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Comparative Efficacies of Ciprofloxacin, Amoxicillin, Amoxicillin-Clavulanic Acid, and Cefaclor against Experimental *Streptococcus pneumoniae* Respiratory Infections in Mice

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Experimental respiratory infections were established in mice by intranasal inoculation of *Streptococcus pneumoniae*. Inoculation of 10^7 CFU of either *S. pneumoniae* 1629 or *S. pneumoniae* 7 produced a fatal pneumonia in nontreated mice 2 to 3 days after infection. Oral therapy was commenced 1 h after infection and was continued three times a day for 2 days. The doses used in mice produced peak concentrations in serum and lung tissue similar to those measured in humans. Ciprofloxacin failed to eliminate either strain of pneumococcus from mouse lungs at any of the doses tested (40, 80, or 160 mg/kg of body weight) by the end of therapy (33 h). Mice that received ciprofloxacin at 160 mg/kg were clear of *S. pneumoniae* 7 5 days later, whereas persistence and regrowth of *S. pneumoniae* 1629 resulted in the death of 20% of animals treated with ciprofloxacin. Therapy with cefaclor (20 mg/kg) produced an effect similar to that of ciprofloxacin. In contrast, amoxicillin (10 and 20 mg/kg) and amoxicillin-clavulanic acid (10/5 and 20/10 mg/kg) were significantly ($P < 0.05$) more effective in eliminating both strains of *S. pneumoniae* from the lungs by the end of therapy and, by 168 h, had prevented mortality in 80 to 100% of treated animals. The efficacy of ciprofloxacin against these experimental pneumococcal respiratory infections was poor, despite good penetration into lung tissue, and is a reflection of the low in vitro activity of the quinolone against *S. pneumoniae*, one of the most common pathogens in community-acquired pneumonia.

Pneumonia has been reported to be one of the most serious infectious diseases in both industrialized and underdeveloped countries (2) and is a major cause of morbidity and mortality. Approximately 7% of patients with community-acquired pneumonia require hospitalization, and there is a 5 to 10% mortality rate in such patients. *Streptococcus pneumoniae* remains a highly prevalent pathogen in adult patients (10, 18), and recovery of this organism in 9 to 42% of patients with community-acquired pneumonia has been recorded over the past decade (2). Other organisms implicated in lower respiratory infections include *Haemophilus influenzae* and *Branhamella catarrhalis*, while *Staphylococcus aureus*, *Legionella pneumophila*, influenza A virus, and *Mycoplasma pneumoniae* are less common causes of community-acquired pneumonia or cause atypical pneumonias (8).

Ampicillin and amoxicillin are the most frequently prescribed agents for the oral treatment of lower respiratory tract infections (28) and are generally highly effective against *S. pneumoniae* and non-β-lactamase-producing *H. influenzae*. Both agents are, however, less satisfactory for infections in which β-lactamase-producing organisms such as *H. influenzae*, *B. catarrhalis*, or gram-negative bacilli may be present. In such cases, the combination of amoxicillin and the β-lactamase inhibitor clavulanic acid has been reported to be highly efficacious (3).

In recent years there has been great interest in the role of the 4-fluoroquinolones in the treatment of lower respiratory tract infections. Potential advantages of this class of agents include good absorption following oral administration, good penetration into tissues, and a broad spectrum of antimicrobial activity. In the treatment of respiratory infections, ciprofloxacin, the quinolone carboxylic acid derivative, has been reported to be as effective as ampicillin (27) and amoxicillin-clavulanic acid (15) and superior to the oral cephalosporin cefaclor (13). However, because ciprofloxacin shows poor in vitro activity against *S. pneumoniae*, caution has been advised in the empiric use of the quinolone for the treatment of lower respiratory infections (17, 26). While the failure of ciprofloxacin therapy because of the presence of *S. pneumoniae* in bronchopulmonary infections has been seen (6, 25), other reports suggest that the reduced susceptibility of pneumococci does not interfere with the efficacy of the drug (4, 7, 20). Indeed, ciprofloxacin penetrates the bronchial mucosa efficiently and has been reported to reach concentrations in the tissue in excess of that required to inhibit 90% of *S. pneumoniae* (11, 14), and therefore, it might be considered to be effective in vivo.

Although the efficacy of ciprofloxacin has been demonstrated in a number of experimental models of pneumonia by using *H. influenzae*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* (12, 21, 22), no data have been published on the efficacy of this quinolone against an experimental *S. pneumoniae* pneumonia, and the requirement for further investigations has been suggested (5, 14).

In the studies reported here, the efficacies of ciprofloxacin, amoxicillin, amoxicillin-clavulanic acid, and cefaclor were assessed by using a model of acute *S. pneumoniae* pneumonia in mice.

