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Therapeutic Activities of Cefazolin, Cefotaxime, and Ceftazidime Against Experimentally Induced *Klebsiella pneumoniae* Pneumonia in Rats

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The efficacies of several dosage schedules of cefazolin, cefotaxime, and ceftazidime, started 12 or 36 h after infection, were examined in experimental pneumonia caused by *Klebsiella pneumoniae* in rats. The therapeutic activities of the cephalosporins were compared with the antibacterial activities in vitro and the serum concentration curves. The course of experimental pneumonia was rapid and characterized by tissue necrosis. Response to antimicrobial treatment was evaluated with respect to mortality and numbers of bacteria in lung (left lobe), blood, and pleural fluid. When antibiotic treatment was started early, i.e., 12 h after bacterial inoculation, cefotaxime and ceftazidime were equally effective and superior to cefazolin. Eleven doses of 10 mg of cefotaxime or ceftazidime per kg or 11 doses of 60 mg of cefazolin per kg were required to improve the survival rate. With a delay in administration to 36 h after inoculation, the efficacy of the cephalosporins decreased markedly. In the three dosages tested, cefazolin was ineffective. Survival improved with the administration of nine doses of 60 mg of cefotaxime per kg or nine doses of 10 mg of ceftazidime per kg. These results are not in accordance with the ratio of in vitro activities of cefotaxime and ceftazidime or the serum concentration curves.

Cefotaxime and ceftazidime are new semisynthetic cephalosporins with marked in vitro activity (9, 21, 22). Evaluation of the therapeutic effectiveness of these agents against infections in experimental animals is important because such models allow for comparison of antibiotics under similar conditions of intensity and duration of infection. Both cefotaxime and ceftazidime displayed high levels of therapeutic activity in mice infected intraperitoneally with various strains of bacteria (1, 18). There have been few studies, however, of the therapeutic efficacy of cephalosporins in experimental respiratory infection with gram-negative organisms (12, 13). The present study was undertaken to evaluate the activities of cefazolin, cefotaxime, and ceftazidime against experimentally induced *Klebsiella pneumoniae* pneumonia in rats. This model was selected because pneumonia and septicemia caused by *K. pneumoniae* and other gram-negative bacilli appear to be increasing in incidence and are often difficult to treat in patients undergoing intensive anticancer chemotherapy (6–8, 11, 19, 20).

MATERIALS AND METHODS

Animals. Female R strain albino rats (specific pathogen free; 14 to 18 weeks old; weight, 185 to 215 g; bred at the Laboratory Animals Center of Erasmus University Rotterdam) were used in all experiments.

Bacteria. A *K. pneumoniae* strain (capsular serotype 2) was used in these experiments. This strain was maintained by intrabronchial passage in rats every 6 months and storage in small portions at −70°C in Todd-Hewitt broth (Oxoid Ltd.) with 10% glycerol (Merck). For experimental use, a portion was thawed and used to seed a fresh culture, which was incubated for 16 h at 37°C and then stored at 4°C for 2 h at most. This stationary-phase culture contained 10^9 viable organisms per ml (range, 0.8×10^9 to 1.2×10^9). Inocula were prepared from these 16-h cultures by appropriate dilution with physiological saline just before animal infection. The numbers of viable organisms inoculated in each experiment were determined by plate counts made just before inoculation.

Pneumonia. Experimental pneumonia was produced as previously described (2). In brief, rats were anesthetized with Hypnorm (Duphar) and pentobarbital (Abbott). The left main stem bronchus was intubated, and the left lobe of the lung was inoculated with 0.02 ml of a saline suspension of *K. pneumoniae* containing 8×10^4 (6×10^4 to 10×10^4) colony-forming units (CFU). The severity of the resulting infection was monitored by daily measurements of body weight and rectal temperature. Animals were sacrificed on days 1, 2, 3, 4, and 5 after inoculation for untreated controls and on days 6 and 19 for treated subjects. Treated rats were always sacrificed 12 or more h after the last dose of antibiotic. Samples of blood and pleural fluid were

