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CEPHALEXIN: CLINICAL AND LABORATORY STUDIES†

Cephalexin, 7(D- α -amino- α -phenylacetomido)-3-methyl-3-cephem-4-carboxylic acid, is a semi-synthetic derivative of cephalosporin-C and has an antibacterial spectrum similar to cephalothin, cephaloridine and cephaloglycine. It is the only cephalosporin antibiotic to give high drug concentrations in both the serum and urine of human subjects after oral administration.¹ It differs from cephaloglycine which yields high urine concentrations but only negligible serum concentrations following oral administration.²

The high serum levels attainable with cephalexin make it a promising drug for the treatment of a variety of infections requiring oral therapy. The present study examines the efficacy of the drug in such treatment. This report describes the clinical response of 26 infections in 22 patients who were treated with oral cephalexin and the *in vitro* sensitivity of a number of gram-positive and gram-negative bacteria isolated from patients in the hospital.

METHODS

Clinical studies: Twenty-two patients, four male and eighteen female, at Yale-New Haven Hospital and the West Haven Veterans Administration Hospital, received 25 courses of cephalexin for 26 separate infections. One patient was nine years old; the others were adults. All patients or their guardians gave informed consent to the use of an investigational drug.

Patients with urinary tract infections had urine cultures done prior to therapy, during therapy, and four weeks after treatment was stopped. Urines for culture were obtained by the clean catch method previously reported.³ Significant bacteriuria was defined as 100,000 colonies or more per milliliter of urine per species of bacteria.

A urinary tract infection was defined as the presence of significant bacteriuria on two consecutive urine cultures in an asymptomatic patient, or as the presence of significant bacteriuria on one culture in a patient with urinary tract symptoms. Urinary infections were subdivided into three arbitrary categories. Patients with fever, significant bacteriuria and flank tenderness were considered to have pyelonephritis. Patients with significant bacteriuria accompanied by dysuria without fever or flank tenderness were considered to have cystitis. Asymptomatic bacteriuria was defined as the occurrence of significant bacteriuria without other signs or symptoms of urinary tract infections. All patients with a history of more than one clinical urinary tract infection were given an intravenous pyelogram.

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Patients with skin infections or osteomyelitis had cultures done before treatment; post therapy cultures were performed when possible.

Drug dosage and length of treatment were individualized on the basis of the patient's general condition, renal function, and type of infection. Most patients were given 500 mg of cephalexin four times a day for twelve days. They were instructed to take the drug an hour before meals and at bedtime.

Hematocrit, white blood cell count, blood urea nitrogen, bilirubin, serum glutamic-oxaloacetic transaminase, alkaline phosphatase, cephalin flocculation, thymol turbidity and routine urinalysis were done before, at intervals during, and after therapy in all patients.

Clinical response to cephalexin was divided into five categories. Cures were defined as the elimination of bacteriuria during, and for at least four weeks after, cephalexin treatment, or the healing of skin lesions during treatment. Failures were defined as persistence of bacteriuria with the pre-treatment pathogen during treatment or the lack of healing of skin lesions with persistence of the pre-treatment pathogen. Relapses were defined as the recurrence of bacteriuria with an organism of the same species as the pre-treatment pathogen after eradication during treatment, or the clinical deterioration of an apparently healed skin lesion associated with infection caused by the pre-treatment organism. Reinfections were defined as the occurrence of bacteriuria with an organism different from the pre-treatment pathogen, either during or within four weeks after treatment, or the clinical deterioration of a skin lesion associated with infection by a new species of bacteria. Indeterminate cases were those in which inadequate cultural or clinical data prevented inclusion in one of the above categories.

Laboratory studies. Gram-negative bacteria (148 strains) and gram-positive bacteria (103 strains) isolated from patients with clinical infections were studied. Organisms were collected from the clinical bacteriology laboratory, subcultured and reidentified according to the scheme of Schaub *et al.*⁴ in our research bacteriology laboratory before antibiotic sensitivity tests were performed.

All organisms were tested against cephalexin by both tube dilution and antibiotic disc methods. Each bacterial strain was tested against cephalexin discs containing 30 μ g of antibiotic. As previously reported,⁵ a modification of the single disc method of Kirby *et al.*⁶ and Turck, Lindemeyer, and Petersdorf⁷ was used in the present study. Tube dilution sensitivities were also performed as previously described⁵ except that nutrient broth at pH 6.6 was used to stabilize the antibiotic, thus permitting accurate interpretation of the minimum inhibitory and minimum bactericidal concentrations 24 hours after incubation at 37°C. Nutrient agar at the same pH was also used for the single disc cephalexin sensitivity studies.

