COMPARATIVE CHEMOTHERAPEUTIC ACTIVITY OF CEFPIROME AND IMIPENEM IN EXPERIMENTAL INFECTIONS

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In systemic and local infections, the therapeutic efficacy of cefpirome was compared to that of imipenem and cefotaxime.

Murine septicemia induced with methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* strains responded well to cefpirome and imipenem therapy, the ED_{50} values ranged from 0.8 to 28.40 mg/kg and 0.5 to 15.58 mg/kg, respectively. The carbapenem also displayed high efficacy against Enterococci and was more potent than cefpirome. Cefotaxime, however, exhibited lower activity or proved to be inactive against these strains.

With ED_{50} values of 0.03 to 31.33 mg/kg, cefpirome was the most active of the three antibiotics in protecting mice challenged with Enterobacteriaceae. The corresponding ED_{50} values of imipenem and cefotaxime ranged from 0.72 to 70.95 mg/kg and 0.06 to 66.30 mg/kg, respectively.

Despite distinctly lower *in vitro* activity against the infecting organism, cefpirome showed efficacy similar to imipenem in the treatment of subcutaneous *S. aureus* abscesses in mice. It was more effective than imipenem and cefotaxime against experimental *Klebsiella* pneumonia in mice and the *Escherichia coli* infected granuloma pouch in rats.

Bacterial infections often remain life threatening situations despite the continued development of new antimicrobial agents. The increasing frequency of infections caused by Staphylococci resistant to methicillin or multiresistant Enterobacteriaceae and *Pseudomonas aeruginosa* strains fortified the search for compounds showing extraordinary efficacy, especially against these pathogens. The polar aminothiazolyl-cephalosporin cefpirome and the carbapenem antibiotic imipenem both possess such properties[1~7]. The purpose of this study is to compare the therapeutic activity of both agents in the treatment of experimentally induced infections in rodents. The reference compound used was the cephalosporin derivative cefotaxime.

Materials and Methods

Antibiotics

Cefpirome and cefotaxime were obtained from Hoechst AG, Frankfurt, FRG. Imipenem (MSD, Munich, FRG) is commercially available.

Susceptibility Testing

The *in vitro* sensitivity of the bacteria was determined by the agar dilution method with Mueller-Hinton agar as test medium. In the case of Streptococci, the agar was supplemented with 10% horse blood. Agar plates containing serial dilutions of the antibiotics were inoculated with a Denley Multipoint inoculator which delivered 5×10^5 cfu of a stationary culture of the strain concerned. The MICs were defined as the lowest concentrations of the antibiotics that suppressed visible growth after 24 hours incubation at 37°C. In the case of methicillin-resistant Staphylococci incubation was 48 hours at 30°C[2,3].

Table 1. Comparative activity of cefpirome, imipenem and cefotaxime against experimentally induced septicemia in mice.

Infecting organism	Challenge dose (cfu/mouse)	MIC (μg/ml) and median effective dose (ED_{50}, mg/kg)					
		Cefpirome		Imipenem		Cefotaxime	
		MIC	ED_{50}	MIC	ED_{50}	MIC	ED_{50}
Staphylococcus aureus Giorgio	1.0×10^6	0.20	0.81	<0.002	0.05	1.56	6.38
S. aureus SG 511	1.0×10^8	0.31	1.64	<0.002	0.09	1.56	13.53
S. aureus 31153 meth^R	8.8×10^7	1.00	17.80	0.008	4.59	4.00	70.60
S. aureus E705 meth^R	6.3×10^7	4.00	28.40	2.00	15.58	>32.00	>100.00
S. aureus E710 meth^R	9.3×10^7	2.00	13.10	0.062	1.25	8.00	189.37
Streptococcus pyogenes A77	3.9×10^3	<0.002	0.07	<0.002	0.01	<0.002	0.15
S. pneumoniae	1.5×10^4	<0.002	0.21	<0.002	0.07	<0.002	0.34
Enterococcus faecium FO3	1.6×10^7	16.00	27.50	0.78	2.98	>128.00	>100.00
E. faecalis FO19	9.6×10^7	16.00	71.40	0.25	3.46	>128.00	>100.00
E. faecalis 35	9.0×10^7	16.00	71.30	0.50	2.97	>128.00	>100.00
E. faecalis Kn62	5.6×10^6	16.00	32.20	0.50	0.58	>128.00	>100.00
Escherichia coli 078	1.1×10^4	<0.002	0.03	0.05	1.47	<0.002	0.07
E. coli 04	2.7×10^7	0.03	10.07	0.06	2.15	0.04	66.30
Klebsiella pneumoniae DT-S	3.1×10^3	0.008	0.98	0.39	16.46	0.004	4.01
K. pneumoniae 1976E	1.5×10^6	0.63	0.32	0.13	2.41	0.25	0.31
Salmonella typhimurium MZ II	2.5×10^3	0.02	0.07	0.25	0.72	0.02	0.06
Enterobacter cloacae M 417	5.5×10^6	0.01	0.14	0.78	7.99	0.39	3.15
Serratia marcescens M 378	2.1×10^7	0.01	0.14	0.78	3.13	0.39	2.40
Proteus mirabilis ATCC 14273	7.0×10^7	0.01	0.67	1.56	13.38	<0.002	1.02
Morganella morganii 939	2.6×10^7	0.13	1.50	0.50	4.29	0.13	3.72
Pseudomonas aeruginosa 1	4.0×10^6	0.78	9.87	1.00	7.18	1.00	>100.00
P. aeruginosa 1771	3.2×10^7	12.50	309.00	0.50	1.01	62.50	>100.00
P. aeruginosa 1771m	6.0×10^6	0.63	0.40	0.13	0.42	0.04	2.29
P. aeruginosa NCTC 10701	1.2×10^8	0.63	21.80	0.25	4.42	2.50	153.60
Pasteurella multocida 6525	2.3×10^5	0.06	0.85	0.02	0.80	0.02	0.83

