In vitro and Clinical Studies of Cefaclor, A New Cephalosporin†

Daria Kiani, MD,* Tom Madhavan, MD,* Keith Burch, MD,* Don Pohlod, MD, Evelyn Fisher, MD,* and Edward L. Quinn, MD*

In vitro susceptibility studies of 246 clinical isolates demonstrated that this antibiotic was effective against Group A beta hemolytic streptococci, alpha hemolytic streptococci, S. pneumoniae, both penicillinase producing and nonpenicillinase producing Staphylococci, Klebsiella pneumoniae, and Proteus mirabilis. Cephalothin susceptible E. coli were also susceptible to cefaclor. Pseudomonas aeruginosa, Serratia sp., Enterobacter sp., and Streptococcus faecalis were uniformly resistant to cefaclor. The efficacy and safety of this antibiotic were studied in 27 patients with urinary tract, soft tissue, and respiratory infections. Patients with urinary tract infections became abacteriuric after 48 hours. Patients with soft tissue infections responded well within the first week of therapy, and throat cultures of patients with tonsillitis were negative ten days and six weeks after treatment. The drug was well tolerated, and no significant adverse effect was noted.

Cefaclor is a new, semisynthetic oral cephalosporin, structurally related to cephalaxin. It is well absorbed, with no significant side effects,† and is more active than cephalaxin against most of the susceptible organisms. This report deals with 1) the pharmacology, effectiveness, and tolerance of cefaclor in treating 27 patients with infections caused by susceptible pathogens and 2) the in vitro susceptibility of representative clinical isolates. Clinical observations were made at Henry Ford Hospital and compared with our earlier results with cephalaxin.10

Materials and Methods

Laboratory studies

The susceptibility to cefaclor of 246 strains of gram-positive and gram-negative isolates was determined by agar dilution method with Mueller-Hinton agar (BBL), except for beta hemolytic streptococci, to which blood was added.4 Antibiotics were added to the media at 50°C to avoid antibiotic degradation. Approximately 10⁶ organisms were added to the media. The minimum inhibitory concentration (MIC) was defined as the lowest concentration that inhibited bacterial growth after 18 hours of incubation at 37°C. The susceptibilities of the following bacteria were determined: E. coli, Proteus mirabilis, Enterobacter sp., indole positive Proteus, Serratia sp., staphylococci, Group A beta hemolytic streptococci, alpha streptococci, Streptococcus faecalis, and Streptococcus pneumoniae.

Serum concentrations from 19 patients and volunteers were determined by disc plate assay9 using Bacillus subtilis (ATCC 6633) as the test organism.

Concentrations were determined at 1, 2, 3, 4, and 6 hours after 250 mg and 500 mg of cefaclor had been administered orally. The patients had received it for at least 24 hours when the serum specimens were obtained.

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Clinical studies
The antibiotic was administered orally to 27 patients with urinary tract infections, skin infections, bacterial pharyngitis, and pneumonia due to susceptible organisms. Eight patients were given 750 mg per day, 10 patients were given 1000 mg per day, and 9 were given 2 gm per day for 7 to 10 days. Periodic clinical examinations were performed and appropriate cultures were obtained before, during, and after treatment. Safety studies included evaluations of renal, hepatic and hematologic functions before, during and after antibiotic administration. Patients were followed for six weeks after treatment whenever possible.

Results
Antimicrobial activity
The in vitro activity of cefaclor and its comparison with cephalaxin and cephalothin are shown in Figures 1-9. Cefaclor was considerably more active than cephalaxin against all gram-positive organisms tested, including Group A beta hemolytic streptococci and S. pneumoniae. Cefaclor was less active against both penicillinase-producing and nonpenicillinase-producing staphylococci than cephalothin (Figures 1-5). On the other hand, all 23 strains of enterococci were resistant to all three antibiotics, although for cefaclor the MIC was only 25 \( \mu \text{g} \) per ml and for cephalaxin and cephalothin, 50 \( \mu \text{g} \) per ml.