MATERIALS AND METHODS

Animals. Female MF1 mice (weight, 18 to 22 g) were supplied by Harlan-OLAC (Bicester, England).

Organisms. Two mouse-virulent strains, *S. pneumoniae* 1629 and *S. pneumoniae* 7, were used in these studies. Overnight cultures of each organism were grown in Todd-

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Hewitt broth (Oxoid) and frozen in 1-ml aliquots at −70°C. For each experiment, 200-μl volumes of a thawed suspension were used to seed 5-ml volumes of fresh Todd-Hewitt broth, which were incubated overnight at 37°C to yield approximately 10^8 CFU/ml. The MICs of the agents used in the therapy studies were determined according to the recommendations of the National Committee for Clinical Laboratory Standards (16).

Compounds. Amoxicillin trihydrate and potassium clavulanate were prepared in the laboratories of SmithKline Beecham Pharmaceuticals, Worthing, England. Ciprofloxacin was kindly provided by Bayer UK Ltd., Newbury, England, while cefaclor was a commercial preparation (Distaclor; Dista Products Ltd., Basingstoke, England). All compound weights were adjusted for purity. Amoxicillin was suspended in 0.05 M phosphate buffer (pH 8.0), potassium clavulanate was dissolved in 0.1 M citrate buffer (pH 6.5), and ciprofloxacin and cefaclor were prepared in sterile distilled water. For in vivo studies, the amoxicillin-clavulanic acid combination was tested as a 2:1 ratio.

Establishment of infection and therapy. Mice were lightly anesthetized with ether, and 50 μl (approximately 10^7 CFU) of the overnight broth culture was inoculated intranasally. The mice recovered consciousness within a few minutes. Preliminary studies showed that this inoculum produces a fatal pneumonia in nontreated animals, with onset occurring 2 to 3 days after infection. Therapy was initiated 1 h after infection and was continued three times daily for 2 days. All agents were given orally in 0.2-ml volumes. Solutions of amoxicillin and clavulanic acid were mixed immediately prior to dosing. Amoxicillin was given alone at 10 or 20 mg/kg of body weight or was combined with clavulanic acid at 10/5 or 20/10 mg/kg. Cefaclor was administered at 20 mg/kg, and ciprofloxacin was administered at 40, 80, or 160 mg/kg. Nontreated control animals received 0.9% phosphate-buffered saline (pH 7.2).

Assessment of therapy. The numbers of mice that survived were recorded for 7 days. One hour after infection, control mice ($n = 5$) were killed to determine the numbers of the infecting organism present in the lung tissue at the initiation of therapy. Thereafter, groups of five mice per treatment were sampled at 33 h (2 h after the final dose) and 168 h after infection. The lungs were removed aseptically and washed in phosphate-buffered saline to remove contaminating blood. The lungs were then homogenized in glass tissue grinders containing 1 ml of Todd-Hewitt broth. Homogenates were serially diluted in Todd-Hewitt broth, and 20-μl volumes were plated in triplicate onto 5% blood agar supplemented with 0.5% (vol/vol) β-lactamase (penase; Difco) and incubated at 37°C for 24 h to determine the number of viable *S. pneumoniae* present. Confirmation of the recovery of *S. pneumoniae* from the lung tissue was made by Gram stain and determination of optochin susceptibility (5-μg disk; Mast Laboratories, Liverpool, England). Animals that became moribund prior to the designated sampling times were humanely killed and the lungs were sampled. On occasions when an animal died before a sample could be obtained, mean bacterial counts (7.69 or 8.34 $\log_{10}$ CFU) from moribund mice were substituted.

Distribution. In separate studies, concentrations of the agents were measured in serum and lung tissue of infected mice dosed 1 h after inoculation with *S. pneumoniae* 1629. Infected animals received a single oral dose of amoxicillin-clavulanic acid (20/10 mg/kg), cefaclor (20 mg/kg), or ciprofloxacin (40, 80, or 160 mg/kg). At intervals after dosing, groups of five animals per treatment were humanely killed, and blood was obtained from the axillary vein and centrifuged at 15,000 × *g* for 2 min to obtain a serum fraction. The lungs were removed and rendered free of surface blood by blotting before being homogenized in glass tissue grinders containing 1 ml of sterile distilled water. Serum and lung tissue homogenates were assayed by a large-plate agar diffusion assay: amoxicillin against *Bacillus subtilis* ATCC 6633, clavulanic acid by a β-lactamase inhibition assay with *K. pneumoniae* ATCC 29665, cefaclor against *Staphylococcus saprophyticus* ATCC 9341, and ciprofloxacin against *Escherichia coli* NIHJ. Plates were incubated at 37°C for 18 h. The concentrations of antibiotic in the samples were derived from standard solutions prepared in pooled mouse serum or sterile distilled water. The percent penetration of each agent into lung tissue was calculated as the ratio of the lung tissue drug concentration to the serum drug concentration × 100, as described previously (11).