RESULTS

Twenty-two patients received 25 courses of therapy for 26 infections as summarized in Table 1. One patient (EV) was treated three times and another (RN) was treated twice; one patient (JG) received a single course of therapy for concurrent infection of the skin and the urinary tract.

Of the 26 infections, 22 involved the urinary tract. Results of the treatment of these 22 infections occurring in 19 patients are classified in Table 2 according to the presence or absence of structural urinary tract abnormalities. Ten of the 22 urinary tract infections occurred in patients with no evi-

TABLE 1. RESULTS OF 26 COURSES OF CEPHALEXIN THERAPY IN 22 PATIENTS WITH INFECTIONS

Patient	Age	Disease	Pathogen	Course (days)	Daily dose (gms)	Outcome of therapy	
1	LM	84	Bacteriuria	Klebsiella	12	1	Cure
2	JG-1	55	"	<i>P. vulgaris</i>	46	2	Relapse
3	FVP	58	"	<i>P. mirabilis</i>	12	2	Relapse
4	TZ	55	"	Klebsiella	12	2	Relapse
5	IM	58	"	<i>E. coli</i>	22	2	Indeterminate
6	CW	9	"	<i>E. coli</i>	90	1	Reinfection
7	BL	22	Cystitis	<i>E. coli</i>	12	2	Cure
8	BP	29	"	<i>E. coli</i>	16	1	Reinfection
9	JC	19	"	Klebsiella			
				<i>P. mirabilis</i>	6	2	Cure
10	LN	37	"	<i>E. coli</i>	129	2	Relapse
11	RN	25	"	<i>E. coli</i>	10	2	Relapse
12	RN-2	25	"	<i>E. coli</i>	16	2	Cure
13	JT	26	"	Enterobacter	12	2	Cure
14	NI	23	"	<i>E. coli</i>	12	2	Cure
15	AG	39	"	Klebsiella	12	2	Reinfection
16	DH	56	"	<i>E. coli</i>	12	2	Cure
17	EV-1	46	"	Enterobacter	295	2	Reinfection
18	EV-2	46	"	<i>E. coli</i>	72	2	Reinfection
19	EV-3	46	"	Enterococcus	235	1-2	Reinfection
20	SM	34	Pyelonephritis	<i>E. coli</i>	12	2	Cure
21	EW	36	"	Klebsiella	30	2	Reinfection
22	BS	51	"	<i>P. mirabilis</i>		1	Relapse
23	JG-2	55	Skin infection	Unknown	46	2	Cure
24	FL	58	"	<i>Peptococcus</i>	42	2	Cure
25	SR	31	"	<i>P. mirabilis</i>	60	2	Cure
26	RS	43	Osteomyelitis	<i>S. aureus</i>	107	2	Indeterminate

TABLE 2. RESULTS OF CEPHALEXIN TREATMENT IN 19 PATIENTS WITH 22 INFECTIONS OF THE URINARY TRACT

	Infections	Cure	Failure	Relapse	Reinfection	Indeterminate
<i>Normal urinary tract</i>						
Cystitis	6	5	0	1	0	0
Pyelonephritis	1	1	0	0	0	0
Asymptomatic bacteriuria	3	1	0	1	0	1
<i>Abnormal urinary tract</i>						
Cystitis	7	1	0	1	5	0
Pyelonephritis	2	0	0	1	1	0
Asymptomatic bacteriuria	3	0	0	2	1	0
Total	22	8	0	6	7	1

dence of structural urinary tract abnormalities. Most of these patients were young women with acute cystitis. Seven of these 10 patients were cured with cephalixin treatment. One patient who relapsed was cured with a second course of therapy. One patient who is classified as indeterminate was abacteriuric on treatment but was unavailable for follow-up. One patient with chronic bacteriuria relapsed after treatment. Only one of the 12 infections in patients with anatomic abnormalities of the urinary tract was cured with cephalixin treatment. Four relapses occurred after treatment was stopped, and the other seven were reinfected during or after treatment. No patient, regardless of the state of his urinary tract, was a treatment failure, as defined above.

