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Cefadroxil, a New Broad-Spectrum Cephalosporin

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Cefadroxil is a new semisynthetic cephalosporin with a broad antibacterial spectrum and a high chemotherapeutic potential when administered orally. The inhibitory activity of this compound was similar to that of cephalexin and cephradine when tested against 602 clinical isolates on Mueller-Hinton medium. In the oral treatment of experimental infections of mice, cefadroxil was more effective than cephalexin against *Streptococcus pyogenes*, and comparably effective against *Streptococcus pneumoniae*, *Staphylococcus aureus*, and several gram-negative species. Administered orally to mice, at doses ranging from 25 to 100 mg/kg, cefadroxil attained peak concentrations in the blood similar to those of cephalexin. At a dose of 200 mg/kg, however, higher peak levels were noted with cefadroxil than with cephalexin. In regard to other properties which were investigated, the behavior of cefadroxil compared favorably to that of cephalexin.

Two cephalosporins, cephalexin and cephradine, due to their therapeutic efficacy when administered orally, have gained widespread usage in the treatment of a variety of infectious diseases. In this paper we report on laboratory investigations of a new semisynthetic cephalosporin, cefadroxil (Fig. 1), which has been found effective against a variety of gram-positive and gram-negative organisms in vitro and in vivo after oral administration. For comparison, cephalexin and cephradine were included in all studies designed to determine the antibacterial spectrum of cefadroxil. While investigating other antimicrobial and pharmacological properties, cephalexin alone was used as a reference compound.

MATERIALS AND METHODS

Antibiotics. Cefadroxil, 7-[D-(-)-α-amino-α-(4-hydroxyphenyl)-acetamido]-3-methyl-3-cephem-4-carboxylic acid, is a white, crystalline, water-soluble solid with a molecular weight of 363.4. Cephalexin monohydrate is a product of Eli Lilly and Co. and cephradine is a product of E. R. Squibb & Sons, Inc.

(i) Properties in vitro: antibiotic spectrum. The inhibitory activity of cefadroxil, cephalexin, and cephradine was determined for 157 gram-positive and 445 gram-negative organisms, predominantly of clinical origin. The assays were performed by a serial twofold agar dilution technique, the bacterial inoculum being added by the multiple inoculator of Steers et al. (7).

Mueller-Hinton medium (Difco) was used in these assays for all organisms except strains of *Neisseria* and *Haemophilus*. For other fastidious organisms (*Streptococcus*, *Listeria*, *Vibrio*, *Pasteurella*, and *Bordetella*), the medium was supplemented with 4% defibrinated sheep blood. The antibiotic susceptibility of *Haemophilus* and *Neisseria* was determined on GC medium base (BBL) supplemented with 1% hemoglobin (BBL) and 1% Isovitalex (BBL).

An overnight broth culture or an exponentially growing culture (*Neisseria*) served as the source of inoculum. A volume of approximately 0.003 ml of an undiluted or diluted culture was applied to the surface of the antibiotic-containing agar plates. Cultures of *Neisseria*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes* were used without dilution, whereas all others were diluted 100-fold. Before dilution, however, *Haemophilus* cultures were initially standardized on a Spectronic 20 colorimeter (Bausch and Lomb) to an optical density (OD) of 0.3 at 560 nm, using 11.5-by 100-mm test tubes. All culture plates were incubated at 37°C either overnight (18 h) or for 24 h (*Haemophilus*). Incubation of *Neisseria*, *Haemophilus*, and all other fastidious organisms was carried out in candle jars in a 5 to 10% CO_2 atmosphere.

After incubation, plates were examined for colony development, and the minimal inhibitory concentration (MIC), i.e., the lowest concentration of antibiotic causing virtually complete inhibition of growth, was recorded. In interpreting these results, inhibition was considered to have occurred if the plates contained only a film of growth or five or less colonies.