Statistical analysis. Results were analyzed by the Student *t* test.

RESULTS

In vitro susceptibility. *S. pneumoniae* 1629 and *S. pneumoniae* 7 were highly susceptible to amoxicillin and amoxicillin-clavulanic acid (MICs for both organisms, 0.01 and 0.01/0.005 μg/ml, respectively) but were less susceptible to cefaclor and ciprofloxacin (MICs for both organisms, 1.0 and 0.5 μg/ml, respectively). Clavulanic acid had a low level of activity (MIC, 32 μg/ml).

Distribution studies. Peak concentrations of amoxicillin and clavulanic acid in mouse serum were obtained 15 min after a dose of 20/10 mg/kg (Table 1). The mean peak concentration of cefaclor (Table 1) in serum at 15 min after a dose of 20 mg/kg was similar to that of amoxicillin, and these were both of the same order as those measured in humans following oral doses of 625 mg of amoxicillin-clavulanic acid (1) and 250 mg of cefaclor (23). Oral administration of ciprofloxacin to mice produced lower peak concentrations in serum than amoxicillin or cefaclor did (Table 1). The mean values obtained in mouse serum following administration of 40 or 80 mg of ciprofloxacin per kg encompassed those likely to be achieved in humans following an oral dose of 500 or 750 mg (9).

Measurements from lung tissue homogenates showed that the level of penetration of ciprofloxacin into the tissue was 109, 148, and 233%, respectively, for doses of 40, 80, and 160 mg/kg (Table 1). The concentrations in lung homogenate and the percent penetration achieved after administration of 80 mg of ciprofloxacin per kg to mice were similar to that reported in humans following administration of 500 mg (11). Peak concentrations of amoxicillin in the lung tissue were of the same order as those achieved with the lower doses of ciprofloxacin, but the percent penetration of the β-lactam was much lower (48%; Table 1). The concentration of clavulanic acid present in the lung tissue was below the limit of detection (<1.5 μg/g) of the assay used. The mean peak lung concentration and penetration of cefaclor were similar to those of amoxicillin. Peak concentrations of amoxicillin and cefaclor in mouse lung tissue were on the same order as those reported from human lung biopsy specimens following oral administration (11, 23).

Therapy. (i) Study 1: *S. pneumoniae* 1629. Figure 1 shows individual bacterial counts (i) at the completion of therapy (33 h) and (ii) between 33 h and the end of the study (168 h). Survival-versus-time curves are shown in Fig. 2. At 1 h postinfection, 7.47 ± 0.47 $\log_{10}$ CFU of *S. pneumoniae* was

TABLE 1. Peak concentrations of amoxicillin-clavulanic acid, ciprofloxacin, and cefaclor in mouse serum and lung tissue homogenate, with peak concentrations in human serum given for comparison

Compound	Mouse						Human		
	Dose (mg/kg)	Concn in serum (μg/ml)[a]	$t_{1/2\beta}$ (min)[b]	Concn in lung tissue (μg/g)[a]	$t_{1/2\beta}$ (min)	% Tissue penetration	Dose (mg)	Concn in serum (μg/ml [reference])	$t_{1/2\beta}$ (min)
Amoxicillin	20	7.9 ± 2.6	21.6	3.8 ± 2.5	15.6	48	500	8.0 (1)	56.4
Clavulanic acid	10	3.1 ± 1.2	9.2	<1.5			125	2.9	45.4
Ciprofloxacin	40	1.4 ± 0.3	61.8	1.6 ± 0.5	58.1	109	500	2.37 (9)	292.2
Ciprofloxacin	80	3.9 ± 0.8	81.6	5.8 ± 2.9	117.6	148	750	2.96 (9)	320.4
Ciprofloxacin	160	5.1 ± 1.8	102.6	11.8 ± 6.4	120.0	233			
Cefaclor	20	8.0 ± 2.0	16.0	3.3 ± 1.4	24.6	42	250	7.0 (23)	40.0

[a] Mean peak concentrations, with standard deviation, measured in five animals 15 min after administration of the dose.
[b] $t_{1/2\beta}$, Half-life at β phase.

recovered from the lungs of nontreated control animals. At 33 h the number of pneumococci was 5.6 ± 0.50 $\log_{10}$ CFU per lung (Fig. 1a), and there was evidence of enlargement and consolidation of the lungs. By 120 h, all nontreated mice had succumbed to the infection (Fig. 2). The mean lung bacterial count obtained from moribund control animals was 8.34 ± 0.29 $\log_{10}$ CFU per lung (Fig. 1b).