TABLE 1. Course of *K. pneumoniae* pneumonia in rats[a]

Day after inoculation	Body wt (% loss)	Body temp (°C)[b]	Wt of left lung (g)[c]	Log CFU in left lung	Blood		Pleural fluid (no. of rats positive/no. tested)
					No. of rats positive/ no. tested	log CFU/ml[d]	
1	4.0 (0–6.6)	37.4 (37.1–37.8)	0.5 (0.4–0.5)	6.6 (5.5–7.0)	0/5		0/5
2	4.1 (2–5.6)	38.7 (38.1–38.9)	0.6 (0.5–0.8)	8.8 (8.0–9.5)	2/5	2.8 (1.3–3.1)	2/5
3	8.3 (6.7–10.1)	38.7 (37.8–39.1)	1.2 (0.5–1.5)	10.0 (7.0–10.3)	5/5	4.3 (1.7–5.9)	4/5
4	15.0 (12.3–16.1)	38.5 (36.7–39.0)	2.4 (1.8–4.0)	10.5 (9.9–10.8)	5/5	4.8 (3.1–6.0)	5/5
5	16.6 (15.2–18.0)	36.5 (33.5–38.6)	2.9 (1.9–4.2)	10.3 (10.0–10.9)	5/5	4.2 (3.0–6.6)	5/5

[a] Five groups of five rats each were studied after inoculation of the left lobe of the lung with 8×10^4 CFU. For rats sacrificed on day 5, body weight and body temperature were measured daily. Values given are median values, with ranges in parentheses.

[b] Normal, 37.4 ± 0.34°C.

[c] Normal, 0.6 ± 0.15 g.

[d] Calculated for positive cultures only.

obtained for culture. Pleural exudate was obtained by washing the chest cavity with physiological saline (0.5 ml). After macroscopic examination, the left lung was removed, weighed, and homogenized in 20 ml of physiological saline (VirTis homogenizer; 30 s at 10,000 rpm). Serial 10-fold dilutions of homogenates in saline were prepared, and 0.2-ml volumes of each dilution were spread on blood agar plates. The numbers of viable organisms in blood, pleural exudate, and the residual homogenate of the left lung were measured by the pour-plate method.

Histology. The histological features of the pneumonic lesion were studied in five groups of two rats each on days 1, 2, 3, 4, and 5 after inoculation. Lungs were fixed by injecting the trachea with 10% Formalin under constant pressure to reexpand the lungs. Segments of the left lung were then dehydrated in ethanol and toluol, embedded in paraffin, sectioned, and stained with hematoxylin-eosin or by the Gram stain technique.

Antimicrobial susceptibility tests. Cefazolin (Eli Lilly, S.A., St. Cloud, France), cefotaxime and desacetyl cefotaxime (Roussel, Uclaf, France), and ceftazidime (Glaxo Laboratories, Greenford, Middlesex, England) were used in the experiments. The minimum inhibitory concentrations (MICs) of the respective drugs, defined as the lowest concentrations that suppressed visible growth after incubation of an inoculum of 10^5 CFU for 18 h at 37°C in tubes containing 4 ml of Todd-Hewitt broth (Oxoid) (3), were 2.8, 0.05, 0.15, and 0.3 μg/ml. The minimum bactericidal concentrations (MBCs), defined as the lowest concentrations that reduced the numbers of organisms in the 18-h cultures to fewer than 50 CFU/ml (3), were 2.8, 0.10, 0.15, and 0.3 μg/ml.

Antimicrobial treatment. Doses of 10, 30, and 60 mg of cefazolin, cefotaxime, or ceftazidime per kg of body weight were administered intramuscularly into the thigh muscles of the rear legs, either every 12 h or every 8 h, for totals of 9, 11, or 12 doses. Treatment was started either 12 or 36 h after bacterial inoculation.

Therapeutic results. Response to antimicrobial treatment was evaluated with respect to mortality and numbers of bacteria in lung (left lobe), blood, and pleural fluid at time of sacrifice of surviving rats. Deaths of rats were recorded daily for 19 days.