E. coli was responsible for seven of the ten infections in patients with normal urinary tracts but caused only three infections among the twelve patients with abnormal urinary tracts. In the latter group, infections were more commonly caused by *Klebsiella*, *Enterobacter*, *Proteus vulgaris*, *Proteus mirabilis* and enterococcus species.

The three patients with skin infections all responded to treatment with a daily dose of two grams of cephalixin for two to six weeks. One of these infections was caused by an anaerobic micrococcus, one by *Proteus mirabilis* and one, in a patient with a renal transplant, was nonspecific and grew no organisms on culture.

The single case of osteomyelitis was caused by *Staphylococcus aureus*. This infection was treated with intravenous cephalothin for two weeks, followed by oral cephalixin for 6 weeks in a dose of two grams per day. Because the staphylococcus could not be recovered from the osteomyelitis lesion after cephalothin therapy was begun, the effect of cephalixin on the outcome of this patient's infection could not be accurately evaluated and is recorded as indeterminate even though the infection healed without incident.

One patient (JG) developed elevated bilirubin and serum glutamic oxaloacetic transaminase while receiving cephalixin. At that time he was also receiving azathioprin, which has been known to cause such abnormalities.⁹ This patient's liver function studies remained abnormal until his death, which occurred a year after cephalixin was stopped but while he was still receiving azathioprin. No other patients developed abnormal values of liver function studies.

Two women developed symptomatic *Candida* vaginitis during cephalixin therapy. This condition resolved with the cessation of cephalixin treatment and local use of nystatin.

Three patients experienced mild, transient nausea while taking cephalixin. No patient had diarrhea. Renal dysfunction or peripheral blood abnormalities were not noted in any of the patients.

Laboratory studies. The bacteriostatic and bactericidal activity of cephalixin against 10^4 bacterial cells of various organisms is shown in Figures 1, 2 and 3. All strains of *Staphylococcus aureus* and most strains of *Staphylococcus albus*, *E. coli*, Klebsiella and indole negative Proteus were sensitive to 12.5 $\mu\text{g}/\text{ml}$. or less of cephalixin. In contrast, most strains of Pseudo-