Animals treated with ciprofloxacin responded in relation to dose. A mean bacterial count of 4.06 ± 1.39 $\log_{10}$ CFU per lung was obtained at 33 h from mice treated with 40 mg/kg, and 3.24 ± 1.84 and 2.58 ± 1.09 $\log_{10}$ CFU were present in the lungs of mice treated with 80 or 160 mg of ciprofloxacin per kg, respectively (Fig. 1a). Following cessation of therapy, the mean *S. pneumoniae* 1629 count in animals that received 40 or 80 mg of ciprofloxacin per kg increased to 7.00 ± 3.06 and 7.41 ± 1.81 $\log_{10}$ CFU per lung (Fig. 1b), respectively, with 80 and 60% of mice, respectively, either being sampled early or having died by 144 h (Fig. 2). The number of *S. pneumoniae* 1629 recovered from animals that received 160 mg of ciprofloxacin per kg increased slightly to 3.65 ± 2.79 $\log_{10}$ CFU per lung by 168 h. Twenty percent of animals in this group (Fig. 2) died before the end of the study; however, two of the four remaining mice were clear of the infecting organism (Fig. 1b).

Therapy with cefaclor (20 mg/kg) reduced the mean pneumococcal count in the lungs to 3.59 ± 0.80 $\log_{10}$ CFU per lung by 33 h (Fig. 1a), although by the end of the study the numbers of *S. pneumoniae* 1629 increased to 6.10 ± 3.28 $\log_{10}$ CFU per lung (Fig. 1b) and 40% of the animals had died (Fig. 2).

Oral administration of amoxicillin at 10 or 20 mg/kg reduced the pneumococcal count in mouse lungs to below the limit of detection (<33 CFU per lung) in 60 and 80%, respectively, of animals sampled at 33 h (Fig. 1a). The recovery of *S. pneumoniae* from the remaining animals was low (mean, 2.12 and 2.83 $\log_{10}$ CFU per lung). The reduction in the pneumococcal count following either dose of amoxicillin was significantly greater ($P < 0.05$) than that seen following either cefaclor or the ciprofloxacin treatments. By 168 h, 80% of mice treated with amoxicillin were alive (Fig.

