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THE IN VITRO ACTIVITY, HUMAN PHARMACOLOGY, AND CLINICAL EFFECTIVENESS OF NEW β-LACTAM ANTIBIOTICS

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INTRODUCTION

There have been many factors which have caused proliferation of new β-lactam compounds. The increasing resistance of gram-negative enteric bacteria to existing compounds has been a world wide phenomenon which has accelerated in the decade of the 1970s (1–3). There has been an increased awareness of the toxic properties of the aminoglycosides and antibiotics of other classes (4). Finally, penicillins and cephalosporins are agents which lend themselves to modification which alters both microbiological activity as well as pharmacologic properties. Many structural modifications of the cephem nucleus have been produced since 1970. Moreover, new β-lactam antibiotics with different ring systems have been isolated from natural sources (5) and others have been totally synthesized. This article will consider those cephalosporin agents about which there is sufficient information to determine their future clinical utility.

BASIS OF ACTIVITY OF β-LACTAMS

Studies by a number of investigators have shown that the antibacterial activity of β-lactam antibiotics is based upon several factors (6–9). In gram positive bacteria the presence, type, and specific activity of β-lactam binding proteins (10) [so-called penicillin-binding proteins (PBPs)] determine the

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activity of a compound. In gram negative bacteria there is an outer wall barrier through which the anionic β-lactams must first pass (7). There are β-lactamases in the periplasmic space which exists between the outer bacterial wall and the cytoplasmic membrane. Finally there are the β-lactam binding proteins which are involved in cell-wall division, wall elongation, septum formation, and maintenance of the bacteria in its rod shape (11). β-Lactamases in gram negative bacteria can be genetically controlled by plasmids, in which case the enzymes are primarily constitutive and have greatest activity against penicillins. β-Lactamases which are chromosomally mediated often are inducible enzymes and act primarily as cephalosporinases (12).

It has been possible to isolate mutants of gram negative bacteria which are hyperpermeable or, in contrast, impermeable and to utilize these strains of bacteria to assess the relative role that certain chemical substituents contribute to the activity of compounds. Isolation and characterization of β-lactamases has also clarified the effect that substitution in several parts of the molecules has upon β-lactamase resistance. Finally, methods have been developed for the isolation of the proteins which bind β-lactams and this has explained differences in the activity of the compounds (13).

It is important to realize that a compound which has a defect in one area of activity (entry, β-lactamase stability, PBP-affinity) may still prove to be a useful agent against many bacteria, since its other attributes may be such that it can overcome the defect. Thus an agent which has some β-lactamase instability could by virtue of excellent entry properties and high affinity for PBPs be able to inhibit and kill bacteria which contain a β-lactamase. This is particularly true if the organism makes a small amount of β-lactamase or the β-lactamase has poor K_m and V_{max} properties as far as the particular compound is concerned. The converse of the aforementioned situation exists when the compound is an effective inducer of β-lactamase and the kinetic properties of the enzyme are such that it readily destroys the compound.

AMINOTHIAZOLYL CEPHALOSPORINS

A group of cephalosporin compounds can conveniently be grouped as aminothiazolyl derivatives. It is clear that attachment of the aminothiazolylacetyl side chain to 7-aminocephalosporanic acid confers markedly improved activity over existing compounds (14, 15). Earlier the introduction of a syn methoxyimino group as a substituent in a 7-furylacetyl side chain in the Glaxo compound cefuroxime had been shown to provide excellent β-lactamase stability (16). Thus methoxyimino derivatives of cephalosporins containing the aminothiazolyl side chain provided both

increased activity and β-lactamase stability. These agents are cefotaxime (HR 756) from Hoechst-Roussel, ceftizoxime (FX 749) from Fujisawa, ceftriaxone (Ro 13-9904) from Roche, and ceftmenoxine (SCE 1365) from Takeda. These agents differ in the type of substituent at position 3 of the dihydrothiazolidine ring. Ceftazidime (GR 20263) from Glaxo differs from the aforementioned aminothiazolyl agents in the replacement of the methoxyimino group with a 2-carboxy-2-oxypropane imino group.

CEFOTAXIME

Cefotaxime (Figure 1) is utilized as the syn oximino isomer in the D-form of the sodium salt. It is easily prepared as a sterile dry compound which at temperatures from 0 to 50°C is stable for up to 2 years (15). The compound is stable in a variety of intravenous fluids normally utilized in the hospital setting.

In Vitro Activity

The in vitro activity of cefotaxime has been extensively studied in laboratories representing all parts of the world (17). The in vitro activity against *Staphylococcus aureus* has ranged from 0.8 g to 8 μg/ml with 50% of isolates inhibited by 2 μg/ml and 90% by 4 μg/ml [(18–22), Table 1]. The overall consensus would be that methicillin resistant *S. aureus* are resistant to cefotaxime with MIC values above 64 μg/ml (17–27). *Staphylococcus epidermidis* have shown a much wider range of susceptibility with 8 μg/ml required to inhibit 90%. Methicillin resistant *S. epidermidis* are resistant to cefotaxime, MIC >64 μg/ml. Cefotaxime has excellent in vitro activity against the streptococcal species with the exception of the true enterococci, *Streptococcus faecalis* and *S. faecium* (18). For example, 90% of *S. pyogenes* (group A) are inhibited by 0.1 μg/ml as are *S. agalactiae* (group B) and *S. bovis* (17, 18). The MICs of *S. viridans* group organisms have tended to be somewhat higher with levels of 1.6 μg/ml required to inhibit all isolates. The cefotaxime MICs against *S. pneumoniae* are below 0.1 μg/ml, with 90% inhibited by 0.04 μg/ml. There is some confusion concerning the susceptibility to cefotaxime of the *S. pneumoniae* resistant to penicillin isolated in South Africa. Some workers have found the organisms susceptible, i.e. MIC values ≤ 1 μg/ml, whereas others have not found this. To date, cefotaxime is the aminothiazolyl cephalosporin with the best in vitro

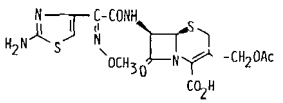

Figure 1 Cefotaxime.