Effect of inoculum size. The influence of inoculum size on the inhibitory activity of cefadroxil and cephalexin was determined on solid Mueller-Hinton medium in a manner similar to that described above. The inoculum, however, consisted of three dilutions (10^0, 10^{-2}, and 10^{-4}) of overnight cultures which were first standardized to an OD of 0.45 at 540 nm on a Coleman Jr. II spectrophotometer in 13.5-

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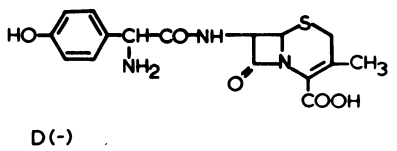

FIG. 1. *Structure of cefadroxil.*

by 150-mm test tubes. The standardized cultures were estimated to contain about 5×10^8 cells/ml before dilution.

Bactericidal activity. The bactericidal activity of cefadroxil and cephalexin was determined by exposing various organisms to a twofold series of antibiotic concentrations in Mueller-Hinton broth. The inoculum was an overnight culture diluted so as to yield an initial cell concentration of 10^4 to 10^5 cells/ml. At the termination of a 20- to 24-h incubation period at 37°C, readings were made for MIC determinations and the cultures were then chilled in ice. After this, 0.1-ml samples from each turbidity-free tube were plated on solid medium. Mueller-Hinton medium was used for most organisms but, to minimize spreading, strains of *Proteus* were plated on nutrient agar (Difco). After incubation of plates, colonies were counted to determine the number of viable cells (colony-forming units) in the original MIC tubes. The minimal bactericidal concentration (MBC) was considered to be the lowest concentration yielding a count of <100 cells/ml.

Susceptibility to β-lactamase. Cell-free extracts containing β-lactamases were employed to determine the rates at which the cephalosporins were hydrolyzed by these enzymes. Hydrolytic activity was measured by the iodometric assay of Perret (3) with the following two modifications: (i) gelatin was omitted, and (ii) the buffer was adjusted to pH 7.0. Extracts from gram-negative organisms were obtained by sonic disruption of cell suspensions, followed by removal of cell debris by centrifugation. The preparations were maintained at −20°C for extended periods of time without significant loss of enzyme activity. The extract from *Staphylococcus aureus* was obtained by acetone and ether treatment of a culture grown in the presence of methicillin. The resulting preparation was stored at 4°C.

Binding to serum proteins. The extent to which cefadroxil and cephalexin are bound to human serum proteins was determined by an ultrafiltration method. Samples containing 10 and 25 μg of the compounds per ml in fresh pooled human serum were incubated at 37°C for 15 min. They were then transferred to CF-50A Centriflo filter cones (Amicon Corp.) and centrifuged for 25 min at $900 \times g$ at 4°C. The resulting ultrafiltrates were assayed on base agar (BBL) plates seeded with *Sarcina lutea* ATCC 9341. Antibiotic concentrations in the filtrates were then determined from reference standard lines which relate the diameter of the inhibition zone to drug concentration. These lines were constructed on the basis of results obtained from the assay of known concentrations of antibiotic in pH 6.0 phosphate buffer (1%). Adequate controls, consisting of antibiotics added to deproteinized serum, were treated identically to ascertain that any decrease in antibiotic activity was due solely to protein binding.

Stability in solution. In determining the stability of cefadroxil and cephalexin at pH 2.0, a 2 mg/ml solution of each antibiotic was prepared in citric acid-HCl buffer (0.002 M) and incubated at 37°C. Aliquots were removed periodically over a 24-h period, neutralized, and assayed on base agar plates seeded with *Bacillus subtilis* ATCC 6633. Residual antibiotic activity was determined with the aid of standard curves obtained by assaying known concentrations of the drugs in phosphate buffer (0.005 M). The length of exposure (in hours) resulting in a 50% decrease in antimicrobial activity (half-life) was then calculated. Stability at pH 7.4 was determined in a similar manner, except that solutions were prepared and incubated in sodium barbital buffer (0.005 M).

(ii) Properties in vivo: antibiotic concentration in blood. Cefadroxil and cephalexin were administered orally to mice to determine the extent of absorption of these antibiotics into the blood stream. Normal male Swiss-Webster mice weighing 20 (±2) g were used in these experiments, in which blood samples were collected for assay at various intervals over a 3.5-h period. The techniques for blood collection and bioassay were similar to those previously described by Price et al. (5) except that *S. lutea* ATCC 9341 and *B. subtilis* ATCC 6633 were the assay organisms and the animals were fasted for only 4 h pretreatment. A minimum of three tests was carried out in this manner, with eight mice being used per dose level in each experiment.