Cefaclor was the most active of the three against E. coli, K. pneumoniae, and P. mirabilis (Figures 6-8). Only 10% of the strains of Enterobacter sp. were inhibited by 25 mg per ml or less of cefaclor, and less than 5% of strains were inhibited by the same concentration of cephalaxin and cephalothin (Figure 9). All strains of indole positive proteus (13), Pseudomonas aeruginosa (20), and Serratia sp. (12) were uniformly resistant to all three antibiotics tested with MICs greater than 50 \( \mu \text{g} \) per ml.

Serum concentrations
After 250 mg of cefaclor, the mean peak serum concentration was 5.6 \( \mu \text{g} \) per ml; at the end of three hours the concentration decreased to 1 \( \mu \text{g} \) per ml or less. Similar results were obtained with the 500 mg oral dose after three hours. Compared to cephalaxin (Table I), the concentrations were slightly less and less sustained.

<table>
<thead>
<tr>
<th>TABLE I</th>
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<tbody>
<tr>
<td>Serum Concentration Of Cefaclor and Cephalaxin</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Hours After Dose 250 mg Orally</td>
</tr>
<tr>
<td>1/2</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
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</tbody>
</table>

* After Cox, et al

Fig. 1
Susceptibility of 33 strains of Group A Beta hemolytic streptococcus.

Fig. 2
Susceptibility of 20 strains of Streptococcus pneumoniae.
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Fig. 3
Susceptibility of 20 strains of alpha streptococcus.

Fig. 4
Susceptibility of 20 strains of nonpenicillinase-producing Staphylococcus aureus.

Fig. 5
Susceptibility of 18 strains of penicillinase-producing Staphylococcus aureus.

Fig. 6
Susceptibility of 15 strains of E. coli.
Clinical results

Cefaclor was administered to 27 patients with culture-proven urinary tract, soft tissue, and respiratory infections caused by susceptible pathogens (Table II). Among these patients, 16 had urinary tract infections, six had soft tissue infections, and five had respiratory infections. Eleven patients with *Escherichia coli* urinary tract infections were treated, and 10 became abacteriuric in 48 hours. In one patient, despite clinical improvement, the antibiotic was stopped because of reported resistance of the organism to cefaclor by the disc method. Three patients with *Klebsiella pneumoniae* urinary tract infection were treated, and two became abacteriuric in 48 hours. However, one patient who had lower urinary tract obstruction secondary to prostatic hypertrophy continued to show significant bacteriuria and required parenteral gentamicin and transurethral resection of the prostate for cure.

One patient with *Proteus mirabilis* bacteriuria and one symptomatic patient with multiple positive urine cultures for *Staphylococcus epidermidis* were treated and cured with this antibiotic. There was no reinfection by other organisms and only one recurrence by the same organism nine days after treatment had been completed. Eight of 16 patients received 250 mg every 8 hours, and the rest received 250 mg every 6 hours for 7-10 days.

Six patients were treated for soft tissue infection and abscesses. Among these, four with acute *Staphylococcus aureus* infections improved on therapy, but the antibiotic had to be stopped after three and five days in two of them because of side effects (nausea and vomiting in one and diarrhea in one); both were drug abusers. One patient with mixed *Staphylococcus aureus* and Group A beta hemolytic streptococcus was treated and cured with cefaclor 500 mg every 6 hours. Clinical improvement was seen also in another patient with polymicrobial infection due to *E. coli*, *A. hydrophila*, and *Enterobacter sp.*, but cultures continued to grow *Enterobacter sp.*

Five patients who received cefaclor for respiratory tract infections were all cured and had negative follow-up cultures. Four of these patients had acute tonsillitis due to Group A beta hemolytic streptococcus and one patient had lobar pneumonia due to *Streptococcus pneumoniae*.

No major adverse reactions were observed with cefaclor treatment. In two parenteral drug abusers, nausea, vomiting and diarrhea were noted, but it was hard to distinguish those symptoms from narcotic withdrawal symptoms. All serum chemistries, including SGOT, SGPT, alkaline phosphatase, bilirubin, serum creatinine and blood urea nitrogen, were normal before, during, and after treatment, except for mild transient elevation of SGOT in one patient. Coomb's test was also negative in all patients. Mild eosinophilia was noted in two patients.