Table 1 Comparative in vitro activity of new agents against bacterial isolates commonly causing infection in man[a]

Organism	Agent	MIC (μg/ml) Range	MIC_{90}
Staphylococcus aureus	Cefotaxime	<0.5 to >128	2
	Ceftizoxime	<0.5 to >128	2
	Ceftriaxone	<0.5 to >128	4
	Cefmenoxime	<0.5 to >128	2
	Ceftazidime	2 to >128	8
	Cefoperazone	<0.1 to >128	4
	Moxalactam	1 to >128	16
	n-Formimidoyl thienamycin	<0.01–1	0.5
	Azthreonam	>128	>128
Streptococcus pneumoniae	Cefotaxime	≤0.01–0.25	0
	Ceftizoxime	≤0.01–0.25	0.12
	Ceftriaxone	≤0.01–0.25	0.25
	Cefmenoxime	≤0.01–0.25	0.06
	Ceftazidime	0.06–0.25	0.25
	Cefoperazone	0.06–0.25	0.25
	Moxalactam	0.5–4	2
	n-Formimidoyl thienamycin	0.003–0.01	0.01
	Azthreonam	>128	>128
Streptococcus pyogenes	Cefotaxime	<0.01–0.1	0.03
	Ceftizoxime	<0.01–0.1	0.03
	Ceftriaxone	<0.01–0.1	0.03
	Cefmenoxime	<0.01–0.1	0.03
	Ceftazidime	0.06–0.5	0.25
	Cefoperazone	0.01–0.25	0.12
	Moxalactam	<0.5–8	4
	n-Formimidoyl thienamycin	<0.01–0.1	0.1
	Azthreonam	>128	>128
Streptococcus faecalis	Cefotaxime	4 to >128	>128
	Ceftizoxime	8 to >128	>128
	Ceftriaxone	4 to >128	>128
	Cefmenoxime	8 to >128	>128
	Ceftazidime	32 to >128	>128
	Ceroperazone	4 to >128	>128
	Moxalactam	32	>128
	n-Formimidoyl thienamycin	0.01–4	2
	Azthreonam	>128	>128
Haemophilus influenzae	Cefotaxime	≤0.01–0.03	0.03
	Ceftizoxime	≤0.01–0.03	0.03
	Ceftriaxone	≤0.01–0.03	0.015
	Cefmenoxime	≤0.01–0.03	0.03

Organism	Agent	MIC (μg/ml) Range	MIC_{90}
Haemophilus influenzae (continued)	Ceftazidime	≤0.01–0.5	0.12
	Cefoperazone	≤0.01–0.5	0.12
	Moxalactam	0.03–0.25	0.06
	n-Formimidoyl thienamycin	0.1–4	2
	Azthreonam	≤0.01–0.2	0.1
Neisseria gonorrhoeae	Cefotaxime	<0.01–0.03	0.015
	Ceftizoxime	<0.01–0.3	0.015
	Ceftriaxone	<0.01–0.03	0.008
	Cefmenoxime	<0.01–0.03	0.015
	Ceftazidime	<0.01–0.25	0.12
	Cefoperazone	<0.01–0.25	0.06
	Moxalactam	<0.01–1	0.06
	n-Formimidoyl thienamycin	<0.01–0.25	0.25
	Azthreonam	<0.01–0.2	0.1
Neisseria meningitidis	Cefotaxime	<0.01–0.025	<0.01
	Ceftizoxime	<0.01–0.025	<0.01
	Ceftriaxone	<0.01–0.025	<0.01
	Cefmenoxime	<0.01–0.025	<0.01
	Ceftazidime	<0.01–0.025	<0.01
	Ceroperazone	<0.01–0.1	0.05
	Moxalactam	<0.01–0.1	0.05
	n-Formimidoyl thienamycin	<0.01–0.1	0.05
	Azthreonam	<0.01–0.1	0.05
Escherichia coli	Cefotaxime	<0.1–8	0.25
	Ceftizoxime	<0.1–8	0.25
	Ceftriaxone	<0.1–8	0.25
	Cefmenoxime	<0.1–8	0.25
	Ceftazidime	<0.1–8	0.5
	Cefoperazone	<0.1 to >128	16
	Moxalactam	<0.1–8	0.25
	n-Formimidoyl thienamycin	<0.1–4	0.25
	Azthreonam	<0.1–8	0.25
Klebsiella pneumoniae	Cefotaxime	<0.1–2	0.25
	Ceftizoxime	<0.1–2	0.25
	Ceftriaxone	<0.1–2	0.25
	Cefmenoxime	<0.1–2	0.25
	Ceftazidime	<0.1–2	0.25
	Cefoperazone	<0.1–128	16
	Moxalactam	<0.1–4	0.25
	n-Formimidoyl thienamycin	<0.1–2	0.25
	Axthreonam	<0.1–2	0.25

Table 1 *(Continued)*

Organism	Agent	MIC (μg/ml) Range	MIC_{90}
Enterobacter cloacae	Cefotaxime	<0.1 to >128	8
	Ceftizoxime	<0.1 to >128	8
	Ceftriaxone	<0.1 to >128	8
	Cefmenoxime	<0.1 to >128	4
	Ceftazidime	<0.1 to >128	8
	Cefoperazone	<0.1 to >128	32
	Moxalactam	<0.1 to >128	4
	n-Formimidoyl thienamycin	<0.1–8	2
	Azthreonam	<0.1 to >128	4
Citrobacter freundii	Cefotaxime	<0.1–16	0.5
	Ceftizoxime	<0.1–16	0.25
	Ceftriaxone	<0.1–16	0.5
	Cefmenoxime	<0.1–16	0.25
	Ceftazidime	<0.1–16	0.5
	Cefoperazone	<0.1–16	1
	Moxalactam	<0.1–16	0.5
	n-Formimidoyl thienamycin	<0.1–16	0.1
	Azthreonam	<0.1–16	0.5
Serratia marcescens	Cefotaxime	0.2 to >128	4
	Ceftizoxime	0.2 to >128	2
	Ceftriaxone	0.2 to >128	4
	Cefmenoxime	0.2 to >128	4
	Ceftazidime	0.2 to >128	2
	Cefoperazone	0.2 to >128	16
	Moxalactam	0.2 to >128	4
	n-Formimidoyl thienamycin	0.1–4	1
	Azthreonam	0.1–8	2
Proteus mirabilis	Cefotaxime	<0.001–0.5	0.1
	Ceftizoxime	<0.001–0.5	0.1
	Ceftriaxone	<0.001–0.5	0.05
	Cefmenoxime	<0.001–0.5	0.1
	Ceftazidime	<0.001–0.5	0.2
	Ceroperazone	<0.001–0.5	1
	Moxalactam	<0.001–0.5	0.2
	n-Formimidoyl thienamycin	0.1–2	2
	Axthreonam	<0.001–0.2	0.1
Morganella morganii	Cefotaxime	0.2–4	2
	Ceftizoxime	0.2–4	0.5
	Ceftriaxone	0.2–4	0.5
	Cefmenoxime	0.2–4	1
	Ceftazidime	0.2–4	2