Recovery in urine. Male Sprague-Dawley rats, weighing 200 (±20) g, were employed to determine the fraction of the orally administered antibiotic that is excreted in the urine. For each drug, a dose of 50 mg/kg in 4 ml of Tween-CMC (carboxymethyl cellulose) was administered by gavage to five rats that were fasted for 18 h pretreatment. Animals were housed individually in metabolism cages and urine specimens were collected over dry ice during intervals of 0 to 6 h and 6 to 24 h postadministration. Aliquots (0.03 ml) of appropriate dilutions of the collected urine were transferred to paper disks (6.35-mm diameter), and antibiotic activity was assayed by the agar diffusion technique on seeded agar plates inoculated with *S. lutea* ATCC 9341. Concentrations of the antibiotic in the urine were calculated from reference standard lines which relate the diameter of the inhibition zone to drug concentration. These lines were constructed from assay data involving known concentrations of the antibiotic added to urine collected from untreated control animals.

To determine the presence of active metabolites, the urine samples were subjected to descending paper chromatography in an *n*-butanol-ethanol-water (80:20:100) system. The paper strips were subsequently assayed in base agar seeded with *B. subtilis* ATCC 6633.

Treatment of experimental infections. Male Swiss-Webster mice weighing 20 (±2) g were challenged intraperitoneally with 0.5 ml of a bacterial suspension containing sufficient organisms to kill

TABLE 1. *Growth inhibitory activity of cefadroxil, cephalexin, and cephradine against miscellaneous bacterial species*

Organism	No. of strains	MIC (μg/ml)[a]		
		Cefadroxil	Cephalexin	Cephradine
Streptococcus faecalis	14	57	84	57
Listeria monocytogenes	7	39	63	39
Bacillus anthracis	1	1	2	1
Edwardsiella tarda	2	4	2	2.8
Arizona hinshawii	2	8	4	8
Citrobacter sp.	5	>72	37	48
Hafnia alvei	2	32	16	32
	1	125	125	125
Serratia marcescens	5	>125	>125	>125
Proteus rettgeri	2	5.7	5.7	8
	1	>125	125	125
Proteus morganii	12	>125	>125	>125
Vibrio cholerae	1	2	2	2
Pasteurella multocida	2	4	2	4
Pseudomonas aeruginosa	3	>125	>125	>125
Alcaligenes sp.	7	7.2	4.4	11
	6	>99	>89	>99
Bordetella bronchiseptica	1	63	125	>125

[a] Geometric mean when applicable.

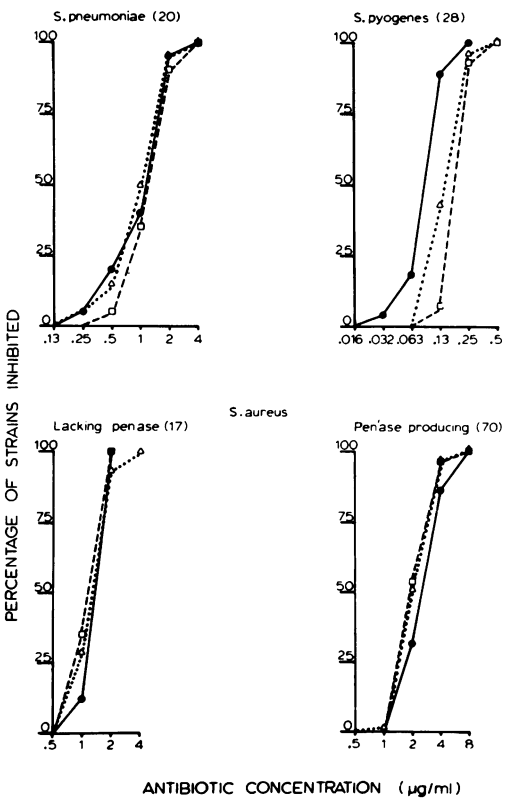

FIG. 2. *Growth inhibitory activity of cefadroxil (●), cephalexin (□), and cephradine (△) against various gram-positive organisms. The number in parentheses indicates the number of strains.*

