discontinued. Patients 7, 10,
13, and 15 developed eosinophilia of 3 to 5%. There
were no rashes.

Patients 6 and 17 had decreases in hematocrit
from 40 and 42% to 34 and 35% respectively
during hydration. These decreases in hematocrit
were not thought to be related to administration
of cefazolin.

Patient 19 had a rise in BUN from 15 to 37
mg/100 ml after bacteremia and a respiratory
arrest associated with hypotension. At the same
time, the SGPT changed from 50 to 250 milli-
units/ml and the alkaline phosphatase rose from
231 to 450 milliunits/ml. Two other patients had

### Table 1. Concentrations of cefazolin sodium in serum and urine of 18 patients after injection of 500 mg intramuscularly

<table>
<thead>
<tr>
<th>Patienta</th>
<th>Creatinine (mg/100 ml)</th>
<th>Concen in serum (µg/ml) at indicated hr</th>
<th>Concen in urine (µg/ml)</th>
<th>Drug in 4-hr collection (mg)</th>
<th>Drug excreted (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.9</td>
<td>35.5</td>
<td>43.5</td>
<td>25.7</td>
<td>80.0</td>
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<td>2</td>
<td>0.9</td>
<td>40.5</td>
<td>56.0</td>
<td>45.0</td>
<td>20.5</td>
</tr>
<tr>
<td>3</td>
<td>0.9</td>
<td>37.0</td>
<td>17.8</td>
<td>16.5</td>
<td>13.8</td>
</tr>
<tr>
<td>4</td>
<td>0.9</td>
<td>20.5</td>
<td>21.0</td>
<td>16.5</td>
<td>12.5</td>
</tr>
<tr>
<td>5</td>
<td>1.1</td>
<td>47.0</td>
<td>43.0</td>
<td>25.5</td>
<td>19.0</td>
</tr>
<tr>
<td>6</td>
<td>1.1</td>
<td>26.0</td>
<td>37.0</td>
<td>24.5</td>
<td>21.0</td>
</tr>
<tr>
<td>7</td>
<td>1.1</td>
<td>8.9</td>
<td></td>
<td></td>
<td>3.8</td>
</tr>
<tr>
<td>8</td>
<td>0.9</td>
<td></td>
<td>3.8</td>
<td>2.0</td>
<td>3.8</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td>3.8</td>
<td>2.0</td>
<td>3.8</td>
</tr>
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</table>