Organism	Agent	MIC (μg/ml) Range	MIC_{90}
Morganella morganii (continued)	Cefoperazone	0.2 to >128	4
	Moxalactam	0.1–0.5	0.5
	n-Formimidoyl thienamycin	0.1–2	1
	Azthreonam	<0.01–0.5	0.1
Providencia, rettgeri & stuartii	Cefotaxime	<0.1–4	2
	Ceftizoxime	<0.1–4	2
	Ceftriaxone	<0.1–4	4
	Cefmenoxime	<0.1–4	4
	Ceftazidime	<0.1–4	1
	Cefoperazone	<0.1–32	16
	Moxalactam	<0.1–4	0.5
	n-Formimidoyl thienamycin	<0.1–4	2
	Azthreonam	<0.1	0.5
Salmonella sp.	Cefotaxime	<0.1–0.5	0.25
	Ceftizoxime	<0.1–0.5	0.25
	Ceftriaxone	<0.1–0.5	0.25
	Cefmenoxime	<0.1–0.5	0.25
	Ceftazidime	<0.1–0.5	0.25
	Ceroperazone	<0.1–128	1
	Moxalactam	<0.1–0.5	0.25
	n-Formimidoyl thienamycin	<0.1–0.5	0.1
	Azthreonam	<0.1–0.5	0.1
Shigella	Cefotaxime	<0.1–0.5	0.25
	Ceftizoxime	<0.1–0.5	0.25
	Ceftriaxone	<0.1–0.5	0.25
	Cefmenoxime	<0.1–0.5	0.25
	Ceftazidime	<0.1–0.5	0.25
	Cefoperazone	<0.1–64	1
	Moxalactam	<0.1–0.5	0.25
	n-Formimidoyl thienamycin	<0.1–0.5	0.1
	Azthreonam	<0.1–0.5	0.1
Pseudomonas aeruginosa	Cefotaxime	2 to >128	64
	Ceftizoxime	2 to >128	64
	Ceftriaxone	2 to >128	64
	Cefmenoxime	2 to >128	64
	Ceftazidime	<0.5–32	8
	Cefoperazone	0.25 to >128	32
	Moxalactam	1 to >128	32
	Cefsulodin	2 to >128	32
	n-Formimidoyl thienamycin	0.5–16	4
	Azthreonam	<0.5–64	8

Table 1 *(Continued)*

Organism	Agent	MIC (μg/ml) Range	MIC_{90}
Pseudomonas (Other)	Cefotaxime	2 to >128	>128
(*P. maltophilia*,	Ceftizoxime	2 to >128	>128
P. cepacia, etc.)	Ceftriaxone	2 to >128	>128
	Cefmenoxime	2 to >128	>128
	Ceftazidime	2 to >128	>128
	Ceroperazone	2 to >128	>128
	Mosalactam	2 to >128	>128
	n-Formimidoyl thienamycin	2 to >128	>128
	Azthreonam	2 to >128	>128
Acinetobacter	Cefotaxime	2 to >128	>128
	Ceftizoxime	2 to >128	>128
	Ceftriaxone	2 to >128	>128
	Cefmenoxime	2 to >128	>128
	Ceftazidime	2 to >128	16
	Cefoperazone	2 to >128	>128
	Moxalactam	4 to >128	>128
	n-Formimidoyl thienamycin	1–16	8
	Azthreonam	16 to >128	64
Bacteroides fragilis	Cefotaxime	1 to >128	64
	Ceftizoxime	1 to >128	32
	Ceftriaxone	1 to >128	64
	Cefmenoxime	1 to >128	64
	Ceftazidime	1 to >128	128
	Cefoperazone	1 to >128	64
	Moxalactam	1 to >128	32
	n-Formimidoyl thienamycin	<1–16	2
	Azthreonam	>128	>128

[a] Range and MIC_{90} are taken from the published data recorded in this review, weighted for number of isolates.

activity against these penicillin-resistant *S. pneumoniae.* Overall, cefotaxime has good activity against gram positive cocci but is not superior to older penicillins or cephalosporins; the MICS for staphylococcal strains are 10-fold greater than those of cephalothin. *Listeria monocytogenes* are resistant, but *Bacillus* species are susceptible, although the MIC values may reach 4 μg/ml for some isolates.

Cefotaxime has been shown to have excellent activity against *Haemophilus influenzae,* including β-lactamase-containing strains (29–35). *H. parainfluenzae* and other *Haemophilus* species have cefotaxime susceptibility

patterns similar to those of *H. influenzae.* Cefotaxime has inhibited β-lactamase-producing *Neisseria gonorrhoeae* at concentrations below 0.5 μg/ml, irrespective of the source of the isolate (35–38). Indeed, the MIC mode against penicillinase-producing *N. gonorrhoeae* has been ≤0.004 μg/ml. Although there is less data on the activity of cefotaxime against *N. meningiditis,* the MIC_{90} of the available studies is ≤0.008 μg/ml.

The activity of cefotaxime against the members of the *Enterobacteriaceae,* as reported in studies of isolates from the United States, Japan, and Europe has shown a small amount of variation for species such as *Escherichia coli, Klebsiella* spp., *Citrobacter diversus, Proteus mirabilis, Salmonella, Shigella, Providencia rettgeri,* and *Providencia stuartii,* with 90% inhibited by ≤1 μg/ml (17–31). In contrast, *Citrobacter freundii, Enterobacters,* particularly *E. cloacae, Morganella morganii,* some *P. vulgaris,* and *Serratia* tend to have higher MICs. Although overall reports would indicate that 90% of the isolates of these species would be inhibited by 6 μg/ml, there are isolates from every country which have cefotaxime MICs above 32 μg/ml.

It appears that certain hospitals have enteric organisms which either produce β-lactamases which hydrolyze cefotaxime or more frequently have surface structure changes which prevent access of the drug to the receptor sites. In general, the organisms among the *Enterobacteriaceae* which are resistant to cefotaxime are resistant to other aminothiazolyl cephalosporins and also to cefoperazone and moxalactam (39–44).

Other organisms which have been reported to be susceptible to cefotaxime are *Aeromonas hydrophilia, A. shigelloides, Arizona hinshawii, Eikenella corredens, Yersinia enterocolitica, Actinobacillus actinomycetemcomitans, Bordetella pertussis, Comanonas terrigena, Pasturella multocida,* and *Vibrio cholera* (17, 44–48). The activity of cefotaxime against *Campylobacter fetus* species is poor, with the MIC_{90} of 32 μg/ml (48). It also does not inhibit *Legionella pneumophila* and some species of *Alcaligenes* are resistant (Table 2).