Statistics. The Wilcoxon rank-sum test was used to estimate whether results of quantitative cultures of the left lobe of the lung differed significantly from those in control groups. The Fisher test was used to determine whether mortalities observed in the treatment groups differed from each other.

Measurements of antibiotic concentrations in serum. Blood specimens, obtained by orbital puncture under light ether anesthesia, were collected from each rat at four times after antibiotic injection, and serum was separated. Cefazolin and ceftazidime were assayed in 0.2-ml samples by the standard large-plate agar diffusion procedure with Oxoid diagnostic sensitivity test agar (4). *Staphylococcus aureus* (ATCC 9144), susceptible to 1 μg drug per ml, was used for cefazolin assays. *Escherichia coli* (ATCC 51A266), susceptible to 0.25 μg of this drug per ml, was used for ceftazidime assays. Cefotaxime and desacetyl cefotaxime in serum were measured via a modified high-pressure liquid chromatographic (HPLC) method (5). Separation was carried out by reverse-phase partitioning on a column of 4.6-mm internal diameter and 15-cm length packed with Lichrosorb RP-8 (Merck) of 5-μm particle size. The eluent was a 1:1 mixture of 0.02 M sodium acetate and 15% methanol. Column elution was carried out with a flow of 1.4 ml/min at a pressure of 230 atm (23,306 kPa). A Spectra Physics 3500 B HPLC with an SP 770 variable UV detector was used. The eluent was monitored at 256 nm. Standards of known cefotaxime or desacetyl cefotaxime content were made up in pooled rat serum to give concentrations ranging from 0.2 to 174 μg/ml. Volumes of 100 μl of serum were mixed with 400 μl of methanol and centrifuged for 5 min at 4,000 × *g*; 300 μl of the supernatant was evaporated to dryness. The residue was dissolved in 400 μl of water, and 100 μl was applied directly to the column.

RESULTS

Course of untreated infection. The course of untreated infection was studied in five groups of five rats, sacrificed on days 1, 2, 3, 4, and 5 after inoculation (Table 1). For rats sacrificed on day 5, body weights and rectal temperatures were measured daily. After inoculation, infection de-