untreated animals within 72 h. The challenge medium was brain heart infusion broth (Difco) for *Klebsiella pneumoniae* and all streptococci, a suspension of 2% hog gastric mucin (type 1701W, Wilson Laboratories, Inc., Park Forest South, Ill.) for *S. aureus* A9606, and 4% mucin for the remaining organisms. Various concentrations of the antibiotics in a Tween-CMC mixture were administered orally to five mice for each dose level. The animals were treated twice in this manner, in accordance with the treatment schedule shown in Table 4. The number of mice surviving the challenge for 3 or 5 days (depending on the test organism) was recorded and the PD_{50} (dose in milligrams per kilogram required to protect half the infected animals from death) was then estimated by a log probit plot.

RESULTS

(i) Properties in vitro: antibiotic spectrum. Cefadroxil, cephalexin, and cephradine very effectively inhibited a broad spectrum of gram-positive and gram-negative organisms. This is evident upon examination of the susceptibility data shown in Table 1 and Fig. 2 to 5.

Although the three cephalosporins were about equally effective in inhibiting the growth of *S. pneumoniae* and *S. aureus*, cefadroxil was twice as active as cephalexin and slightly more active than cephradine against *S. pyogenes* (Fig. 2). None of the antibiotics displayed any appreciable inhibitory effect for *Streptococcus faecalis* and *Listeria monocytogenes* (Table 1).

In tests involving gram-negative organisms, cefadroxil, cephalexin, and cephradine were comparably active against *Escherichia coli* and

Proteus mirabilis. However, against *K. pneumoniae* (Fig. 3), *Proteus vulgaris* (Fig. 4), and *Salmonella* sp. (Fig. 5), cefadroxil and cephradine were approximately twofold less active then cephalexin. When tested against *Shigella* sp., *Haemophilus influenzae*, and *Neisseria gonorrhoeae*, cefadroxil was again about two-

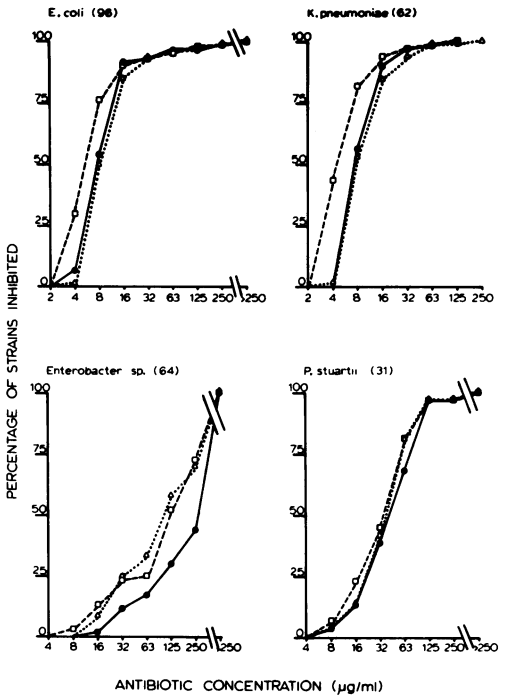

FIG. 3. *Growth inhibitory activity of cefadroxil (●), cephalexin (□), and cephradine (△) against various Enterobacteriaceae. The number in parentheses indicates the number of strains.*

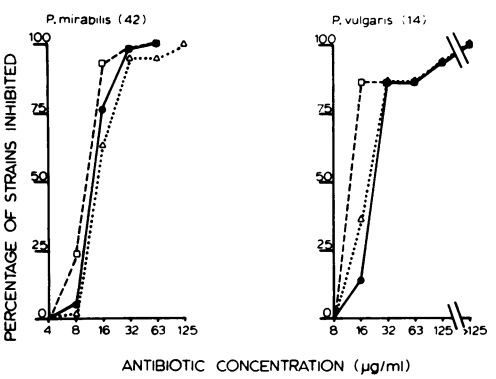

FIG. 4. *Growth inhibitory activity of cefadroxil (●), cephalexin (□), and cephradine (△) against strains of Proteus mirabilis and Proteus vulgaris. The number in parentheses indicates the number of strains.*