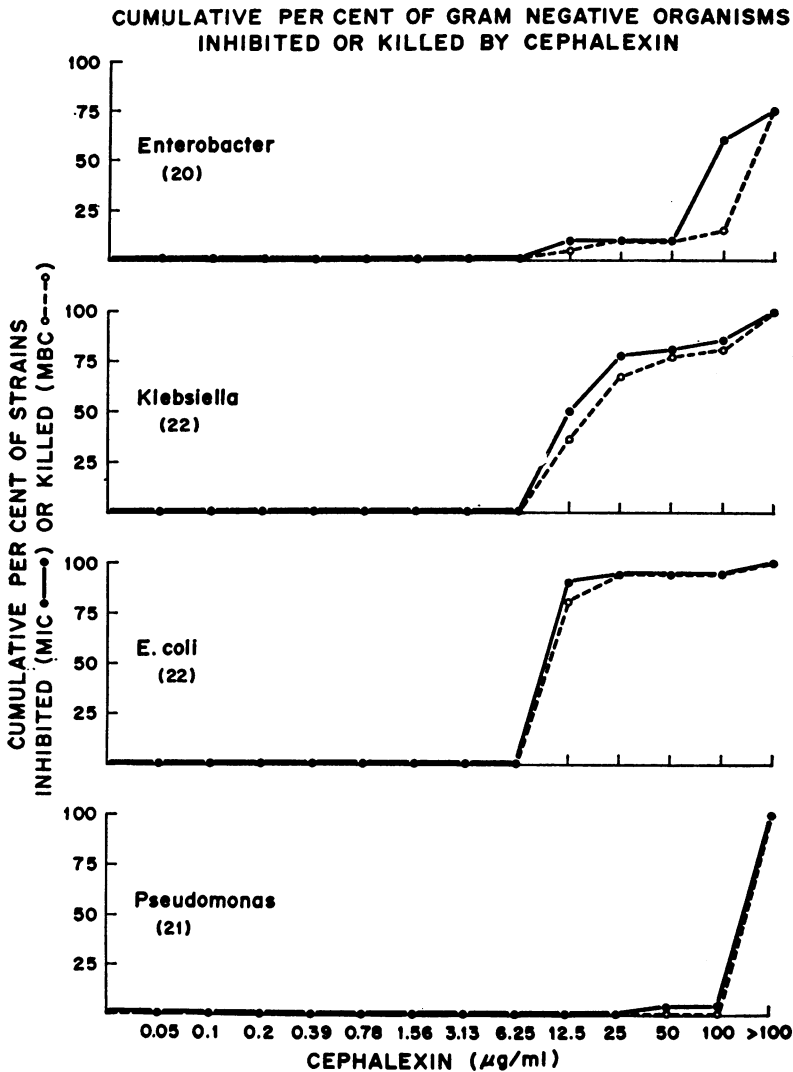


FIG. 1. Susceptibility of four species of gram-negative bacteria to increasing concentrations of cephalixin.

monas, Enterobacter, indole positive Proteus, and Serratia and enterococcus were resistant to concentrations of cephalixin in the range of 50 to 100 $\mu\text{g}/\text{ml}$.

The diameter of the zone of inhibition of bacterial growth around a 30 μg cephalixin disc was compared with the tube dilution sensitivity of a number of strains of gram-positive and gram-negative bacteria by the method used in this laboratory and reported previously.⁹ The results of this comparison are shown in Figs. 4 and 5. Since the 6 mm. diameter of the antibiotic disc is included in the final reading, a zone size of 6 mm. indicates no inhibition of bacterial growth. A zone of inhibition of 16 mm. or more correlated well with a minimal inhibitory concentration of 12.5 $\mu\text{g}/\text{ml}$. or less of cephalixin

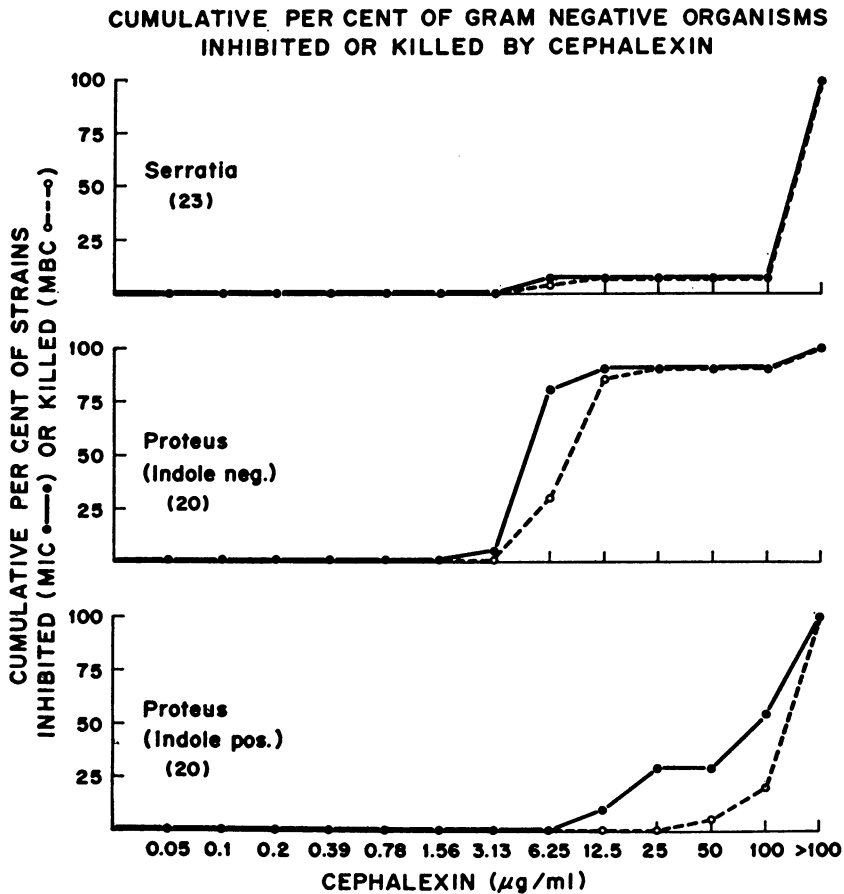


FIG. 2. Susceptibility of three species of gram-negative bacteria to increasing concentrations of cephalixin.

in all species tested except indole negative *Proteus* and *Klebsiella*. Among the indole negative *Proteus*, 9 of the 19 strains tested gave a zone size of less than 16 mm. in spite of being inhibited by 12.5 $\mu\text{g}/\text{ml}$. of cephalexin. Six of 22 strains of *Klebsiella* gave zone sizes greater than 16 mm. although they required 25 $\mu\text{g}/\text{ml}$. of cephalexin to inhibit their growth.