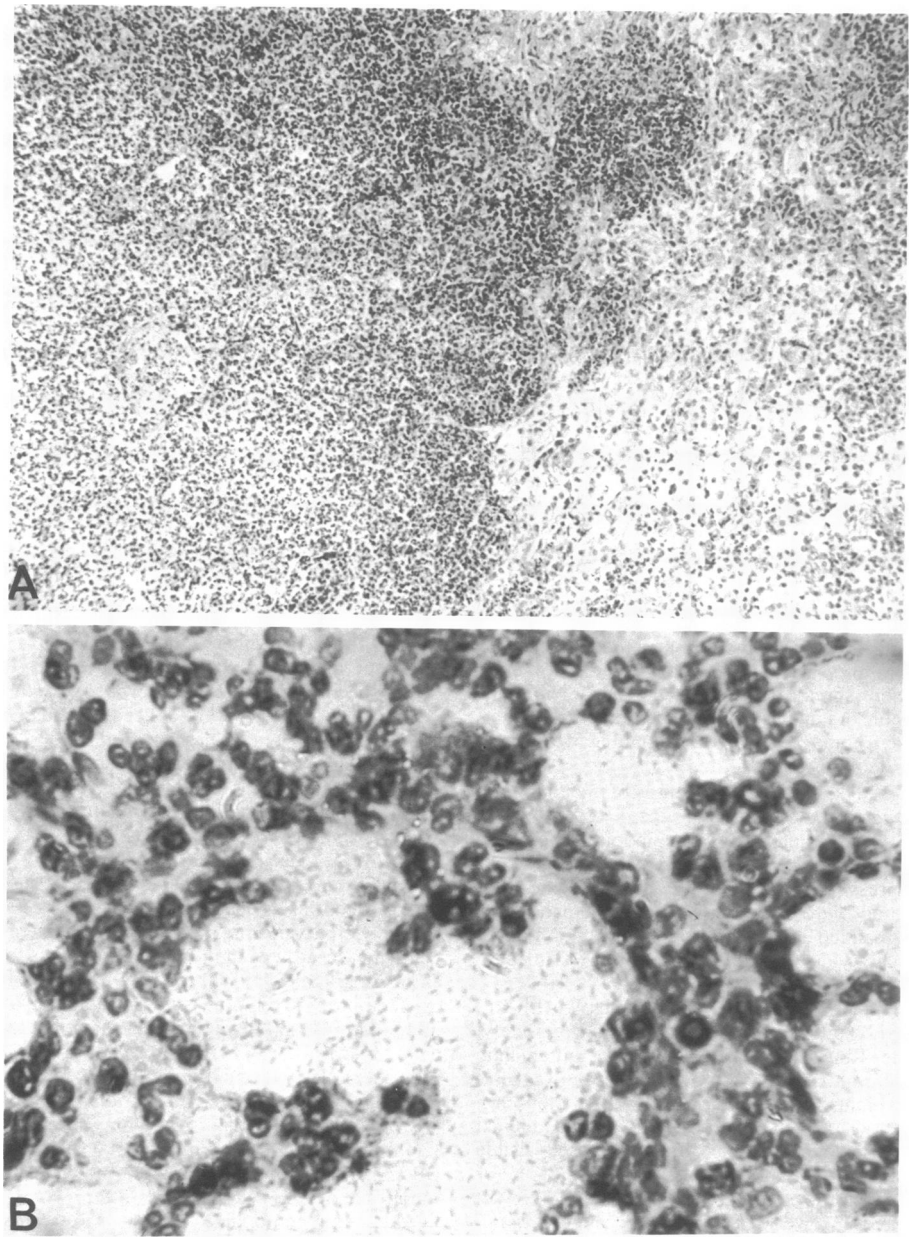

FIG. 1. Sections of the left lobes of lungs from rats inoculated with *K. pneumoniae*. (A) Section stained with hematoxylin-eosin (×40). (B) Section stained with Gram stain (×400).

veloped within 24 h. Initially, the pneumonia was confined to the left lobe of the lung. By 96 to 120 h, the pulmonary lesion involved the entire left lobe, and the infection was spreading to the right lobes. Within 5 to 6 days, animals died spontaneously from infection. During the course of the infection, total body weight decreased constantly, and rectal temperature usually fell below normal values after an initial rise. On days 4 and 5, some rats had increased temperatures, whereas others had subnormal temperatures. Involvement of the lung tissue in the infectious process was reflected by a proportional increase in weight (up to sixfold) of the left lobe of the lung. On day 5, an average number of 2×10^{10} CFU was cultured from the left lobe of the lung; all rats had bacteria in the blood and pleural fluid. A control experiment revealed that the technique of intubation itself did not influence total body weights or rectal temperatures.

TABLE 2. Efficacy of various dose regimens started 12 h after inoculation and repeated every 12 h for 11 doses