- Patients 1–8 had normal serum creatinine concentrations, and patients 9–17 had abnormal serum creatinine concentrations.
- Dose of 1 g administered intramuscularly.
## Table 2. Clinical data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex</th>
<th>Diagnosis</th>
<th>Infecting microorganism</th>
<th>MIC* (µg/ml)</th>
<th>Site of isolation</th>
<th>Dose/interval</th>
<th>Days of therapy</th>
<th>Underlying disease</th>
<th>Adverse reactions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42/M</td>
<td>Pneumonia</td>
<td><em>S. pneumoniae</em></td>
<td>—</td>
<td>Transtracheal aspirate</td>
<td>500 mg/6 hr</td>
<td>7</td>
<td>Alcoholism</td>
<td>None</td>
<td>Cured</td>
</tr>
<tr>
<td>2</td>
<td>57/F</td>
<td>Pneumonia</td>
<td><em>S. pneumoniae</em></td>
<td>—</td>
<td>Sputum</td>
<td>500 mg/6 hr</td>
<td>8</td>
<td>Mitral insufficiency</td>
<td>None</td>
<td>Cured</td>
</tr>
<tr>
<td>3</td>
<td>69/M</td>
<td>Pneumonia</td>
<td><em>S. pneumoniae</em></td>
<td>—</td>
<td>Transtracheal aspirate</td>
<td>500 mg/6 hr</td>
<td>8</td>
<td>Hypertension</td>
<td>None</td>
<td>Cured</td>
</tr>
<tr>
<td>4</td>
<td>69/F</td>
<td>Pneumonia</td>
<td><em>S. pneumoniae</em></td>
<td>0.01</td>
<td>Transtracheal aspirate</td>
<td>500 mg/6 hr</td>
<td>8</td>
<td>None</td>
<td>None</td>
<td>Cured</td>
</tr>
<tr>
<td>5</td>
<td>40/M</td>
<td>Pneumonia</td>
<td><em>S. pneumoniae</em> (microaerophile)</td>
<td>—</td>
<td>Transtracheal aspirate</td>
<td>500 mg/6 hr</td>
<td>7</td>
<td>Alcoholism</td>
<td>None</td>
<td>Cured</td>
</tr>
<tr>
<td>6</td>
<td>51/M</td>
<td>Pneumonia</td>
<td><em>S. pneumoniae</em></td>
<td>S</td>
<td>Transtracheal aspirate</td>
<td>500 mg/6 hr</td>
<td>7</td>
<td>Alcoholism</td>
<td>Anemia</td>
<td>Cured</td>
</tr>
<tr>
<td>7</td>
<td>62/M</td>
<td>Pneumonia</td>
<td><em>S. pneumoniae</em></td>
<td>S</td>
<td>Transtracheal aspirate</td>
<td>500 mg/6 hr</td>
<td>7</td>
<td>Alcoholism</td>
<td>Eosinophilia</td>
<td>Cured</td>
</tr>
<tr>
<td>8</td>
<td>30/F</td>
<td>Pneumonia</td>
<td><em>S. pneumoniae</em></td>
<td>0.02</td>
<td>Transtracheal aspirate</td>
<td>500 mg/6 hr</td>
<td>7</td>
<td>Heroin addiction</td>
<td>None</td>
<td>Cured</td>
</tr>
<tr>
<td>9</td>
<td>69/M</td>
<td>Pneumonia</td>
<td><em>S. pneumoniae</em></td>
<td>0.01</td>
<td>Transtracheal aspirate</td>
<td>500 mg/6 hr</td>
<td>7</td>
<td>None</td>
<td>Elevated alkaline phosphatase</td>
<td>Cured</td>
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<tr>
<td>10</td>
<td>53/M</td>
<td>Pneumonia</td>
<td><em>S. pneumoniae</em></td>
<td>0.01</td>
<td>Transtracheal aspirate</td>
<td>500 mg/8 hr</td>
<td>6</td>
<td>Obstructive pulmonary disease; alcoholism</td>
<td>Eosinophilia</td>
<td>Cured</td>
</tr>
<tr>
<td>11</td>
<td>72/M</td>
<td>Pneumonia</td>
<td><em>S. pneumoniae</em></td>
<td>0.01</td>
<td>Transtracheal aspirate</td>
<td>500 mg/12 hr</td>
<td>9</td>
<td>Obstructive pulmonary disease; alcoholism</td>
<td>None</td>
<td>Cured</td>
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<tr>
<td>12</td>
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<td>Pneumonia</td>
<td><em>S. pneumoniae</em></td>
<td>S</td>
<td>Sputum</td>
<td>500 mg/6 hr</td>
<td>9</td>
<td>Coronary artery disease; rheumatic valvular disease</td>
<td>None</td>
<td>Cured, then expired of cardiac causes</td>
</tr>
<tr>
<td>13</td>
<td>70/M</td>
<td>Pneumonia</td>
<td><em>S. pneumoniae</em></td>
<td>0.1</td>
<td>Sputum</td>
<td>500 mg/6 hr</td>
<td>8</td>
<td>Obstructive pulmonary disease</td>
<td>Eosinophilia</td>
<td>Cured</td>
</tr>
<tr>
<td>14</td>
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<td>Pneumonia</td>
<td><em>S. pneumoniae</em></td>
<td>0.2</td>
<td>Transtracheal aspirate</td>
<td>500 mg/6 hr</td>
<td>6</td>
<td>Obstructive pulmonary disease; alcoholism</td>
<td>None</td>
<td>Cured</td>
</tr>
<tr>
<td>15</td>
<td>54/M</td>
<td>Pneumonia</td>
<td>Anaerobic streptococcus</td>
<td>0.1</td>
<td>Lung aspirate</td>
<td>500 mg/6 hr</td>
<td>22</td>
<td>Alcoholism</td>
<td>Eosinophilia</td>
<td>Cured</td>
</tr>
<tr>
<td>16</td>
<td>67/M</td>
<td>Pneumonia</td>
<td>Anaerobic streptococcus</td>
<td>S</td>
<td>Transtracheal aspirate</td>
<td>1 g/8 hr</td>
<td>7</td>
<td>Alcoholism</td>
<td>None</td>
<td>Cured</td>
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<tr>
<td>Case</td>
<td>Age</td>
<td>Gender</td>
<td>Diagnosis</td>
<td>Pathogen</td>
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<td>MIC</td>
<td>Dose</td>
<td>Duration</td>
<td>Complications</td>
<td>Laboratory Findings</td>
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<td>17</td>
<td>57</td>
<td>M</td>
<td>Pneumonia</td>
<td><em>H. parainfluenza</em></td>
<td>Transtracheal</td>
<td>S</td>
<td>500 mg/8 hr</td>
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<td>Seizure-disorder; pulmonary embolus</td>
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<tr>
<td>18</td>
<td>73</td>
<td>M</td>
<td>Pneumonia</td>
<td><em>H. influenzae</em></td>
<td>Transtracheal</td>
<td>0.8</td>
<td>500 mg/6 hr</td>
<td>9</td>
<td>Obstructive pulmonary disease</td>
<td>Elevated BUN, SGPT, alkaline phosphatase</td>
</tr>
<tr>
<td>19</td>
<td>39</td>
<td>M</td>
<td>Pyelonephritis</td>
<td>Enterococcus</td>
<td>Urine</td>
<td>0.8</td>
<td>500 mg/6 hr</td>
<td>5</td>
<td>Intracerebral hemorrhage</td>
<td>Bacteremia on therapy</td>
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<tr>
<td>20</td>
<td>67</td>
<td>M</td>
<td>Pyelonephritis</td>
<td><em>E. coli</em></td>
<td>Urine and blood</td>
<td>0.8</td>
<td>1 g/8 hr</td>
<td>8</td>
<td>Prostatic hypertrophy</td>
<td>None</td>
</tr>
<tr>
<td>21</td>
<td>88</td>
<td>F</td>
<td>Pyelonephritis</td>
<td><em>E. coli</em></td>
<td>Urine</td>
<td>S</td>
<td>500 mg/6 hr</td>
<td>11</td>
<td>Carcinoma of bladder; thrombocytopenia Diabetes mellites</td>
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<tr>
<td>22</td>
<td>49</td>
<td>F</td>
<td>Pyelonephritis</td>
<td><em>E. coli</em></td>
<td>Urine and blood</td>
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<td>500 mg/6 hr</td>
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<td>Relapse of bacteremia and bacteriuria</td>
<td>Relapse of bacteriuria</td>
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<tr>
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<td>70</td>
<td>M</td>
<td>Pyelonephritis</td>
<td><em>K. pneumoniae</em></td>
<td>Urine</td>
<td>1.6</td>
<td>500 mg/6 hr</td>
<td>10</td>
<td>Alcoholism</td>
<td>None</td>
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<tr>
<td>24</td>
<td>65</td>
<td>F</td>
<td>Cystitis</td>
<td><em>P. mirabilis</em></td>
<td>Urine</td>
<td>0.3</td>
<td>500 mg/6 hr</td>
<td>11</td>
<td>Pituitary adenoma</td>
<td>None</td>
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<tr>
<td>25</td>
<td>74</td>
<td>F</td>
<td>Cellulitis</td>
<td>Group A streptococcus</td>
<td>Skin lesion</td>
<td>0.1</td>
<td>500 mg/6 hr</td>
<td>9</td>
<td>Heart failure</td>
<td>Drug fever</td>
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<tr>
<td>26</td>
<td>31</td>
<td>M</td>
<td>Skin abscesses</td>
<td>Group A streptococcus</td>
<td>Skin lesion</td>
<td>0.2</td>
<td>500 mg/6 hr</td>
<td>8</td>
<td>Heroin abuse, &quot;skin popper&quot;</td>
<td>None</td>
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</table>