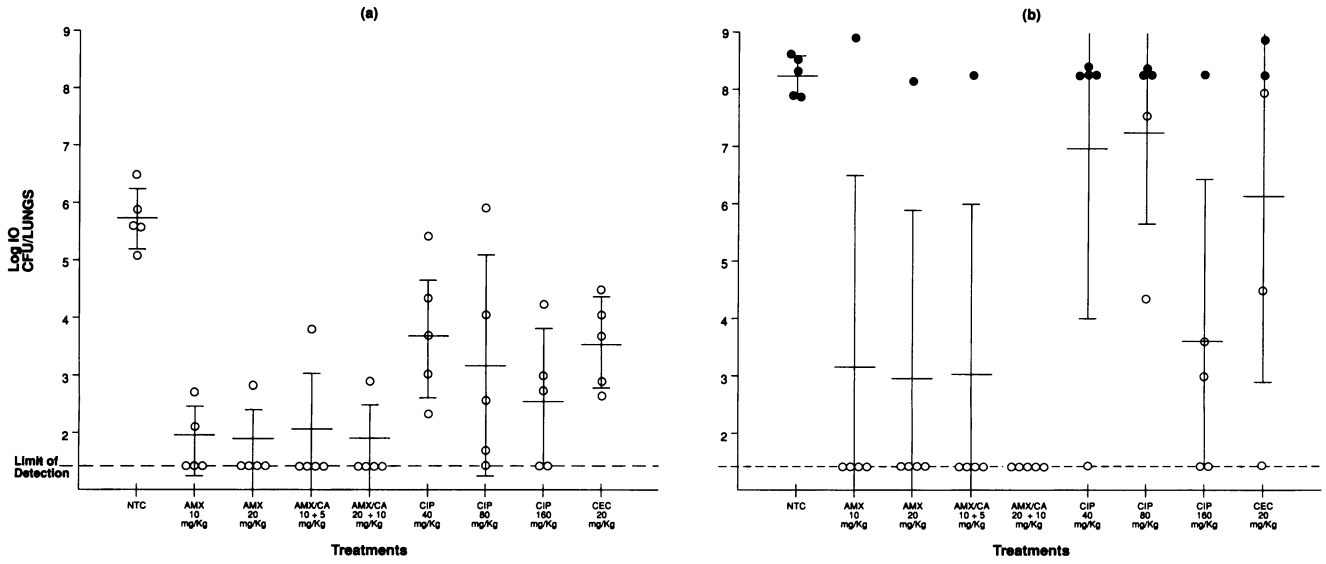

FIG. 1. Efficacies of amoxicillin (AMX), 10 and 20 mg/kg; amoxicillin-clavulanic acid (AMX/CA), 10/5 and 20/10 mg/kg; ciprofloxacin (CIP), 40, 80, and 160 mg/kg; and cefaclor (CEC), 20 mg/kg, in preventing the development of an *S. pneumoniae* 1629 pneumonia in mice. NTC, Nontreated controls. ○, Individual mouse lung pneumococcal counts at 33 h (a) and between 33 h and the end of the study (168 h) (b); ●, samples were obtained from the animals prior to 168 h or when the animal died (substituted value).

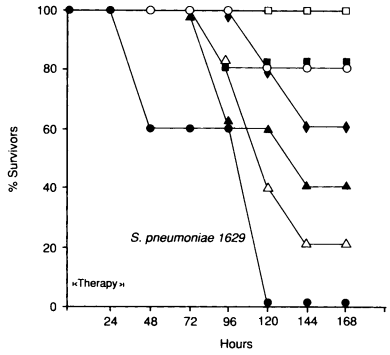

FIG. 2. Survival of mice infected with *S. pneumoniae* 1629. ●, Nontreated controls; ○, amoxicillin, 10 and 20 mg/kg; amoxicillin-clavulanic acid, 10/5 mg/kg; □, amoxicillin-clavulanic acid, 20/10 mg/kg; △, ciprofloxacin, 40 mg/kg; ▲, ciprofloxacin, 80 mg/kg; ■, ciprofloxacin, 160 mg/kg; ◆, cefaclor, 20 mg/kg.

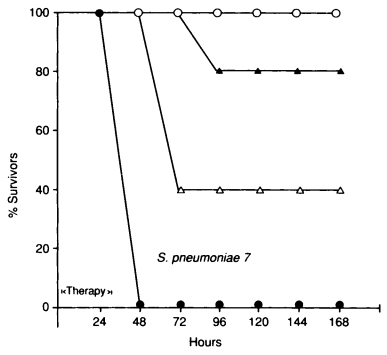

FIG. 4. Survival of mice infected with *S. pneumoniae* 7. ●, Nontreated controls; △, ciprofloxacin, 40 mg/kg; ▲, ciprofloxacin, 80 mg/kg; ○, amoxicillin, 10 and 20 mg/kg; amoxicillin-clavulanic acid, 10/5 and 20/10 mg/kg; ciprofloxacin, 160 mg/kg; cefaclor, 20 mg/kg.

2) and remained clear of the infecting organism. The mean numbers of *S. pneumoniae* 1629 recovered from these groups were significantly lower ($P < 0.05$) than those obtained from cefaclor-treated animals or those mice that received 40 or 80 mg of ciprofloxacin per kg (Fig. 1b).

Similarly, treatment with amoxicillin-clavulanic acid, 10/5 and 20/10 mg/kg, produced a significantly greater ($P < 0.05$) reduction in the lung pneumococcal count by 33 h (Fig. 1a) than did therapy with either ciprofloxacin or cefaclor. As with the groups treated with amoxicillin alone, the majority of animals that received amoxicillin-clavulanic acid had no detectable *S. pneumoniae* 1629 present in the lung tissue when sampled at the end of the study (Fig. 1b).

Susceptibility testing of the *S. pneumoniae* 1629 isolates recovered from the lungs during this study failed to show any alteration in susceptibility to any of the agents.

(ii) Study 2: *S. pneumoniae* 7. Counts of *S. pneumoniae* 7 in the lungs of individual mice obtained at 33 h and between 33 and 168 h postinfection are shown in Fig. 3a and b, respectively. Survival-versus-time curves are shown in Fig. 4. The mean number of pneumococci present in the lungs of nontreated control mice at 33 h after infection was similar to that measured at 1 h, which was 7.28 ± 0.42 $\log_{10}$ CFU per lung. As in mice with the *S. pneumoniae* 1629 infection, evidence of enlargement and consolidation of the lungs was seen at 33 h in mice infected with *S. pneumoniae* 7. The infection rapidly progressed to a fatal pneumonia, so that by 48 h after infection all control mice were either dead or moribund (Fig. 4).