meth^R: Methicillin-resistant strain.

Microorganisms

25 Gram-positive and Gram-negative pathogens were used as test organisms (Table 1). Among them the methicillin-resistant Staphylococci (MRSA) 31153, E710 and E705, the Enterococci Kn62, 35, FO3 and FO19, *Enterobacter cloacae* M 417, *Serratia marcescens* M 378 and *Pseudomonas aeruginosa* 1 were clinical isolates. All the other pathogens used were laboratory strains.

Protection Tests

In the protection tests, NMRI mice weighing 18~22 g were infected intraperitoneally with 0.3 ml of bacterial suspension in 5% hog gastric mucin[8]. Depending on the infecting organism, the challenge inoculum contained 2 to 500 times the LD_{100} of the pathogens. A group of eight untreated mice was always used as control. The controls died between 6 and 48 hours after infection, depending on the bacterial strain used.

Eight mice were used for each of the doses of the β-lactam antibiotics tested. The compounds were administered subcutaneously, immediately and 4 hours after infection. In the *Pseudomonas* infections, mice were treated four times, *i.e.* 1 hour prior to challenge and immediately, 1 and 4 hours after infection.

The median effective dose (ED_{50}, mg/kg, total dose) was calculated by probit analysis from the number of mice surviving on day 10. The antibiotics were tested in parallel against each test strain.

Subcutaneous Staphylococcal Abscesses in Mice

hrCH3-mice (hairless mice, Bomholdgard Ltd., Denmark) of both sexes weighing 18~23 g were subcutaneously infected under the loose skin of the right flank with the methicillin-sensitive *Staphylococcus*

aureus (MSSA) strain SG 511[9]. Abscess formation was already evident at 20 hours. Up to 8.80 $\log_{10}$ cfu/ml could be found in the abscess pus of the untreated controls on day 4 after infection.

Therapy was initiated 1 hour after challenge by subcutaneous administration of 50 mg/kg of imipenem, cefpirome or cefotaxime on the opposite flank to the abscesses and continued twice daily for 3 days. An additional dose was injected on the fourth day. The total dosage of each compound was 350 mg/kg. At day 4 after infection, the number of cfu/g abscess was determined.

Experimental Pneumonia

Murine pneumonia was produced as previously described[10,11]. In brief, up to 120 NMRI mice were placed in an exposure chamber and challenged during 40 minutes with an aerosol containing the infecting organism *Klebsiella pneumoniae* DT-S. The bacterial suspension (4 ml) was nebulized by means of a nebulizer (Vaponefrin Pocket Nebulizer, USV Pharmaceutical Co., U.S.A.). Pneumonia was allowed to become well established before treatment with the different antibiotics was carried out. The compounds were injected subcutaneously in serial 2-fold dose concentrations, once at 18 or 28 hours after challenge, twice at 21 and 28 hours after challenge or three times at 18, 19 and 20 hours after aerosol exposure. Eight control mice remained untreated. The number of dead mice was recorded daily. On day 10 after infection, the surviving animals were sacrificed. The lungs were removed and homogenized with nine times the weight of 10 mM phosphate buffered saline (PBS) in an Ultra Turrax homogenizer (Janke & Kunkel KG, FRG). Ten-fold serial dilutions of the homogenate were prepared and plated on Mueller-Hinton plates (Difco). After an incubation period at 37°C for 20 hours, the cfu/g lung tissue were counted. The ED_{50} and the median clearance dose (CD_{50}, mg/kg), *i.e.* the antibiotic amount required for eradication of *K. pneumoniae* DT-S from the lungs of 50% of the infected mice, were calculated by probit analysis.