Dosage regimen (mg/kg every 12 h)	6 days after infection						19 days after infection					
	Survival rate (no. surviving/total)	Bacterial recovery					Survival rate (no. surviving/total)	Time to death (days) (mean ± SD)	Bacterial recovery			
		Lung		Blood		Pleural fluid			Lung		Blood		Pleural fluid
		No. positive/total	log CFU/left lung[a]	No. positive/total	log CFU/ml of blood[a]	No. positive/total			No. positive/total	log CFU/left lung[a]	No. positive/total	log CFU/ml of blood[a]	No. positive/total
Cefazolin													
10	8/10	10/10	10.0 (3.3–10.5)	8/10	3.8 (1.3–7.6)	7/10	3/10	7.6 ± 2.5	8/10	1.2	7/10		7/10
30	10/10	10/10	3.6 (1.8–11.6)	1/10	3.1	1/10	3/10	7.9 ± 2.8	8/10	0.6	7/10		7/10
60	10/10	10/10	2.4 (1.4–7.4)	0/10		0/10	10/10		4/10	1.2 (0.5–1.4)	0/10		0/10
Cefotaxime													
10	10/10	9/10	2.2 (1.2–6.5)	0/10		0/10	10/10		2/10	0.5 (0.3–0.6)	0/10		0/10
30	10/10	9/10	2.3 (0.8–4.1)	0/10		0/10	10/10		5/10	1.0 (0.7–1.0)	0/10		0/10
60	10/10	10/10	2.1 (0.5–3.1)	0/10		0/10	10/10		3/10	0.3 (0.3–1.4)	0/10		0/10
Ceftazidime													
10	10/10	9/10	2.2 (1.3–2.7)	0/10		0/10	10/10		0/10		0/10		0/10
30	10/10	9/10	2.1 (0.6–3.2)	0/10		0/10	10/10		2/10	1.1 (0.3–1.9)	0/10		0/10
60	10/10	9/10	2.1 (0.3–2.8)	0/10		0/10	10/10		3/10	0.6	0/10		0/10

[a] Calculated for positive cultures of surviving rats only. Values given are median values, with ranges in parentheses.

TABLE 3. Efficacy of various dosage regimens started 36 h after inoculation and repeated every 12 h for nine doses

Dosage regimen (mg/kg every 12 h)	6 days after infection						19 days after infection					
	Survival rate (no. surviving/total)	Bacterial recovery					Survival rate (no. surviving/total)	Time to death (days) (mean ± SD)	Bacterial recovery			
		Lung		Blood		Pleural fluid			Lung		Blood		Pleural fluid
		No. positive/total	log CFU/left lung[a]	No. positive/total	log CFU/ml of blood[a]	No. positive/total			No. positive/total	log CFU/left lung[a]	No. positive/total	log CFU/ml of blood[a]	No. positive/total
Cefazolin													
10	4/10	10/10	9.5 (3.4–10.3)	9/10	6.6 (2.3–6.6)	9/10	1/10	4.8 ± 0.9	9/10	0	9/10		9/10
30	8/10	10/10	9.5 (3.1–10.3)	6/10	3.1 (1.5–3.2)	8/10	4/10	7.8 ± 2.6	8/10	5.0 (1.0–9.0)	6/10		6/10
60	9/10	10/10	7.4 (3.5–9.9)	2/10	6.5	3/10	4/10	10.3 ± 1.5	8/10	6.9 (5.8–7.9)	7/10	2.0	6/10
Cefotaxime													
10	8/10	10/10	8.7 (3.3–9.6)	5/10	3.8 (2.7–4.5)	6/10	2/10	7.4 ± 2.2	9/10	0.7	8/10		8/10
30	10/10	10/10	6.8 (2.3–8.9)	1/10	1.6	2/10	4/10	7.7 ± 2.6	9/10	1.5 (0.8–2.6)	6/10		6/10
60	10/10	10/10	5.6 (1.6–7.9)	0/10		0/10	10/10		5/10	1.1 (0.3–1.5)	0/10		0/10
Ceftazidime													
10	10/10	10/10	6.4 (2.0–9.6)	1/10	3.5	3/10	6/10	12.8 ± 5.1	9/10	1.3 (1.0–9.2)	4/10		4/10
30	10/10	10/10	4.8 (2.6–7.7)	0/10		2/10	10/10		4/10	5.2 (0.7–9.1)	0/10		0/10
60	10/10	10/10	4.3 (2.0–7.5)	1/10	1.5	0/10	10/10		4/10	1.1 (0.7–5.6)	0/10		1/10

[a] Calculated for positive cultures of surviving rats only. Values given are median values, with ranges in parentheses.