A clear dose response was again seen in mice treated with ciprofloxacin. Oral therapy given at 40, 80, or 160 mg/kg reduced the bacterial counts in the lungs to 4.28 ± 0.95, 3.50 ± 0.42, and 2.00 ± 1.22 $\log_{10}$ CFU per lung, respectively, by 33 h (Fig. 3a). By 168 h, 60% of animals that had received 40 mg of ciprofloxacin per kg had died or were moribund (Fig. 4), although the remaining animals were clear of the infecting

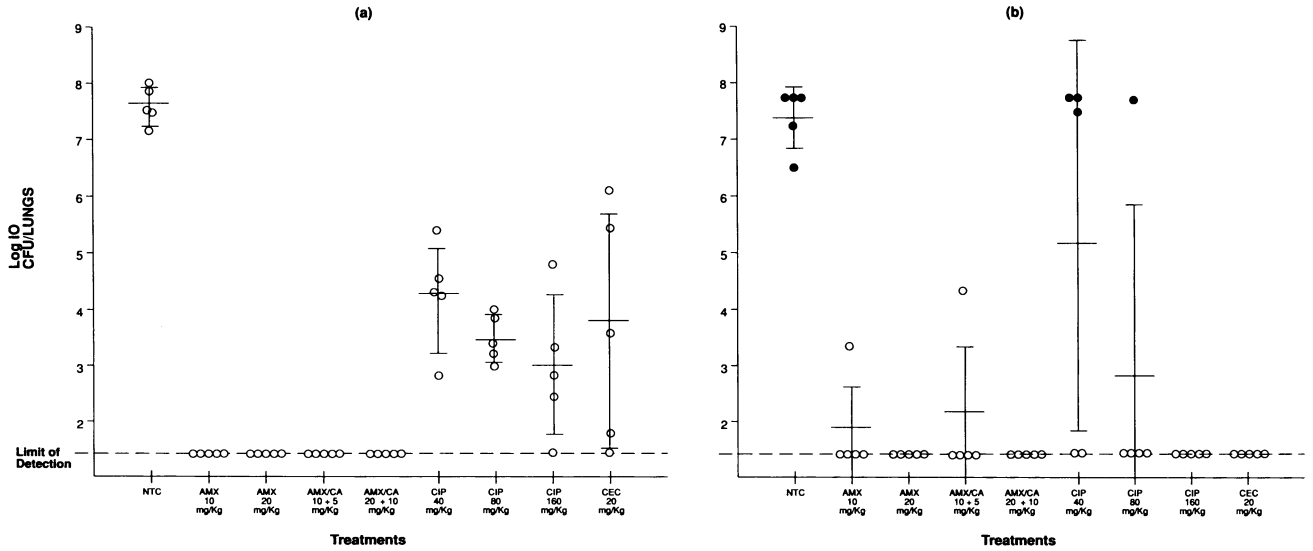

FIG. 3. Efficacies of amoxicillin (AMX), 10 and 20 mg/kg; amoxicillin-clavulanic acid (AMX/CA), 10/5 and 20/10 mg/kg; ciprofloxacin (CIP), 40, 80, and 160 mg/kg; and cefaclor (CEC), 20 mg/kg, in preventing the development of a *S. pneumoniae* 7 pneumonia in mice. NTC, Nontreated control. ○, Individual mouse lung pneumococcal counts at 33 h (a) and between 33 h and the end of the study (168 h) (b); ●, samples were obtained from the animals prior to 168 h or when the animals died (substituted value).

organism. In the groups dosed with either 80 or 160 mg of ciprofloxacin per kg, 80 to 100% of the mice that survived to 168 h yielded no pneumococci (Fig. 3b).

Treatment with cefaclor at 20 mg/kg reduced the *S. pneumoniae* 7 count to 3.26 ± 2.01 $\log_{10}$ CFU per lung by 33 h after infection (Fig. 3a), and pneumococci could not be detected in the lungs of cefaclor-treated animals at the end of the study (Fig. 3b).

Therapy with amoxicillin (10 or 20 mg/kg) alone or in combination with clavulanic acid (5 or 10 mg/kg) reduced the numbers of *S. pneumoniae* 7 to below the limit of detection (<33 CFU per lung) in all treatment groups by 33 h (Fig. 3a). As with therapy against *S. pneumoniae* 1629, the reduction in the *S. pneumoniae* 7 lung count was significantly greater ($P < 0.05$) than that achieved with the other antibiotics tested. All treated mice were alive at 168 h postinfection (Fig. 4). Of the animals that received amoxicillin (10 mg/kg) alone or in combination with clavulanic acid (5 mg/kg), 80% were clear of the infecting organism; the one remaining animal in each of these groups yielded counts of 3.30 and 4.36 $\log_{10}$ CFU per lung, respectively (Fig. 3b). *S. pneumoniae* 7 could not be isolated from the lungs of mice treated with amoxicillin (20 mg/kg) or amoxicillin-clavulanic acid (20/10 mg/kg) when samples were obtained at 168 h.