Time-kill Curve Studies in Pneumonic Mice

Mice with experimentally induced pneumonia were injected with 50 mg/kg of the β-lactam antibiotics 18 hours after challenge[11]. Groups of eight mice were killed prior to and at intervals between one and 48 hours after antibiotic administration. 0.1 ml of blood was taken from the inferior vena cava, plated and incubated for colony counts. The lungs were excised, diluted in nine times the weight of PBS, homogenized and plated. The cfu were counted after 20 hours incubation at 37°C. The detection limits were 10^1 cfu/ml for blood and 10^2 cfu/g for the lungs.

Granuloma Pouch Model

Female Wistar rats weighing 180~200 g were used. Granuloma was induced by injecting 0.5 ml of cottonseed oil containing 5% croton oil into a pouch produced on the back of the animals by the subcutaneous injection of 20 ml of sterile air[12]. On the seventh day the pouches were filled with about 10 ml inflammatory exudate. By injection of 8.9 $\log_{10}$ cfu/ml of *Escherichia coli* 078 into the pouch exudate, a persistent localized infection was induced. Therapy was initiated 1 hour after the inoculation of the pouches. The compounds were given intramuscularly in seven individual doses of 20 mg/kg to groups of eight rats, injected twice a day for 3 days. An additional dose was injected on the fourth day. Growth of *E. coli* 078 in the pouches was monitored by determining the colony counts in 0.1 ml pouch exudate sampled prior to the first administration and immediately prior to the third, fifth and seventh injection of the drugs, *i.e.* 24, 48 and 72 hours after inoculation of *E. coli* 078 into the pouches, and 8 hours after the last dosing, *i.e.* 80 hours after infection.

Bioassays

Concentrations in blood and abscess pus were determined by the agar diffusion technique with *Streptococcus pyogenes* A77 as test organism.

Results

Protection Tests in Mice

The results of the *in vitro* susceptibility test and of the protection tests in mice are summarized in

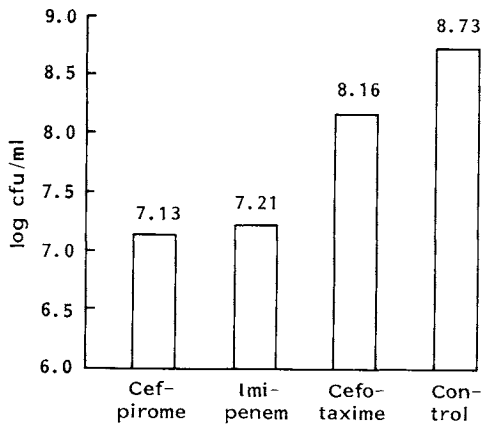
Table 1. As shown in the table, the high *in vitro* activity of the carbapenem imipenem against *S. aureus* strains and Enterococci was reflected by good chemotherapeutic efficacy against murine staphylococcal and enterococcal septicemias. The ED_{50} values of imipenem were 0.05 and 0.09 mg/kg in the case of MSSA infections and ranged from 1.25 to 15.58 mg/kg against MRSA. The carbapenem was thus distinctly more effective than cefpirome and, in particular, more effective than cefotaxime which exhibited only limited activity against MRSA. All the Enterococci tested were resistant to cefotaxime but showed susceptibility to cefpirome and were influenced by comparatively low imipenem concentrations. Very low doses of all three compounds, however, had to be given for eradication of the *S. pyogenes* A77 and the *Streptococcus pneumoniae* infection.