The reported activity of cefotaxime against *Pseudomonas aeruginosa* has shown a great range (17–28, 49). In general, 32 μg/ml has inhibited 50%

Table 2 Species of bacteria generally resistant to new β-lactams

Streptococcus pneumoniae, penicillin-resistant	*Listeria monocytogenes*
Staphylococcus aureus, methicillin-resistant	*Clostridium difficile*
Staphylococcus epidermidis, methicillin-resistant	*Pseudomonas maltophilia*
Streptococcus faecalis	*Pseudomonas putida*
	Campylobacter jejunii
	Legionella pneumophilia
	Bacteroides thetaiotamicron (15%)

of isolates, but the MIC_{90} has ranged from 32 μg to >400 μg/ml. In general, 20% of isolates would be considered resistant to cefotaxime with MICs >64 μg/ml. Other *Pseudomonas* species have extremely variable susceptibility to cefotaxime. *P. cepacia, P. acidovorans, P. diminuta,* and *P. denitrificans* often are susceptible, whereas *P. maltophilia, P. putida,* and *P. fluorescens* have been resistant. Other nonfermenting organisms which have been resistant are *Achromobacter xyloseoxidans, Bordetella bronchiseptica, Flavobacterium* species, and the CDC group IVc-2 organisms. *Acinetobacter calcoaceticus* species *Iwoffi* have been susceptible, but the *anitratus* species are resistant with MIC_{90} values about 64 μg/ml.

The in vitro activity of cefotaxime against anaerobic bacteria varies by species (17, 20, 21). The *Fusobacteria* have been inhibited at concentrations below 1 μg/ml. Although most (90%) of peptococci and peptostreptococci have been inhibited by ≤ 1 μg/ml, a few organisms have had MICs of 8 μg/ml. *Clostridium perfringens* have been inhibited by ≤ 2 μg/ml. *C. difficile* has been resistant. *Bacteroides melaninogenicus* have been inhibited by ≤1 μg/ml. *Bacteroides bivius* and *B. disiens,* organisms found in the female genital tract, all have been inhibited by 8 μg/ml. The susceptibility of *Bacteroides fragilis* has been reported to be 4 to 8 μg/ml for 50% of isolates and 32 to ≥128 μg/ml for 90% (18, 51–55). A number of *B. fragilis* produce β-lactamases which hydrolyze cefotaxime (55). Some *B. fragilis* strains have been resistant to cefotaxime. They do not hydrolyze the compound and have been resistant on the basis of other mechanisms. *B. thetaiotamicron* often have been resistant to cefotaxime, MIC >64 μg/ml.

Activity of Desacetyl Cefotaxime

Although desacetyl metabolites of agents such as cephalothin, cephapirin, and cefacetrile have been markedly less active than the parent compounds, this has not been true for desacetyl cefotaxime. The derivative is approximately four to eightfold less active than the parent compound against most isolates, with the exception of *Morganella, Bacteroides,* and *P. aeruginosa,* against which it should be considered inactive (56, 57). Desacetyl cefotaxime will inhibit the majority of *Neisseria, Haemophilus, E. coli, Klebsiella, P. mirabilis, S. pneumoniae, S. pyogenes,* and *S. agalactiae* at concentrations ≤1 μg/ml.

Bactericidal Activity and Effects of Testing Conditions

Increasing the bacterial inoculum for from 10^5 colony forming units (CFU)/ml to 10^7 CFU has not caused a major increase in either MIC or MBC values against streptococcal species, *Haemophilus, Neisseria,* methicillin, susceptible *S. aureus,* and certain members of the *Enterobacteriaceae,* such as *E. coli, Klebsiella, Salmonella,* and *Shigella* (18). But

marked increases in MIC have occured at 10^7 CFU for *Citrobacter freundii, Enterobacter cloacae, Morganella, Pseudomonas aeruginosa,* and *Bacteroides fragilis* (18).

In most studies there have been less than 10% of isolates with MBC/MIC ratios greater than 2. Similarly, the type of medium used to determine MIC values and the pH of the medium have had minimal effect upon the MIC or MBC values (18).

Bactericidal activity of cefotaxime against *Enterobacteriaceae* is similar to that of ampicillin and other cephalosporins without more rapid killing rates at higher concentrations of the drug (58).

There have been differences of opinion regarding the optional disk susceptibility testing technique (59, 60). Utilizing a 30 μg cefotaxime disk, a criteria of susceptible has been <23 mn (<8 μg/ml), indeterminate 15–22 mm (16,32 μg/ml), and resistant > 14 mm (≥ 32 μg/ml) (19).

β-Lactamase Stability of Cefotaxime

Cefotaxime is not hydrolyzed by the most common plasmid β-lactamase, the so-called TEM enzyme, which belongs in the Richmond type III group (61). The β-lactamase stability of cefotaxime is shown in Table 2. Plasmid-mediated enzymes of the TEM-1, TEM-2 OXA-1,2,3, SHV-1, PSE 1,2,3,4 minimally hydrolyze cefotaxime with a few exceptions, as noted in Table 3. Cefotaxime also has been shown to be a competitive inhibitor of the Richmond type I β-lactamases, which act primarily as cephalosporinases and are found in *Citrobacter, Morganella, Providencia,* and *Enterobacters* (61). Some *Enterobacters* and *P. vulgaris* contain β-lactamases which hydrolyze cefotaxime. Some *B. fragilis* β-lactamases hydrolyze cefotaxime (55). Cefoxitin has been shown to induce β-lactamases in certain strains of *E. cloacae,* making these strains resistant to cefotaxime (62).

Cell Membrane Permeability

Studies of the ability of cefotaxime to reach its receptor sites in *E. coli* have been performed with the isogenic mutants of Richmond DCO and DC2. Cefotaxime readily entered *E. coli* cells, although its penetration has not been as good as that of cefazolin and cephaloridine (9). Similar studies of the ability of cefotaxime to enter *Enterobacter cloacae* have been done in comparison to ceftizoxime, and have shown that ceftizoxime will enter bacteria more readily (63). Cefotaxime also has been shown to enter *Pseudomonas* in comparison to earlier cephalosporins (10).