The histological features of the pneumonic lesion were studied in five groups of two rats each on days 1, 2, 3, 4, and 5 after inoculation. Few organisms were visible in the alveoli 12 to 14 h after bacterial inoculation; hemorrhagic edema fluid and a light polymorphonuclear infiltrate were present. From day 2 after inoculation, the outer edema zone of the lesion was characterized by a cellular infiltrate composed almost exclusively of polymorphonuclear leukocytes and a few macrophages; more to the center of the lesion, edema-filled alveoli were packed with leukocytes; small lung abscesses demonstrating numerous polymorphonuclear leukocytes and large numbers of gram-negative bacilli were common (Fig. 1).

Response to therapy. The drugs were administered in various dosage schedules, with treatment starting either 12 or 36 h after bacterial inoculation. Each treatment schedule was evaluated in two groups of 10 rats each for effects on mortality and numbers of bacteria in lung (left lobe), blood, and pleural fluid of surviving rats on day 6, 12 h after the last dose, and on day 19. Table 2 shows that mortality of rats treated with 10 mg of cefazolin, cefotaxime, or ceftazidime per kg every 12 h for 11 doses starting at 12 h was less than that of controls at the end of treatment ($P < 0.01$). However, mortality in recipients of cefazolin increased after the end of treatment. Survival of rats on day 19 was significantly increased after doses of 10 mg of cefotaxime or ceftazidime per kg or 60 mg of cefazolin per kg ($P < 0.01$). Although bacteria were not completely eliminated from the lungs of rats treated with cefotaxime or ceftazidime, the numbers of bacteria were low. A dosage of 30 mg of cefazolin per kg or 10 mg of cefotaxime or ceftazidime per kg effected sterilization of blood and pleural fluid of almost all animals. Table 3 shows that mortality of rats treated with 30 mg of cefazolin per kg or 10 mg of cefotaxime or ceftazidime per kg every 12 h for nine doses starting at 36 h was less than that of controls at the end of treatment ($P < 0.01$). However, mortality of rats increased in most cases with termination of treatment. Survival of rats on day 19 was significantly increased after 60 mg of cefotaxime per kg or 10 mg of ceftazidime per kg ($P \leq 0.01$). None of the treatment schedules effected sterilization of the left lobe of the lung by day 6. Doses of 60 mg of cefazolin per kg, 30 mg of cefotaxime per kg, or 10 mg of ceftazidime per kg effected sterilization of blood and pleural fluid in 70% of the animals or more. Table 4 shows that mortality of rats treated with 30 mg of cefazolin, cefotaxime, or ceftazidime per kg every 8 h for 12 doses starting at 36 h was less than that of controls at the end of treatment ($P <$ 0.01). Survival of rats on day 19 was significant-

TABLE 4. Efficacy of various dosage regimens started 36 h after inoculation and repeated every 8 h for 12 doses

Dosage regimen (mg/kg every 8 h)	6 days after infection						19 days after infection							
	Survival rate (no. surviving/ total)	Bacterial recovery					Time to death (days) (mean ± SD)	Survival rate (no. surviving/ total)	Bacterial recovery					
		Lung		Blood		Pleural fluid			Lung		Blood		Pleural fluid	
		No. positive/ total	log CFU/left lung[a]	No. positive/ total	log CFU/ml of blood[a]	No. positive/ total			No. positive/ total	log CFU/left lung[a]	No. positive/ total	log CFU/ml of blood[a]	No. positive/ total	
Cefazolin (30)	8/10	10/10	8.0 (3.5–10.6)	5/10	3.6 (1.5–5.4)	5/10	8.4 ± 3.9	4/10	9/10	4.9 (1.0–8.5)	6/10		6/10	
Cefotaxime (30)	10/10	10/10	5.5 (2.3–6.4)	0/10		0/10		10/10	4/10	1.3 (0.9–8.4)	0/10		0/10	
Ceftazidime (30)	10/10	10/10	4.7 (0.9–6.8)	1/10	2.3	0/10		10/10	4/10	2.4 (1.1–9.7)	0/10		0/10	

[a] Calculated for positive cultures of surviving rats only. Values given are median values, with ranges in parentheses.