In subsequent in vitro testing, the isolates of *S. pneumoniae* 7 recovered from the lungs of mice sampled in this study showed no alteration in susceptibility to the agents used.

DISCUSSION

The experimental model used here produced an acute pneumonia in mice and represents a strict test for any antibiotic because of the rapid onset of a fatal infection. Both strains of *S. pneumoniae* used were highly virulent in mice, although persistence and subsequent regrowth of the mucoid *S. pneumoniae* 1629 strain after cessation of therapy was more evident than was the case with *S. pneumoniae* 7. The doses of the antibiotics administered to mice in the therapy studies produced peak concentrations in serum and lung tissue of the same order as those achieved in humans, except for the highest dose of ciprofloxacin, which was clearly in excess. Penetration of the agents into mouse lung tissue was also of the same order as that quoted for humans (11, 23).

These studies demonstrated that, although it reduced the pneumococcal count, therapy with ciprofloxacin failed to eliminate these strains of *S. pneumoniae*, even when high doses of the agent were used and good penetration into the lung tissue was achieved. Eventual removal of *S. pneumoniae* 7 occurred after cessation of treatment with the higher doses of ciprofloxacin, but failure to eradicate *S. pneumoniae* 1629 during therapy led to regrowth of the organism and death of animals when treatment ended. The emergence of resistant *S. pneumoniae* strains in cases of therapy failure was not demonstrated in these studies.

The in vitro activity of cefaclor against these strains of *S. pneumoniae* was similar to that of ciprofloxacin, and the response of infected mice to treatment with cefaclor was similar to that achieved with the quinolone. Cefaclor was chosen as a standard agent because it is widely used for the treatment of community-acquired pneumonia. Its poor efficacy in these studies was unexpected. However, this can probably be explained by the low lung tissue concentrations attained, which barely exceeded the MICs for the strains used.

In contrast, therapy with either amoxicillin or amoxicillin-clavulanic acid eliminated both strains of *S. pneumoniae* in the majority of treated mice by the end of the therapy period and thus prevented mortality. Although penetration of amoxicillin into lung tissue was not as efficient as that of ciprofloxacin, the concentrations achieved were in excess of the MICs for the two strains. The results of these studies concur with those of others (19), who demonstrated the superior activity of amoxicillin vis-à-vis the variable efficacy of the quinolones in experimental models of pneumonia. Although the presence of the β-lactamase inhibitor played no part in the efficacy of amoxicillin-clavulanic acid against the pneumococcal experimental infections reported here, studies in a rat model of pneumococcal pneumonia (24) have demonstrated the lack of efficacy of amoxicillin when β-lactamase-producing organisms were present, and the protection of amoxicillin by clavulanic acid resulted in the successful therapy of the mixed infection.

The results obtained from this experimental model of an acute *S. pneumoniae* respiratory infection underline the uncertainty about the effectiveness of ciprofloxacin in the treatment of respiratory infections in which *S. pneumoniae* may be present.

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REFERENCES

1. **Adam, D., I. De Visser, and P. Koeppe.** 1982. Pharmacokinetics of amoxicillin and clavulanic acid administered alone and in combination. Antimicrob. Agents Chemother. **22**:353–357.
2. **Bartlett, J. G.** 1989. Community-acquired bacterial infections. Curr. Opin. Infect. Dis. **2**:512–525.
3. **Beumer, H. M.** 1989. Cefixime versus amoxycillin/clavulanic acid in lower respiratory tract infections. Int. J. Clin. Pharmacol. Ther. Toxicol. **27**:30–33.
4. **Chrysanthopoulos, C. J., and H. P. Bassaris.** 1989. Use of oral ciprofloxacin in community-acquired pneumonia. J. Chemother. **1**:103–106.
5. **Cooper, B., and M. Lawlor.** 1989. Pneumococcal bacteremia during ciprofloxacin therapy for pneumococcal pneumonia. Am. J. Med. **87**:475.
6. **Davies, B. I., F. P. Maesen, and C. Baur.** 1986. Ciprofloxacin in the treatment of chronic bronchitis. Eur. J. Microbiol. **5**:226–231.
7. **Ernst, J. A., E. R. Sy, H. Colon-Lucca, N. Sandhu, T. Rallos, and V. Lorian.** 1986. Ciprofloxacin in the treatment of pneumonia. Antimicrob. Agents Chemother. **29**:1088–1089.
8. **File, T. M., and J. S. Tan.** 1986. Antimicrobial therapy of serious pneumonia: an update. Hosp. Formul. **21**:162–168.
9. **Gonzalez, M. A., F. Uribe, S. D. Moisen, A. P. Fuster, A. Selen, P. G. Welling, and B. Painter.** 1984. Multiple-dose pharmacokinetics and safety of ciprofloxacin in normal volunteers. Antimicrob. Agents Chemother. **26**:741–744.
10. **Harrison, D. B., B. M. Farr, S. Pugh, J. B. Selkon, and R. J. Prescott.** 1987. Community-acquired pneumonia in adults in British hospitals in 1982–1983: a survey of aetiology, mortality, prognostic factors and outcome. Q. J. Med. **239**:195–220.
11. **Honeybourne, D., J. M. Andrews, J. P. Ashby, R. Lodwick, and R. Wise.** 1988. Evaluation of the penetration of ciprofloxacin and amoxycillin into bronchial mucosa. Thorax **43**:715–719.
12. **Kemmerich, B., K. Borner, and J. E. Pennington.** 1987. Comparative efficacies of ciprofloxacin, ampicillin, and chloramphenicol in the treatment of experimental *Haemophilus influenzae* pneumonia. J. Antimicrob. Chemother. **20**:77–83.
13. **Kobayshi, H., K. Takamura, H. Takeda, and Multicentric Group.** 1986. Comparative clinical study of ciprofloxacin and cefaclor in the treatment of respiratory tract infections. Chemotherapy (Tokyo) **34**:1011–1034.
14. **Mazzulli, T., A. E. Simor, R. Jaeger, S. Fuller, and D. E. Low.** 1990. Comparative in vitro activities of several new fluoroqui-