*Minimal inhibitory concentration. S = susceptible by disc testing.
changes in alkaline phosphatase from 74 to 93 microunits/ml (no. 9) and 55 to 100 microunits/ml (no. 22) during therapy. The cause of the elevations of alkaline phosphatase is not known.

All other laboratory tests which were previously normal were not altered by therapy. No patient complained of pain at the site of intramuscular injection.

DISCUSSION

Cefazolin and cephalothin seem to be equivalent drugs with respect to antibacterial activity against gram-positive cocci. Cefazolin is four- to eight-fold more active than cephalothin against E. coli and slightly more active against K. pneumoniae, whereas cephalothin is slightly more active against Proteus sp. other than P. mirabilis and is equivalent in activity against P. mirabilis. The major advantages of cefazolin over cephalothin would seem to be that of higher, more sustained concentrations in serum and the lack of pain after intramuscular injection.

The present investigation has demonstrated that cefazolin reaches high concentrations in the blood and urine after parenteral administration. The mean serum concentration 1 hr after intramuscular injection of 500 mg of cefazolin was 36.4 µg/ml in patients with normal renal function (serum creatinine, 1.1 mg/100 ml or less). Four hours after intramuscular injection of 500 mg of cefazolin, the mean serum concentration was 16.1 µg/ml. This compares with a mean peak concentration of about 8 µg/ml at 0.5 hr and about 1 µg/ml at 4 hr after intramuscular injection of 500 mg of cephalothin (1). There were still measurable levels of cefazolin present 12 hr after injection. With cephalothin, there were no measurable serum levels after 6 hr. The peak serum concentrations of cefazolin were high enough to inhibit all strains of S. pneumoniae, S. aureus, group A streptococci, E. coli, K. pneumoniae, and P. mirabilis, as well as 60% of strains of Proteus species other than P. mirabilis. All strains of E. coli, P. mirabilis, and K. pneumoniae were inhibited by concentrations obtained in the urine.

In this study, all of the 26 patients responded clinically and bacteriologically to cefazolin therapy. The relapses which occurred in three of six patients with urinary tract infection were probably related more to the nature of the patients than to failure of therapy. One of these patients had carcinoma of the urinary bladder and another had prostatic hypertrophy, both of which caused obstructive uropathy.

The eosinophilia observed in 4 of the 26 patients was probably related to cefazolin. The elevation of BUN in one patient was thought to be due to hypotension following a respiratory arrest. This patient also had a rise in alkaline phosphatase and SGPT, also probably related to hypotension. Two other patients had unexplained rises in alkaline phosphatase. The drop in hematocrit in two patients was probably caused by hydration. The most bothersome side effect was drug fever in one patient which promptly disappeared at the end of therapy.

From these studies, it can be concluded that cefazolin is an effective cephalosporin which can be used intramuscularly for therapy of serious bacterial infections. It results in higher and more sustained blood levels than cephalothin and has the advantage of being well tolerated intramuscularly.

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LITERATURE CITED