TABLE 5. Concentrations of cefazolin, cefotaxime, desacetyl cefotaxime, and ceftazidime in serum at various intervals after intramuscular administration of various doses[a]

Compound	Dose (mg/kg)	Drug concentration (μg/ml of serum ± SD) at the following times (min) after dosage:						
		5	15	30	60	90	120	180
Cefazolin	10	28.5 ± 5.5	62.4 ± 12.0	53.0 ± 6.5	26.2 ± 9.3	11.0 ± 1.8	5.8 ± 2.0	<1.0
	30	119.3 ± 19.3	140.4 ± 12.9	119.9 ± 3.4	59.2 ± 2.9	22.6 ± 4.2	10.4 ± 1.0	2.5 ± 0.4
	60	179.4 ± 33.4	205.3 ± 18.2	187.9 ± 9.5	115.4 ± 14.0	43.3 ± 12.8	19.0 ± 3.5	4.5 ± 0.4
Cefotaxime (parent compound)	10	17.5 ± 6.9	30.5 ± 5.1	20.0 ± 4.3	4.5 ± 0.4	1.6 ± 0.4	0.42 ± 0.16	
	30	32.0 ± 6.1	35.5 ± 16.1	30.9 ± 10.0	14.2 ± 6.3		1.8 ± 0.2	0.58 ± 0.13
	60	53.1 ± 20.2	51.1 ± 8.4	30.6 ± 10.9	22.6 ± 7.0		2.4 ± 0.2	0.38 ± 0.19
Desacetyl cefotaxime	10	6.2 ± 3.2	13.0 ± 1.6	11.8 ± 1.3	4.6 ± 0.5	1.5 ± 0.9	0.46 ± 0.30	
	30	26.1 ± 4.1	55.0 ± 3.8	47.5 ± 12.3	20.4 ± 8.1		2.7 ± 0.5	0.38 ± 0.11
	60	58.7 ± 12.4	115.0 ± 6.3	100.8 ± 20.8	42.6 ± 6.8		5.5 ± 1.7	0.66 ± 0.26
Ceftazidime	10	18.1 ± 7.1	27.4 ± 5.2	19.3 ± 2.1	8.6 ± 2.4	2.0 ± 0.4	0.74 ± 0.22	<0.25
	30	58.6 ± 2.4	80.6 ± 12.5	70.6 ± 11.0	22.1 ± 4.1	10.7 ± 1.2	3.7 ± 0.8	0.41 ± 0.10
	60	80.6 ± 16.3	132.8 ± 23.9	128.6 ± 28.8	46.3 ± 5.0	23.6 ± 5.6	6.8 ± 0.9	0.44 ± 0.08

[a] Each value represents the mean of five rats ± standard deviation.

ly increased after doses of 30 mg of cefotaxime or ceftazidime per kg ($P < 0.01$). None of the treatment schedules effected sterilization of the left lobe of the lung by day 6. Doses of 30 mg of cefotaxime or ceftazidime per kg effected sterilization of blood and pleural fluid of almost all rats on day 6. Multiple colonies of *K. pneumoniae* isolates recovered from infected sites of rats treated with cefazolin, cefotaxime, or ceftazidime in the treatment schedules mentioned in Tables 2 to 4 were sampled; the MBC values of the isolates for these antibiotics were not different from the MBC values of the parent strain.

Concentrations of cefazolin, cefotaxime, and ceftazidime in serum. The concentrations of cefazolin, cefotaxime, and ceftazidime in sera of rats after intramuscular administration of doses of 10, 30, and 60 mg/kg are shown in Table 5. Cefazolin concentrations in excess of 2.8 μg/ml, the MBC for the *Klebsiella* strain used in this study, were present for about 2.5, 3, and 3.5 h at the respective doses. Cefotaxime undergoes desacetylation in vivo. Cefotaxime concentrations in excess of 0.10 μg/ml and desacetyl cefotaxime concentrations in excess of 0.15 μg/ml, the respective MBCs of these agents for the *Klebsiella* strain, were present for about 2.5, 3.5, and 4 h at the respective doses. Ceftazidime concentrations in excess of 0.3 μg/ml, the MBC for the *Klebsiella* strain, were present for about 2.5, 3, and 3.5 h at the respective doses.