Affinity of Cefotaxime to Penicillin-Binding Proteins

As noted earlier, the activity of β-lactams has been shown to be related to binding to penicillin-binding proteins (PBPs). Cefotaxime binds with greatest affinity to PBP 3, 1a, 1b, and 2 in that order (10). It has a stronger affinity for PBPs 1a, 1b, and 3 of *E. coli* than do cephalothin, cefamandole, cefoxi-

Table 3 Stability of new β-lactams to β-lactamases (relative hydrolysis in percent)

Type of β-lactamase	Cefotaxime	Ceftizoxime	Cefmenoxime	Ceftriaxone	Ceftazidime	Cefoperazone	Cefsulodin	Moxalactam	Thienamycin	Azthreonam
TEM-1[a]	<1	<1	<1	<1	<1	50	10	0	0	<1
TEM-2[a]	<1	<1	<1	<1	<1	60	10	0	0	<1
OXA-1[a]	20	20	20	20	20	20	0	0	0	<1
OXA-2[a]	<1	<1	<1	<1	<1	80	—	0	0	<1
OXA-3[a]	<1	<1	<1	<1	<1	50	—	0	0	<1
SHV-1[a]	<1	<1	<1	<1	<1	75	—	0	0	<1
PSE-1[a]	<1	<1	<1	<1	0	10	10	0	0	<1
PSE-2[a]	25	25	25	25	30	150	100	0	0	<1
PSE-3[a]	5	5	5	5	10	225	250	0	0	<1
PSE-4[a]	<1	<1	<1	<1	<1	10	10	0	0	<1
Staphylococcus aureus[a]	<1	<1	<1	<1	<1	60	<1	0	0	<1
Klebsiella pneumoniae	<1	<1	<1	<1	<1	5	—	0	0	<1
P 99	1	1	1	1	1	1	1	0	0	<1
Proteus vulgaris	25	25	25	25	25	50	—	0	0	<1
Pseudomonas aeruginosa		<1	<1	<1	<1	0	<1	0	0	<1
Bacteroides fragilis	75	50	75	75	25	50	—	0	0	<1

[a] Plasmid-mediated
— not evaluated

tin, or cefoperazone. The high binding to PBP 3 explains the filamentation of bacteria exposed to cefotaxime, since that protein has been shown to be associated with septum formation (13).

The PBPs in gram positive coccal species are slightly different and the designations of PBP 1, 2, 3 should not be considered to represent the same proteins as are present in gram negative bacilli. Cefotaxime has been shown to bind to PBP 1, 2, 3 in *S. aureus,* but the affinity for PBP 3 is only 5% the affinity of cephalothin (64). This would seem to explain the poorer activity of cefotaxime against *S. aureus* with MICs of 1.6 μg/ml compared to a cephalothin MICs of 0.1 μg/ml. All cephalosporins show a poor affinity for the PBPs 1 and 3 of *S. faecalis,* whereas penicillins with low MICs against *S. faecalis* have high affinity for PBP 3 and 1 (64). Cefotaxime binds to PBPs of *P. aeruginosa* and resistance so far has not been correlated with poor binding to PBPs.

Cefotaxime Interaction with Aminoglycosides and Other β-Lactams

Combination of cefotaxime with aminoglycosides such as amikacin, gentamicin, netilmicin, and tobramycin resulted in synergy against both members of the *Enterobacteriaceae* and *Pseudomonas aeruginosa* (18, 65). Synergy has been infrequently found with *E. coli* or *Klebsiella* since cefotaxime is so active against these species, but it has been seen with *S. marcescens, P. aeruginosa* and indole positive *Proteus* species.

Combination of cefotaxime and other cephalosporins usually has not resulted in synergy nor in antagonism, with the exception of combination of cefoxitin and cefotaxime when tested against cefoxitin-resistant *E. cloacae, C. freundii,* and *Pseudomonas* (62).

Interestingly, the combination of desacetyl cefotaxime and cefotaxime acts synergistically against most bacteria, with the exception of *Morganella,* in which the combination shows antagonism (57).

Pharmacology of Cefotaxime

Serum levels of cefotaxime after intramuscular (IM) or intravenous (IV) administration have yielded remarkably reproducible results in studies carried out in the United States, France, Japan and Germany (66–69). Mean peak serum levels after 0.25, 0.5, and 1.0 g doses administered by IM injection were 5.2, 11.9, and 25 μg/ml (Table 4). When the doses were normalized to a 1 g dose there were no differences between doses. Detectable serum levels were found at 6 hours after 0.5 g, and at 8 hours after a 1 g IM dose a serum level of 1 μg/ml still could be detected. After doses of 0.5, 1, and 2 g administered as an IV bolus, mean peak levels have been 38, 102, and 215 μg/ml for the three doses respectively (70). At 4 hours the

Table 4 Comparative pharmacokinetic parameters of new β-lactams

Parameter	Cefotaxime	Ceftizoxime	Ceftriaxone	Cefmenoxime	Ceftazidime	Cefoperazone	Cefsulodin	Moxalactam	Azthreonam
Peak serum concentration after 1 g IV[a] (grams per milliliter)	41	85	145	?	83	125	60	70	70
Serum $T_{1/2}$ (hours)	1.1	1.9	8	1	1.8	2	1.6	2.3	1.7
Renal excretion (%)	60	80	80	80	85	20	65	80	70
Protein binding	40	30	90	30	17	90	30	43	NA
Volume distribution (liters)	27	18	9	NA	16	12	23	20	13
Total clearance (milliliters per minute)	250	150	16	NA	110	75	145	90	85
Effects of probenecid	+	+	0	+	0	0	+	0	0

[a] Infusion
NA, not available

serum level was 1 μg/m for the 0.5 g and 3.3 μg/ml for the 2 g dose. Following infusion of 1 g cefotaxime over 30 min the mean serum levels at the end of the infusion have been 45 μg/ml with serum levels of 1 μg/ml at 6 hours (66).

Cefotaxime is rapidly eliminated with serum half-life of 1 hour after both IM and IV administration, and no change in half-life with doses of 0.25 to 2 g (67, 70). Administration of lidocaine with the IM doses does not alter elimination pharmacokinetics. In multiple dose studies there is no evidence of drug accumulation when administered 6 hourly (67). The volume of distribution of cefotaxime approximates 0.25 L/kg with a total body serum clearance of 300 ml/min.

Cefotaxime is metabolized to a desacetyl derivative which begins to appear shortly after cefotaxime is injected and reaches a peak at 2 hours (66), but the half-life of desacetyl cefotaxime is approximately between 1.4 and 1.9 hours in normal individuals. Further metabolism of cefotaxime in serum to the lactone derivatives does not occur in normal individuals (71).

Cefotaxime is widely distributed to different body tissues. Levels between 33 and 82 μg/ml have been found in bile after 1 g doses IV (72). Sputum levels have been low, 0.1 μg/ml (73). Levels in cancellous bone after 2 g have reached 15 μg/ml. Penetration into normal cerebrospinal fluid, agueous humor, and breast milk is negligible (74). In contrast, levels of cefotaxime in the CSF of patients with meningitis have reached levels of 4–8 μg/ml after doses of 2 g.