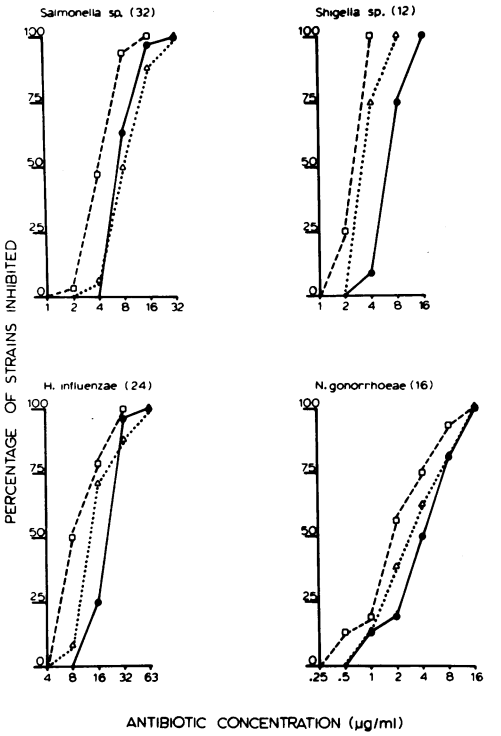

FIG. 5. *Growth inhibitory activity of cefadroxil (●), cephalexin (□), and cephradine (△) against various gram-negative organisms. The number in parentheses indicates the number of strains.*

fold less active than cephalexin, whereas the activity of cephradine was intermediate. On the basis of geometric mean MIC values, cephalexin was more than twice as active as cephradine against sensitive *Alcaligenes* strains, whereas the activity of cefadroxil was closer to that of cephalexin (Table 1). The three cephalosporins were virtually ineffective in inhibiting growth of *Enterobacter* sp., *Providencia stuartii*, *Pseudomonas aeruginosa*, *Serratia marcescens*, and *Proteus morganii*.

Few conclusions can be drawn about the susceptibility of the remaining miscellaneous species listed in Table 1 because of the small number of strains studied. Nevertheless, these results are in overall agreement with those obtained with the other clinical isolates in that no major differences in activity between the three compounds were found.

Effect of inoculum size. Four strains of *S. aureus* and 23 members of the *Enterobacteriaceae* family (eight *E. coli*, six *K. pneumoniae*, four *P. mirabillis*, three *P. rettgeri*, and two *P. vulgaris*) were employed to determine the influence of inoculum size on the activity of cefadroxil and cephalexin. In these studies, the pat-

tern of response to cefadroxil was similar to that of cephalexin in that for about two-thirds of the organisms, the size of the inoculum had relatively little or no effect on antibiotic activity. However, increases in cell concentrations of the remaining strains resulted in a substantial reduction (eightfold or more) in the activity of both antibiotics. Although the greatest inoculum effect on the activity of the two cephalosporins occurred with *Proteus*, a considerable decrease in their inhibitory action was also noted with high inocula of two strains of *E. coli* and one of *K. pneumoniae*.

Bactericidal activity. Bactericidal activity was determined on the basis of antibiotic effectiveness in killing cells of 17 strains of *Enterobacteriaceae* (six each of *E. coli* and *K. pneumoniae*, two of *P. mirabilis*, and three of *P. vulgaris*). Once again, the behavior of the two antibiotics was similar. Both had excellent bactericidal activity since, in every instance, killing concentrations were either equal to or no more than twofold higher than inhibitory concentrations.

Susceptibility to β-lactamase. The relative susceptibility of cefadroxil and cephalexin to hydrolysis by β-lactamases present in cell-free extracts was determined. For comparison, rates of hydrolysis of two other commercially available cephalosporins, cefazolin and cephaloridine, are also presented in Table 2.