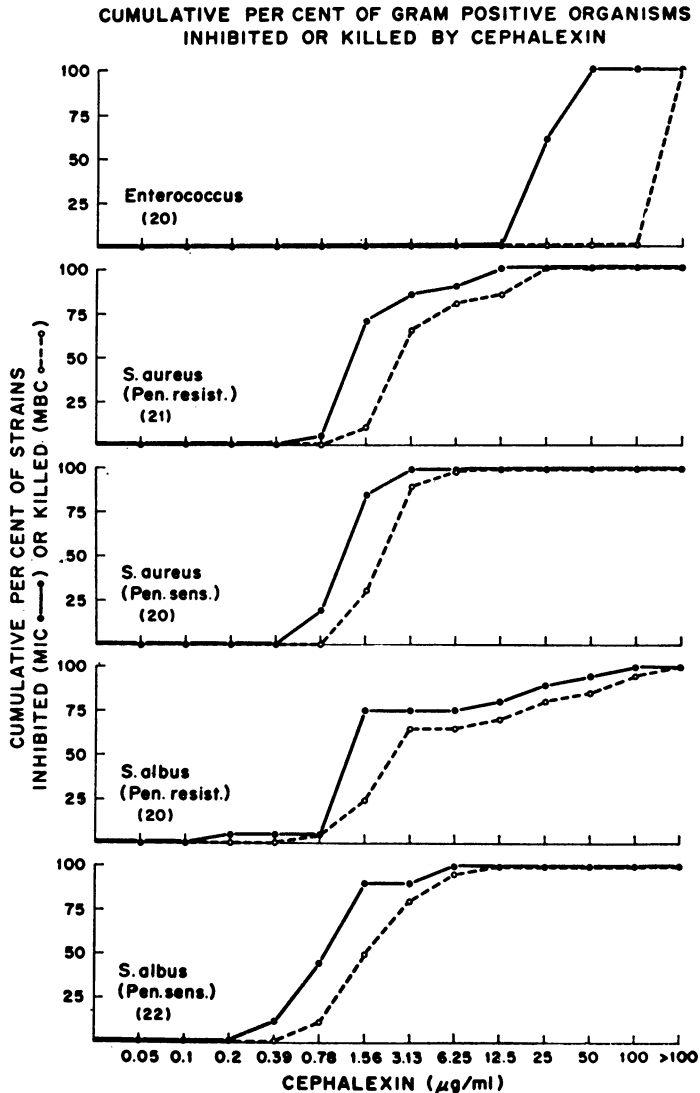


FIG. 3. Susceptibility of gram-positive bacteria to increasing concentrations of cephalexin.

DISCUSSION

The oral administration of 500 mg. of cephalixin gives a peak serum level of about 18 $\mu\text{g}/\text{ml}$.¹ This is 75% of the serum level achieved with the same dose of parenteral cephaloridine and nearly twice that achieved by intra-