Cefotaxime is excreted primarily by renal mechanisms; tubular excretion is the major mechanism. Approximately half of a dose is excreted in the first 6 hours after administration, with 40% of a dose excreted in the first 2 hours (66). Total recovery of cefotaxime in a 24 hour period is 50 to 60%. The remainder of the drug is recovered as the desacetyl derivative or lactone

metabolites (71). Administration of probenecid prolongs the half-life of cefotaxime by blocking tubular excretion.

Renal disease with creatinine clearance below 7 ml/min causes a minimal increase in the serum half-life of cefotaxime, but increases the half-life of the desacetyl derivative to 11 hours.

Clinical Efficacy

Cefotaxime has been shown to be effective therapy for a variety of infections due to susceptible bacteria (Table 5). Respiratory infections due to *S. pneumoniae, H. influenzae, S. aureus, Klebsiella,* and *E. coli* have been treated with success rates of 94%. The agent has been utilized to treat abdominal infections with results comparable to those achieved with clindamycin and gentamicin (92%). Urinary tract infections due to *E. coli, Klebsiella,* and *Proteus* species have shown response rates comparable to those achieved with other agents with 97% clinical cures and 81% bacteriologic cures. Endometritis and salpingitis have been shown to respond, as has gonorrhoea due to β-lactamase-producing *N. gonorrhoea* (75). Skin and skin-structure infections and bone and joint infections have shown response rates comparable to those achieved with other β-lactam agents (82%) (personal communication, A. Yakabu). Cefotaxime has produced 92% cure rates in patients with bacteremia. It has also proved effective therapy of meningitis caused by *H. influenzae, S. agalactiae, N. meningitidis,* and *E. coli* (76). Infections due to ampicillin-, cephalothin-, carbenicillin-, and gentamicin-resistant organisms have been cured.

Toxicity

Adverse reactions to use of cefotaxime have been minimal (77). Phlebitis has been the most common occurence in 3 to 7% of patients. No major allergic, hematologic, hepatic, renal, or neurologic problems have been

Table 5 Response rates of infections to new β-lactams[a]

Type of infection	Percent satisfactory			
	Cefotaxime	Ceftizoxime	Cefoperazone	Moxalactam
Urinary tract	81	86	70	83
Lower respiratory tract	94	93	93	90
Intra-abdominal	92	88	89	91
Skin-skin structure	94	94	89	93
Gynecologic	93	NA	98	95
Bone and joint	87	67	75	88
Bacteremia	91	98	90	96
Meningitis	NA	NA	NA	94

[a] Calculated from investigator data
NA, not available

reported. Antabuse reactions and prolongation of prothrombin time have not been noted (Cefotaxime Symposium, Phoenix, Arizona, January 1981).

CEFTIZOXIME

The development and synthesis of ceftizoxime (Figure 2) has been well described recently (14, 78). Ceftizoxime differs from cefotaxime only by the lack of a side chain at position 3 of the dihydrothiazolidine ring. Studies by the Fujisawa group demonstrated that the presence of a hydrogen at position 3 of the dihydrothiazolidine ring provided activity similar to that achieved when acetoxy side chains or thiomethyl tetrazole substituents were present (78).

In Vitro Activity

Ceftizoxime has an in vitro spectrum of antibacterial activity similar to that of cefotaxime, with some differences which will be noted (79, 80, 81). Ceftizoxime is slightly less active than cefotaxime against *S. aureus,* with an MIC_{90} of 6.3 μg/ml compared to 3.1 μg/ml. This has also been true for its activity against *S. epidermidis.* In contrast, there has been minimal or no difference in the activity of ceftizoxime and cefotaxime against the streptococcal species (79, 80–82, 84). The majority of *S. pyogenes* and *S. pneumoniae* have been inhibited by ≤ 0.1 μg/ml. *Enterococci, S. faecalis,* have been resistant to ceftizoxime.

Among the *Enterobacteriaceae, E. coli, Klebsiella,* and *P. mirabilis* have been inhibited by ≤ 1 μg/ml at levels very similar to cefotaxime. Ceftizoxime may be slightly more active than cefotaxime against *Klebsiella* and *Proteus,* but the differences are minor (79). Ceftizoxime has had greater activity than cefotaxime against *Proteus* species with MICs of ≤ 0.01 μg/ml against *P. mirabilis.* It has inhibited the majority of *P. rettgeri, P. vulgaris,* and *Morganella* at concentrations ≤ 1 μg/ml. Ceftizoxime has been more active than cefotaxime against highly resistant *Serratia marcescens,* with MICs two- to eightfold lower (83). Ceftizoxime does not inhibit *Enterobacter* or *Citrobacters,* which are resistant to cefotaxime.

Activity of ceftizoxime against nonfermenting gram negative rods is similar to cefotaxime. It is less active against *P. aeruginosa.* It inhibits *P. cepacia,* but not *P. putida, P. maltophilia, P. fluorescens,* and *Achromobacter.* It inhibited 90% of *Alcaligenes* at 12.5 μg/ml, and 90% of *Flavobac-*

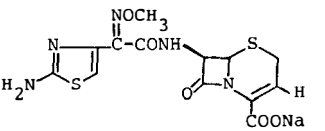

Figure 2 Ceftizoxime.

terium meningosepticum at 25 μg/ml. *Acinetobacters* tend to be fairly resistant with MIC_{90} of 25 μg/ml. Anaerobic activity of ceftizoxime is similar to that of cefotaxime, with excellent inhibition of gram positive species. However, ceftizoxime MICs against *Bacteroides fragilis* are higher, with 32 to 64 μg/ml required to inhibit 90% of isolates. Ceftizoxime is the most active aminothiazolyl cephalosporin against *Bacteroides* (85). Fusobacteria also have ceftizoxime MICs of 12 μg/ml. *Bacteroides bivius* are inhibited by $\leq$ 8 μg/ml. Activity of ceftizoxime against the other bacteria mentioned earlier for cefotaxime is similar. *Campylobacter* and *Legionella* are not inhibited.

Other Biological Parameters

Increasing the size of the bacterial inocedum and variation in type of test medium has had little effect on MIC or MBC values for most organisms except *Enterobacter, Pseudomonas,* and *Bacteroides* (79). Bactericidal activity has been rapid, as it is with the other agents in this class (80).