The compound most effective in protecting mice from infection caused by Enterobacteriaceae was cefpirome, followed by cefotaxime. In the case of the septicemia caused by *Escherichia coli* 04, however, imipenem was clearly superior to the two cephalosporin antibiotics. *P. aeruginosa* infections responded poorly to treatment with cefotaxime. The ED_{50} values ranged from 2.25 mg/kg to >100 mg/kg. High cefpirome concentrations of 309.00 mg/kg also had to be given in the case of *P. aeruginosa* 1771 infection, whereas the other pseudomonal septicemias could be eradicated by distinctly lower concentrations. The ED_{50} values of cefpirome for these infections were 0.40 to 21.80 mg/kg compared to 0.42 to 7.18 mg/kg for imipenem. All three antibiotics exhibited similar activity against *Pasteurella multocida.*

Activity in Subcutaneous Staphylococcal Abscesses in Mice

Staphylococcal abscesses are very difficult to treat with β-lactam antibiotics. In spite of distinctly lower MIC against *S. aureus* SG 511 (<0.002 *versus* 0.31 μg/ml), imipenem was not more effective than cefpirome. After therapy with seven times 50 mg/kg of imipenem or cefpirome, a reduction about 1.5 and 1.6 $\log_{10}$ cfu, respectively, was found (Fig. 1). This discrepancy between the *in vitro* and *in vivo* activity of imipenem may be due to the pharmacokinetic behavior of the drug. Whereas 1 hour after the seventh dosage, cefpirome concentrations in blood and pus were 12.58 ± 1.38 and 8.26 ± 2.51 μg/ml, the respective imipenem levels were only 7.86 ± 0.42 μg/ml in blood and 4.43 ± 0.99 μg/ml in pus. In cefotaxime treated mice only a slight efficacy of the compound, *i.e.* a reduction of only 0.57 $\log_{10}$ cfu/ml, could be observed. The cefotaxime concentrations 1 hour after last dosing were 9.38 ± 2.07 and 7.09 ± 2.37 μg/ml in blood and abscess material, respectively.

Fig. 1. Chemotherapeutic activity against *Staphylococcus aureus* SG 511 abscesses in mice: Viable bacteria from the abscesses after therapy with seven doses of 50 mg/kg of cefpirome, imipenem and cefotaxime.



Experimental Pneumonia in Mice

Table 2 compares the therapeutic efficacy of the three β-lactams against murine *Klebsiella* pneumonia. With ED_{50} values ranging from 3.74 to 20.56 mg/kg and CD_{50} values ranging from 17.78 to 387.37 mg/kg, cefpirome was two to seven times more active than imipenem and cefotaxime. The outcome of antibiotic therapy varied widely depending on the treatment regimen used, *i.e.* the later initiation of therapy, the higher ED_{50} and CD_{50}. For instance, when given 28 hours after challenge it was necessary to increase the antibiotic dosage by

Table 2. Comparative chemotherapeutic activity of cefpirome, imipenem and cefotaxime against experimentally induced *Klebsiella pneumoniae* DT-S pneumonia in mice.

Regimen (hours after infection)	Median effective dose (ED_{50}, mg/kg/dose) and median clearance dose (CD_{50}, mg/kg/dose)					
	Cefpirome		Imipenem		Cefotaxime	
	ED_{50}	CD_{50}	ED_{50}	CD_{50}	ED_{50}	CD_{50}
18	20.56	94.85	127.93	>400.00	63.00	173.85
28	47.79	387.37	354.18	>400.00	246.66	557.50
21, 28	6.20	17.78	28.39	55.28	20.58	56.65
18, 19, 20	3.74	19.64	18.07	48.59	19.80	43.60

Fig. 2. Chemotherapeutic activity of cefpirome (■), imipenem (▲) and cefotaxime (●) in lungs of mice infected with *Klebsiella pneumoniae* DT-S: Viable bacteria from the lungs after a single subcutaneous-injection of 50 mg/kg of the antibiotics at 18 hours after aerosol exposure.

□ Control.

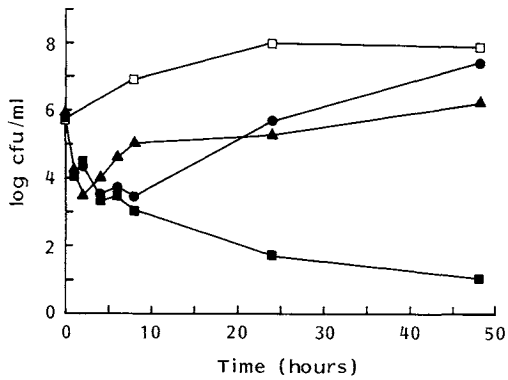
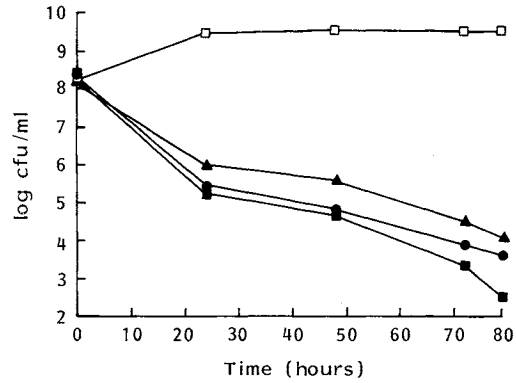


Fig. 3. Chemotherapeutic activity of cefpirome (■), imipenem (▲) and cefotaxime (●) in rat pouches infected with *Escherichia coli* 078: Bacterial numbers in the pouch exudate after therapy with seven 20 mg/kg doses of each test compound.