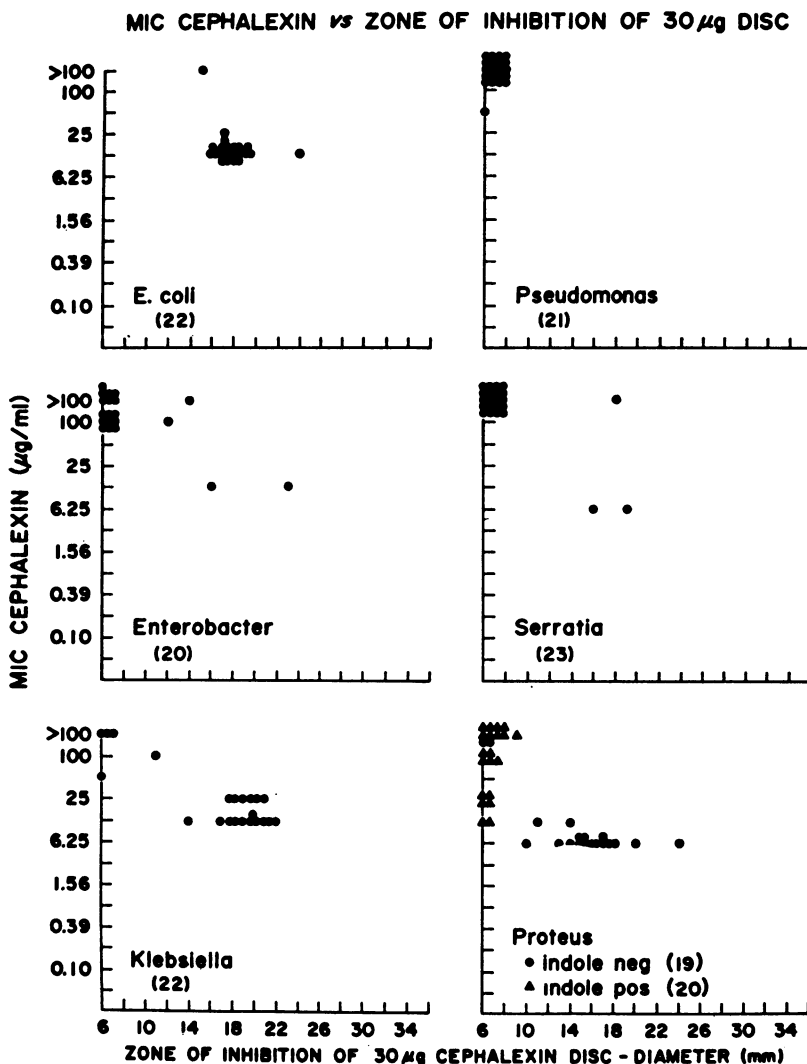


FIG. 4. Correlation of results of 30 μg disc and tube-dilution sensitivities of cephalixin against gram-negative bacteria.

muscular administration of cephalothin; it is far in excess of the barely measurable serum levels achieved with oral cephaloglycin.²

Eighty percent of an oral dose of cephalexin is excreted unchanged in the urine in the first six hours after administration, resulting in urine concentrations of the drug in the order of 800 $\mu\text{g}/\text{ml}$.¹ The high serum levels

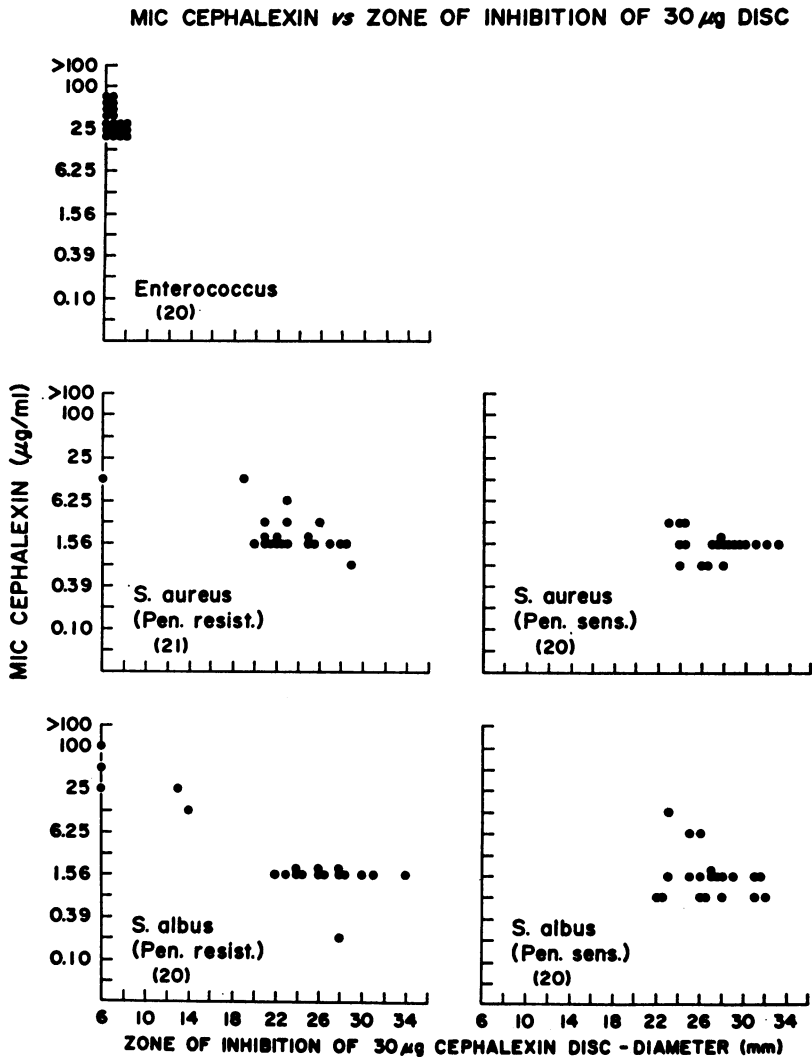


FIG. 5. Correlation of results of 30 μg disc and tube-dilution sensitivities of cephalixin against gram-positive bacteria.