Ceftizoxime is not hydrolyzed by the common plasmid and chromosomal β-lactamases. β-Lactamases TEM-1,2; OXA 1,2,3; and PSE 1,2,3,4 cause minimal destruction of the compound (79). Ceftizoxime is more stable to *Bacteroides* β-lactamases than is cefotaxime. Minimal destruction of the compound follows incubation with β-lactamases of *Enterobacter.* It is a competitive inhibitor of Richmond Class I β-lactamases (unpublished data).

Studies of the entry of ceftizoxime into bacteria show that it has a low permeability coefficient and enters gram negative bacteria readily (63). Furthermore, EDTA had no effect on the ceftizoxime MICs against *Serratia,* whereas it did for cefazolin (83). Utilizing a stereoisomer of ceftizoxime in which the imino methoxy group is in the *anti* rather than *syn* position has shown that the *syn* configuration not only contributes to β-lactamase stability but also affects binding to PBPs (86). Presence of the imino methoxy group in the *syn* position causes greater binding of the compound to PBB 1b in both *E. coli* and *E. cloacae* (86).

The interactions of ceftizoxime with other antibiotics, particularly the aminoglycosides, is similar to that seen with cefotaxime (79). Synergy with aminoglycosides has been found for *Enterobacteriaceae* and *Pseudomonas.* Antagonism of the activity of ceftizoxime has been seen when combined with cefoxitin against *Enterobacters* (unpublished data).

Pharmacology

Much less has been published about the human pharmacology of ceftizoxime than about cefotaxime (87). Ceftizoxime yields mean peak blood levels of 137 μg/ml after a 0.5 g IM dose and mean peak serum levels of 84 μg/ml after infusion of 1 g over 30 min (Table 4). The half-life of the

drug is 1.4 to 1.6 hours in normal individuals and increases to 8 hours in individuals with creatinine clearances of 10 to 30 ml/min, and increases to 24 hours in anuric individuals (88, 89). The drug is not metabolized and is widely distributed to various body tissues (90). Levels of 0.3 to 1.8 μg have been found in sputum (91). The drug enters the CSF during inflammation (B. Scully and H. C. Neu, in preparation), but studies comparing its entry into CSF with other new agents have not been published. Urinary recovery in normal individuals is 80–85%, with the majority of the recovery occurring in the first 6 hours (87).

Clinical Studies

Preliminary reports of the clinical efficacy of ceftizoxime at the 12th International Congress of Chemotherapy indicated that the compound has been effective in the therapy of respiratory, urinary, gynecologic, surgical, skin, and skin-structure infections (89–93) (Table 5). It has proved to be as effective as aminoglycosides or cefamandole when used to treat serious infections in controlled, comparative trials (D. Parks, Smith-Kline & French).

Adverse reactions to ceftizoxime have been infrequent in our own experience with the drug and in reports from Fujisawa in Japan and Smith-Kline & French (D. Parks, personal communication) in the United States. No hematologic, hepatic, renal, or neurologic toxicity has been reported. Diarrhea has been uncommon and antabuse reactions have not been encountered. The drug appears to be very similar in in vitro spectrum, clinical efficacy, and tolerance to cefotaxime.

CEFMENOXIME

Cefmenoxime (SCE-1365) (Figure 3) contains a tetrazolylthiomethyl group at position 3 of the dihydrothiazolidine ring. This change in the structure of this aminothiazolyl, imino methoxy cephalosporin has had minimal effect upon the antibacterial activity and β-lactamase stability of the compound. The differences in the in vitro activity of this compound from cefotaxime and ceftizoxime are minor (94–98). It has been slightly more active against some of the *Enterobacteriaceae* than are the aforementioned compounds so that the MIC might be 0.01 μg/ml versus 0.02 μg/ml for some *E. coli.* It has shown slightly superior activity compared to cefotaxime against *E. coli, Morganella,* and *Serratia,* but against other members of the *Enterobacteriaceae* it is not more effective. The compound is not active against *Pseudomonas aeruginosa* nor a number of the other nonfermenting gram negative bacilli, such as *P. maltophilia* and *Acinetobacter.* It has activity comparable to cefotaxime against anaerobic cocci, but most *Bacteroides fragilis* have cefmenoxime MICs of 32 to 64 μg/ml (97, 89).

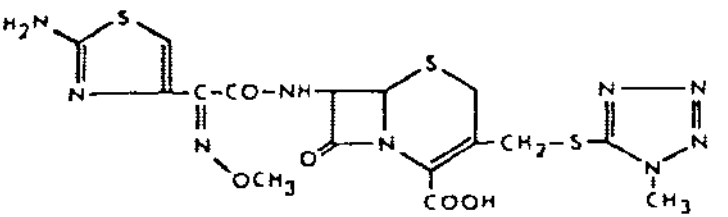

Figure 3 Cefmenoxime.

The agent is as stable to β-lactamases, whether plasmid or chromosomal mediated, as are the other agents of this class, except that it appears to be hydrolyzed to a minor degree by PSE 2 and PSE 3 plasmid β-lactamases (97).

The pharmacology of cefmenoxime is similar to that of other cephalosporins of similar structure. The mean serum half-life is 1 hour by the IV route and 1.5 hours after IM administration. Mean peak serum levels of 128 μg/ml follow bolus injection of 1 g and mean peak levels of 24 μg/ml after IM injection of 1 g. Urinary recovery is 75–80% (J. Guibert, personal communication).

Clinical studies have not been reported with cefmenoxine, but personal communication from R. Fujii of the use of the drug in pediatric infections in Japan in 19 institutions showed a clinical efficacy of 92% in 348 patients. Cefmenoxine entered the CSF and five of seven patients with meningitis were cured. There were no severe reactions in the pediatric patients.

CEFTRIAXONE

Ceftriaxone (Ro 13-9904) (Figure 4) differs from the aforementioned agents by addition of a side chain of a thiol methyl oxo thia azabicycle ring at position 3 of the dihydrothiazolidine nucleus. The in vitro activity is similar to the aforementioned compounds cefotaxime, ceftizoxime, and cefmenoxime with the following exceptions. Ceftriaxone is less active than cefotaxime against *S. aureus* (99, 102). It has, however, similar activity against group A and group B streptococci and *S. pneumoniae* so that 90% are inhibited by 0.2 μg/ml (99, 100–105). It is more active than the other agents against *P. mirabilis* and possibly against *H. influenzae, N. gonorrhoeae,* and *N. meningiditis* (99, 100, 102–104).