□ Control.



at least two to four times to achieve an effect similar to that obtained by medication after 18 hours. For each β-lactam the ED_{50} and CD_{50} values were, however, considerably lower when antibiotics were administered twice, 21 and 28 hours, or three times, 18, 19 and 20 hours after aerosol exposure.

In studies on the bactericidal activity in pneumonic mice (Fig. 2), cefpirome was again remarkably effective. Over the first 8 hours after a single subcutaneous dose of 50 mg/kg cefpirome given 18 hours after challenge, the bacterial counts in the lungs of pneumonic mice decreased drastically to 1/100 of the pretreatment level. Over the next 40 hours a continued intrapulmonary killing of 4.3 $\log_{10}$ cfu/ml was observed and lungs were cleared from viable bacteria in seven out of ten mice. With imipenem and cefotaxime, however, only in the first 2 and 8 hours after dosing, respectively, pronounced reduction of pathogens was observed. From then on the bacteria multiplied rapidly so that mean bacterial counts in lung homogenates at 48 hours were only slightly lower than in the control group. Moreover, at 48 hours blood cultures gave positive results, not only for the untreated controls but also for most animals of the imipenem and the cefotaxime groups.

Therapeutic Effects on *E. coli* Infections in the Granuloma Pouch

Fig. 3 shows the efficacy of the three β-lactam antibiotics on *E. coli* 078 infection in rat pouches. As can be seen from the figure, *E. coli* 078 grew well in pouch exudate with 9.39 $\log_{10}$ cfu/ml of the pathogen being detected in the pouches of untreated controls at 80 hours after challenge. Antimicrobial therapy with seven 20 mg/kg doses of each test compound, however, significantly reduced bacterial counts from an initial level of 8.28 $\log_{10}$ cfu/ml to 3.97 $\log_{10}$ cfu/ml in the imipenem group and to 3.51 $\log_{10}$ cfu/ml in the cefotaxime group. Reduction was most pronounced with cefpirome, with marked lowering of pathogens in pouches to 2.42 $\log_{10}$ cfu/ml of exudate.

Discussion

The outstanding efficacy of the cephalosporin derivative cefpirome and the carbapenem imipenem in comparison with other β-lactam antibiotics was described in several recent publications[1~7]. Our study confirms previous investigations on the excellent activity of both compounds against Enterobacteriaceae as well as staphylococcal and pseudomonal pathogens.

In mouse protection tests using 11 Gram-positive and 14 Gram-negative strains, cefpirome and imipenem both were more active than cefotaxime. In particular, the carbapenem showed high efficacy against Staphylococci and Enterococci and was more active than cefpirome in two out of four infections induced with *P. aeruginosa*. Against Enterobacteriaceae, however, cefpirome was the most potent of the three antibiotics tested. Cefotaxime also displayed higher efficacy against six out of nine Enterobacteriaceae strains than imipenem.

The unequivocal advantages of imipenem *in vitro* and in protection tests, especially against Gram-positive bacteria, were less outstanding with respect to localized infections. Excellent pharmacokinetic properties (*e.g.* serum half-life, metabolic stability, high tissue penetration) are of particular importance for treatment of such infections. Despite considerably higher activity against Staphylococci imipenem was, therefore, only equiactive to cefpirome in subcutaneous staphylococcal abscesses or lesser effective in *Klebsiella* pneumonia and *E. coli* pouch infection as could be expected by the MICs. A further disadvantage of imipenem is its metabolic instability in the kidney[13]. Therefore, it should only be coadministered with the dehydropeptidase-I-inhibitor cilastatin[14]. Although cefotaxime showed also some metabolic instability, the compound possesses good combined activity with its metabolite desacetylcefotaxime[15,16]. Hitherto, no metabolites have been found from cefpirome.

In conclusion, in consideration of its promising antibacterial and pharmacokinetic properties, cefpirome appeared more favorable in comparison to other cephalosporin antibiotics and also when compared to the carbapenem imipenem. Cefpirome promises to be most suitable for the treatment of a wide range of bacterial infections and may be a valuable alternative to currently available β-lactam antibiotics.

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