nolones and β-lactam antimicrobial agents against community isolates of *Streptococcus pneumoniae*. Antimicrob. Agents Chemother. **34**:467–469.
15. **Mouton, Y., C. Beuscart, O. Leroy, B. Sivery, and Multicentric Group.** 1989. Program Abstr. 29th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 550.
16. **National Committee for Clinical Laboratory Standards.** 1990. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Approved standard M7-A2. National Committee for Clinical Laboratory Standards, Villanova, Pa.
17. **Pendersen, S. S.** 1989. Clinical efficacy of ciprofloxacin in lower respiratory tract infections. Scand. J. Infect. Dis. **60**(Suppl.): 89–97.
18. **Perlman, P. E., and D. R. Ginn.** 1990. Respiratory infections in ambulatory adults—choosing the best treatment. Postgrad. Med. **87**:175–184.
19. **Pocidalo, J. J., J. P. Bedos, and E. Azoulay-Dupuis.** 1989. Abstr. 4th Eur. Congr. Clin. Microbiol., abstr. 165/056.
20. **Raoof, S., C. Wollschlager, and F. Khan.** 1986. Treatment of respiratory tract infections with ciprofloxacin. J. Antimicrob. Chemother. **18**(Suppl. D):139–145.
21. **Roosendaal, R., I. A. J. M. Bakker-Woudenberg, M. van den Berghe-van Raffe, J. C. Vink-van den Berg, and M. F. Michel.** 1987. Comparative activities of ciprofloxacin and ceftazidime against *Klebsiella pneumoniae* in vitro and in experimental leukopenic rats. Antimicrob. Agents Chemother. **31**:1809–1815.
22. **Schiff, J. B., G. A. Small, and J. E. Pennington.** 1984. Comparative efficacies of ciprofloxacin, ticarcillin, and tobramycin against experimental *Pseudomonas aeruginosa* pneumonia. Antimicrob. Agents Chemother. **26**:1–4.
23. **Sides, G. D., T. R. Franson, K. A. DeSante, and H. R. Black.** 1988. A comprehensive review of the clinical pharmacology and pharmacokinetics of cefaclor. Clin. Ther. **11**(Suppl. A):5–15.
24. **Smith, G. M., R. J. Boon, and A. S. Beale.** 1990. Influence of clavulanic acid on the activity of amoxicillin against an experimental *Streptococcus pneumoniae-Staphylococcus aureus* mixed respiratory infection. Antimicrob. Agents Chemother. **34**:210–214.
25. **Thys, J.-P.** 1988. Quinolones in the treatment of bronchopulmonary infections. Rev. Infect. Dis. **10**(Suppl. 1):S212–S217.
26. **Vellend, H.** 1989. Role of fluoroquinolones in lower respiratory tract infections. Clin. Invest. Med. **12**:39–43.
27. **Wollschlager, C. M., S. Raoof, F. A. Khan, J. J. Guarneri, V. LaBomardi, and Q. Afzal.** 1987. Controlled, comparative study of ciprofloxacin versus ampicillin in the treatment of bacterial respiratory infections. Am. J. Med. **82**(Suppl. 4A):164–168.
28. **Woodhead, M. A., J. T. Macfarlane, J. S. McCracken, D. H. Rose, and R. G. Finch.** 1987. Prospective study of the aetiology and outcome of pneumonia in the community. Lancet **ii**:671–674.