achieved with oral cephalixin provide this drug with a therapeutic potential for systemic as well as urinary tract infections.

Cephalixin has been used successfully in Pneumococcal and Staphylococcal pneumonias and in sepsis due to a variety of gram-positive and gram-negative organisms.⁹ That cephalixin can halt such infections is valuable information, but life threatening infections in acutely ill patients are more often treated with parenteral antibiotics. The present study examines the efficacy of cephalixin in the treatment of skin and urinary tract infections, clinical conditions in which oral antibiotics are commonly employed.

Results of our cephalixin studies showed that the outcome of therapy in patients with urinary tract infections is influenced by the presence or absence of structural abnormalities of the urinary tract, a finding consistent with the behavior of other drugs. Seventy percent of patients with no structural urinary tract abnormalities were cured with cephalixin therapy while only 8% of those with such abnormalities were cured. Fass, *et al.*,⁹ and Levinson, *et al.*,¹⁰ noted the same association of urinary tract abnormalities with the therapeutic efficacy of cephalixin.

In the present study, cephalixin therapy cured skin infections in three patients. Similar results have been observed by Fass and colleagues⁹ who noted cures in 24 of 29 infections of the skin and soft tissue in their clinical trials.

Our *in vitro* studies showed cephalixin to be effective at clinically achievable concentrations against all strains of Staphylococcus, except for a few strains of *Staphylococcus albus*, an organism whose multiple drug resistance has been previously noted.¹¹

Among the gram-negative organisms most strains of *Klebsiella*, *E. coli*, and *Proteus mirabilis* were inhibited by concentrations of cephalixin approaching maximum serum levels. Urinary infections with these organisms could easily be treated, but systemic infections might be expected to respond less well unless the organism was a particularly sensitive one.

In general Enterococci, Enterobacter, indole positive *Proteus*, *Pseudomonas* and *Serratia* strains were only sensitive to very high levels of cephalixin. Infections with most strains of these organisms are unlikely to respond to cephalixin although in the present series a urinary infection with Enterobacter and one with enterococcus were both treated successfully with the drug.

Although no attempt was made to compare the effectiveness of cephalixin with other oral antibiotics commonly used in the treatment of urinary tract infections, the cure rate was similar to that observed in studies with sulfonamides or ampicillin in patients without structural abnormalities of the urinary tract. Cephalixin offers no definite advantage over other agents

but it does provide an alternate drug in treating urinary tract infections caused by organisms resistant to the antibiotics commonly employed in these infections. Cephalexin may also be useful in treating such infections in patients allergic to other antimicrobial agents.

The *in vitro* spectrum of cephalexin, the evidence of clinical efficacy and the lack of toxic side effects in this series and others suggest that cephalexin may be a valuable agent in the treatment of a variety of infections requiring oral therapy.

SUMMARY

Oral cephalexin was used to treat 22 urinary tract infections, three skin infections and one case of osteomyelitis. The drug was effective in treating infections in anatomically normal urinary tracts but not in deformed or obstructed urinary tracts. Infections of the skin were cured. The effect of cephalexin on the one bone infection could not be properly evaluated.

In vitro tests showed the drug inhibited growth of most strains of *Staphylococcus aureus*, *Staphylococcus albus*, *Klebsiella*, *E. coli* and indole negative *Proteus*, at clinically achievable serum levels. Enterococci, Enterobacter, indole positive *Proteus*, *Pseudomonas* and *Serratia* strains were usually not inhibited by drug levels attainable in the serum.

A zone of growth inhibition of 16 mm. or more around a 30 μ g cephalexin disc was a good indication of drug sensitivity except with indole negative *Proteus* and *Klebsiella* where false negative and false positive tests, respectively, occurred.

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