Results indicate that cefadroxil and cephalexin are about equally stable to the seven β-lactamases investigated. Both appear to be poor substrates for enzyme types IIa, IIIa, IVa, and the staphylococcal β-lactamase, and are relatively resistant to type IVb. Although cefadroxil, like cephalexin, is hydrolyzed at a significant rate by types Ia and Ib, it is considerably less susceptible to these enzymes than are cefazolin and cephaloridine.

Serum binding. As determined by an ultrafiltration method, cefadroxil and cephalexin are bound to human serum proteins to a similar extent—20 and 17%, respectively. Results obtained with cephalexin are in agreement with those of Kind et al. (2) who reported 13 to 19% binding at a concentration of 10 μg/ml.

Stability in solution. At 37°C, cefadroxil and cephalexin are stable in solution at both pH 2.0 and 7.4, the half-life in all cases being in excess of 24 h.

(ii) Properties in vivo: antibiotic concentration in blood. Concentrations of cefadroxil and

TABLE 2. *Relative susceptibility of several cephalosporins to hydrolysis by β-lactamases in cell-free extracts*

Enzyme[a]		Organism (source of enzyme)	Relative rate of hydrolysis (benzylpenicillin = 100)			
Class	Type		Cefadroxil	Cephalexin	Cefazolin	Cephaloridine
I	a	*Enterobacter cloacae* 214	595	900	10,000	7,900
	b	*Escherichia coli* 719	48	55	760	370
II	a	*Proteus mirabilis* 1266	<1	<1	<1	2
III	a	*Escherichia coli* TEM	<1	<1	12	93
IV	a	*Klebsiella pneumoniae* 53	<1	<1	12	100
	b	*Klebsiella pneumoniae* 1169	2	4	31	50
		Staphylococcus areus A9606	<1	<1	<1	<1

[a] Enzyme classification according to Richmond and Sykes (6).

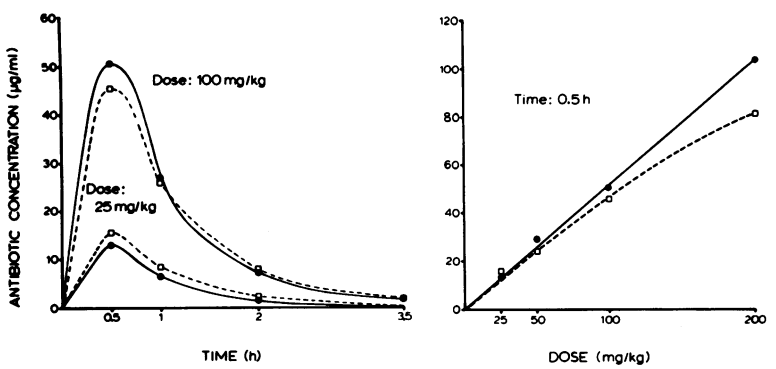

FIG. 6. *Antibiotic concentration in blood after oral administration to mice. Symbols: cefadroxil (●), cephalexin (□).*

cephalexin attained in the blood of mice after oral administration can be seen in Fig. 6. When dosed at 25 and 100 mg/kg, the levels of cefadroxil in blood were virtually identical to those of cephalexin (Fig. 6, left). The highest detectable concentrations of both were found 30 min after administration. Drug levels then declined at similar rates for the two antibiotics. Maximum concentrations (in micrograms per milliliter) observed for cefadroxil and cephalexin were, respectively, 13.7 and 15.1 for a 25 mg/kg dose, as compared to 50.8 and 45.8 when the dose was 100 mg/kg.

Concentrations of the two compounds found at 30 min after administration are plotted as a function of dose (Fig. 6, right). Up to a dose of 100 mg/kg, values for the two cephalosporins were similar, with concentrations being proportional to dose. However, a linear relationship was maintained for cefadroxil, but not for cephalexin, up through a dose of 200 mg/kg.

TABLE 3. *Urinary recovery of cefadroxil and cephalexin after oral administration to rats*

Compound	Urinary recovery as % of administered dose		
	0-6[a]	6-24[a]	0-24[a]
Cefadroxil[b]	63	5	68
Cephalexin	65	3	68

[a] Hours after administration.