**TABLE II**

Results of Treatment of 27 Patients with Cefaclor

<table>
<thead>
<tr>
<th>Diseases and No. of Cases</th>
<th>Organisms</th>
<th>Results</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary Tract Infection (16)</td>
<td>Escherichia coli</td>
<td>10</td>
<td>1</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Klebsiella pneumoniae</em></td>
<td>2</td>
<td>-</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Proteus mirabilis</em></td>
<td>1</td>
<td>-</td>
<td>-</td>
<td></td>
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<tr>
<td></td>
<td><em>Staphylococcus epidermidis</em></td>
<td>1</td>
<td>-</td>
<td>-</td>
<td></td>
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<tr>
<td></td>
<td><em>Staphylococcus aureus</em></td>
<td>2</td>
<td>2</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Staph. aureus + beta hemolytic streptococci group A</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>E. coli + Enterobacter sp.</em></td>
<td>-</td>
<td>1</td>
<td>-</td>
<td></td>
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<tr>
<td></td>
<td><em>A. hydrophila</em></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
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<tr>
<td>Soft Tissue Infections (6)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Respiratory Tract Infection (5)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia (1)</td>
<td><em>Streptococcus pneumoniae</em></td>
<td>1</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Tonsillitis (4)</td>
<td><em>Beta Streptococci Group A</em></td>
<td>4</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
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Discussion

Cefaclor is a new, semisynthetic oral cephalosporin related to cephalexin. It has wide spectrum of activity, and the earlier reports\(^2\) indicated greater in vitro activity against more of the gram-positive bacteria and all of the susceptible gram-negative bacteria when it was compared with other available oral cephalosporins. Against penicillinase-producing and nonpenicillinase-producing \textit{Staphylococcus aureus}, cefaclor was more active than cephalexin but less than cephalothin.\(^{11,12}\) Against different species of streptococci, it was at least four times more active than cephalexin.\(^4,11\) Cefaclor was uniformly more active than cephalexin and other oral or parenteral cephalosporins against susceptible gram-negative organisms, including \textit{Hemophilus} isolates.\(^{2,3,11,13}\) Animal studies\(^1\) showed that this drug is well absorbed orally with a peak of 5.8 to 6.9 \(\mu\)g per ml after a single dose of 250 mg. Our study revealed a one-hour concentration of 5.6 \(\mu\)g per ml and less than 0.1 \(\mu\)g per ml after four hours. This concentration is slightly lower and less sustained\(^10\) than cephalexin, but better results in therapy of experimental animals can be explained by higher activity against almost all susceptible organisms. \textit{Streptococcus faecalis}, indole positive \textit{Proteus}, \textit{Serratia sp.}, and \textit{Pseudomonas aeruginosa} were all uniformly resistant to this antibiotic in our study, as was also shown in earlier reports. Although \textit{enterobacter} species were slightly more susceptible to cefaclor than cephalexin and cephalothin, only 10-30\% of the strains have been shown to be susceptible to cefaclor.\(^2,6\)

Although clinical trial of cefaclor is limited,\(^12,16\) in our study 26 of 27 infections were cured or showed significant symptomatic improvement. Bacteriuria recurred in one patient nine days after therapy had been completed. One patient with urinary tract infection failed on therapy, although obstructive uropathy might account for this failure. He also failed on cephalexin, co-trimoxazole, and amoxicillin. Cefaclor was as effective as amoxicillin in treating lower urinary tract infections in women.\(^18\) In soft tissue and respiratory tract infections, all patients but one were cured. The one exception was a patient with polymicrobial infection secondary to drug abuse who had a continued positive culture for \textit{enterobacter} sp.

In our study, cefaclor was well absorbed orally and almost all was excreted by the kidney. It was also well tolerated, except for two patients who had gastrointestinal side effects. No significant hematologic or hepatic dysfunctions were noted. Experimental animal studies have confirmed the safety of this antibiotic. Large doses of cefaclor administered to animals produced minimal changes in serum with transient changes in hemoglobin and platelets.\(^17\)

In conclusion, cefaclor is a wide spectrum antibiotic shown to be well absorbed and well tolerated. It is more active \textit{in vitro} than cephalexin against all common gram-positive and gram-negative organisms tested, and when administered orally, it is effective against infections caused by susceptible organisms.

Acknowledgments

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References