DISCUSSION

The activities of cefazolin, cefotaxime, and ceftazidime against experimentally induced *K. pneumoniae* pneumonia in rats were evaluated. The pathological features of the experimental pneumonia were the same as those described by Sale and co-workers (15, 16). The course of infection was rapid and characterized by tissue necrosis. Bacteremia and pleurisy occurred as a complication of the fatal infection. These characteristics closely simulate those observed in fatal cases of *Klebsiella* pneumonia in humans. Tissue necrosis and abscess formation in the lung as seen at autopsy constitute a very severe complication of lobar pneumonia due to *Klebsiella* (14, 17). The infection is often difficult to control, especially in immunocompromised patients.

The inability of the antibiotic treatment schedules to sterilize the left lobe of the lung within the 5-day treatment period probably resulted from the existence of small lung abscesses in the consolidated lobes of infected rats. With treatment at 12-h intervals, started 36 h after infection, large numbers of *Klebsiella* were still recovered from the left lobes on day 6. The variation in numbers of bacteria in the left lobes of individual rats probably reflects the variation

in extent of necrosis in the lung 36 h after bacterial inoculation. In contrast, when started at 12 h, doses of 10 mg of cefotaxime or ceftazidime per kg or 60 mg of cefazolin per kg given at 12-h intervals markedly reduced the numbers of bacteria recovered from the lungs of all animals.

The tendency of *K. pneumoniae* to give rise to abscess formation constitutes a characteristic that differentiates it from *Streptococcus pneumoniae*. In experimentally induced pneumococcal pneumonia, no abscesses were found, and pneumococci were completely eradicated with administration of penicillin in a sufficient amount at an adequate time (2).

Due to the persistence of large numbers of bacteria in lungs at the end of treatment starting at 36 h, mortality of rats increased again. For that reason, treatment schedules were evaluated for effects on mortality on day 19 (13 days after termination of therapy). Significant differences were noted among the therapeutic effectiveness of the cephalosporins. The results obtained generally indicate that cefotaxime and ceftazidime were superior to cefazolin. When antibiotic treatment was started early, i.e., 12 h after bacterial inoculation, cefotaxime and ceftazidime in small doses were equally effective and superior to cefazolin, the latter being effective only in large doses. When the institution of treatment was delayed until 36 h after inoculation, again cefotaxime and ceftazidime were more effective than cefazolin, but in addition, ceftazidime was superior to cefotaxime. These results do not reflect the greater in vitro activity of cefotaxime against the *Klebsiella* strain used.

Acred and co-workers compared ceftazidime with cefotaxime in infections in mice and rats (1; P. Acred, D. M. Ryan, and A. E. Collard, 12th Int. Congr. Chemother., Florence, Italy, abstr. no. 863, 1981). Whereas cefotaxime was more active than ceftazidime against the *Klebsiella* strains in vitro, both agents were equally effective against experimentally induced intraperitoneal *Klebsiella* infections in mice (1). In experimentally induced *K. pneumoniae* urinary tract infections in rats, the activity of cefotaxime proved to be superior to that of ceftazidime (Acred et al., 12th Int. Congr. Chemother.).

The mean serum concentration curves of cefazolin were above those of cefotaxime or ceftazidime after administration of similar doses. The cephalosporins were equal as to the time during which their serum concentrations exceeded the MIC for the *Klebsiella* strain. However, they differed with regard to the ratio between serum level and MIC, which was largest with cefotaxime and smallest with cefazolin. It has been reported that cefotaxime is desacetylated in vivo (10, 23). In this experimental model, desacetyl cefotaxime was also formed in considerable amounts. In view of the antibacterial activity of desacetyl cefotaxime, the metabolite contributed substantially to the activity of cefotaxime administered. In view of the discrepancies between the in vitro antibacterial activities and the therapeutic efficacies of cefotaxime and ceftazidime, efforts are being made to measure the tissue penetration of these antibiotics.

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