[b] The compounds, prepared in Tween-CMC, were administered to five male rats each at a dose of 50 mg/kg body weight.

Urinary excretion. The extent to which cefadroxil and cephalexin were recovered from the urine of rats after a 50 mg/kg dose can be seen in Table 3. A total of 68% of the administered dose of both cephalosporins was found in the urine during the first 24 h postadministration. No bioactive metabolites of either cefadroxil or cephalexin were detected in the urine.

Treatment of experimental infections. The comparative therapeutic effectiveness of cefadroxil and cephalexin in treating mice experimentally infected with various gram-positive and gram-negative bacteria is indicated in Table 4. In vivo, just as in vitro, cefadroxil was more effective than cephalexin against *S. pyogenes*. Against the three infecting strains of this organism, the activity of cefadroxil was three- to sixfold greater than that of cephalexin. In the treatment of mice infected with *S. pneumoniae*, the two compounds were about equally effective. This was also true for the *S. aureus* infections, regardless of ability of the organism to produce penicillinase.

Both compounds were very effective in treating systemic infections caused by *K. pneumoniae*, *E. coli*, and *P. mirabilis*, although PD_{50} values of cephalexin were somewhat lower (generally less than twofold) than those of cefadroxil.

DISCUSSION

Results reported in this paper for cephalexin and cephradine are consistent with those noted by other workers in the field. Stewart and Bodey (8) showed similarities in antibacterial

TABLE 4. *Therapeutic efficacy of orally administered cefadroxil and cephalexin in experimental infections of mice*

Organism[a]	Challenge (no. of organisms)	PD_{50}/treatment (mg/kg)[b]	
		Cefadroxil	Cephalexin
Streptococcus pyogenes A9604	6×10^4	2.4	6.8
S. pyogenes A15041	7×10^4	0.7	3.5
S. pyogenes A20202	2×10^7	0.6	3.4
S. pneumoniae A20759	1×10^4	18	16
S. pneumoniae A9585	3×10^5	24	38
S. pneumoniae A20769	3×10^4	24	41
Staphylococcus aureus A9537[c]	2×10^5	0.3	0.18
S. aureus A9497[c]	3×10^8	5.1	3.4
S. aureus A20405	4×10^6	8	6
S. aureus A9606	2×10^9	29	24
Klebsiella pneumoniae A9977	4×10^4	85	41
Escherichia coli A15119	2×10^4	12	8
E. coli A9675	1×10^5	18	12
Proteus mirabilis A9900	3×10^6	64	38

[a] The organisms selected for this study were typical wild-type strains in terms of their in vitro susceptibility to the test compounds.

[b] Results are averages of two or three experiments, each consisting of five mice for each dose per experiment. Animals infected with *S. aureus* strains A9497, A20405, and A9606 were treated 0 and 2 h after infection; all others were treated 1 and 3.5 h after infection.

[c] Lack penicillinase. Other strains of *S. aureus* are penicillinase producers.

activity between the two compounds against a series of gram-positive and gram-negative organisms. Clark and Turck (1) also reported on the inhibitory and bactericidal activity of cephalexin and commented on the fact that its activity is reduced in the presence of high inocula of certain strains, particularly *P. mirabilis*. Wick (9), in addition to providing evidence for the bacteriostatic and bactericidal effectiveness of cephalexin, demonstrated good oral absorption in mice and excellent efficacy in treating experimental mouse infections after oral dosage.

It is not surprising that cefadroxil, because of its similarity in structure, possesses many of the same characteristics as cephalexin and cephradine. The most apparent advantages of cefadroxil over the reference compounds, however, lie in its pharmacokinetic properties. In a companion paper (4), cefadroxil has been shown to have a longer serum half-life after oral dosage to humans, a slower urinary excretion rate, and a greater area under the serum level vs. time curve than either cephalexin or cephradine. In addition, it was also noted that the apparent volume of distribution of cefadroxil is greater than that of cephalexin.

Because of cefadroxil's broad range of antimicrobial activity and its favorable pharmacokinetic profile in man, clinical trials with this antibiotic are currently under way.

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