Ceftriaxone has less activity against *Pseudomonas* than some of the other aminothiazolyl cephalosporins and it has poor activity against *Bacteroides fragilis* (102). It also does not have activity against nonfermenting gram negative rods resistant to the other compounds, such as *Acinetobacter.* It does inhibit *Yersinia, Arizona, Aeromonas, Eikonella,* and *Pasturella mul-*

tocida (102). It does not inhibit *Campylobacter, Legionella, Listeria,* or *P. maltophilia* (102).

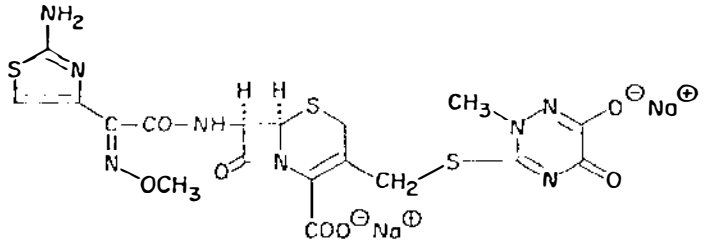

Figure 4 Ceftriaxone.

Pharmacology

Ceftriaxone differs from the other agents in its pharmacology (Table 4). The compound is bound to a greater extent to protein than are other drugs of this type, namely 90%. The protein binding is concentration-dependent and appears to alter the clearance of the drug. Serum levels of 150 μg/ml follow infusion of 1 g over 30 min with serum levels of 35 μg/ml present at 12 hours and 15 μg/ml at 24 hours. Administration of 0.5 g by the IM route produces mean peak serum levels of 50 μg/ml with levels of 8 μg/ml at 24 hours. When given as 1 g every 12 hours, after the first and last dose, the mean plasma concentrations were 145 and 168 μg/ml, respectively, and after 2 g dose were 255 and 280 μg/ml, respectively. In general, plasma concentrations have been proportional to the dose, and $T_{½}$ and fraction of excretion are not dose-dependent (106–109). As noted, there is a 20% accumulation of the drug over a 3 day period. Probenecid had no effect upon excretion of ceftriaxone. The compound also diffuses well into tissue cage fluids and into CSF (110, 111). The $T_{½}$ of the compound is 6.6 to 10 hours with a mean $T_{½}$ of 8 hours. This is in contrast to 1 hour for ceftoxime and 1.6 hours for ceftizoxime. Preliminary studies appear to show that the drug does not accumulate in the presence of renal failure.

Models of experimental meningitis in animals have shown that the compound achieves excellent concentrations 10–100 times the MICs for meningococci and *Haemophilus* which persist for long periods. We have treated patients with meningitis due to *P. mirabilis* and *E. aerogenes* and achieved concentrations greater than 6 μg/ml.

Clinical Activity

Clinical studies in the United States [J. Spicehandler and C. Demos (Roche), personal communication] indicate that ceftriaxone is effective therapy of various serious infections when administered as a twice or single daily dose (Table 5). No serious adverse effects have been reported. Studies

in Europe have indicated excellent results of therapy of serious urinary tract infections, gonorrhoea, lower respiratory tract infections, and in a small number of septicemias (112–114). A remarkable treatment of many cases of meningitis has been reported by Cadoz et al from Senegal (114). CSF levels reached 10 μg/ml and the CSF was sterile within 2 days when the compound had been given at 15–20 mg/kg/day as two doses.

CEFTAZIDIME

Ceftazidime (GR 20263) (Figure 5) differs in two essential aspects from the aforementioned agents. Although it has an amino thiazolyl group, it has a carboxypropyl oxyimino group instead of the iminomethoxy group of the other members, and it has a pyridinium group at position 3. These changes cause some loss of gram positive and anaerobic activity but increase the antibacterial activity against *Pseudomonas* (115–119). The MICs are 0.1 to 2 μg/ml for streptococci, 8 to 12 μg/ml for staphylococci, and >64 μg/ml for enterococci. Methicillin-resistant staphylococci are resistant. In general, ceftazidime has been slightly less active than cefotaxime, ceftizoxime, and cefmenoxime against the *Enterobacteriaceae* (119, 120). MICs were 0.1 to 0.4 μg/ml. It also has been less active than ceftriaxone against *H. influenzae* and *N. gonorrhoeae.*

The compound also has been less active against anerobic bacteria than some of the other agents already reviewed. It inhibits less common anaerobic species such as *Propionobacteria,* peptococci, peptostreptococci, *Veillonella,* etc. It has inhibited some *B. fragilis,* but the MICs often are 16 to 64 μg/ml. It has inhibited *Yersinia* and *Legionella* (120). Ceftazidime has been more active than other agents against *Serratia* and *Acinetobacter.* Ceftazidime also has been more active against *P. vulgaris* and *Morganella* than are cefotaxime and ceftizoxime.

Ceftazidime has been the most active new β-lactam against *Pseudomonas aeruginosa* (115–120). It has inhibited 50% of isolates at 4 μg/ml and 90% at 12–16 μg/ml in every study so far reported. Furthermore, it has inhibited carbenicillin-, piperacillin-, and gentamicin-resistant *P. aeruginosa.* It has consistently been more active than cefoperazone and moxalactam (120).

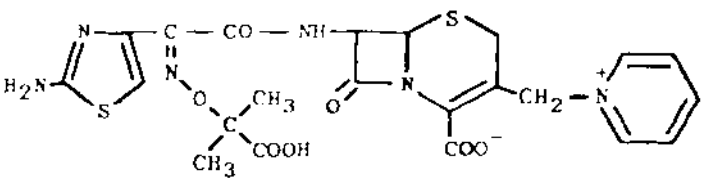

Figure 5 Ceftazidime.

β-Lactamase Stability

Ceftazidime has been highly stable to β-lactamase attack, resisting destruction by enzymes which hydrolyze cefamandole, cefoperazone, and cefsulodin, in addition to the older cephalosporins and penicillins. However, some *Enterobacter* and *Citrobacter* have been resistant to ceftazidime as they have been to all of the new β-lactam agents. Ceftazidime does not act as a potent inducer of β-lactamases, but it does inhibit hydrolysis of other cephalosporins by Richmond type I β-lactamases (120).

Ceftaxidime's activity has been minimally affected by the inoculum size used in MIC and MBC determinations (115–120). It also has been active over a wide pH range and in aerobic and anaerobic environments. Killing rates have been comparable to other agents of this class, and there has been minimal difference between MIC and MBC values. It has acted synergistically with aminoglycosides and is less likely to show antagonism when combined with cefoxitin.

Pharmacology

The pharmacology of ceftaxidime in normal volunteers has shown that serum levels have been 39 μg/ml, 83 μg/ml, and 188 μg/ml after IV infusion of 0.5, 1, and 2 g respectively, with half-life of 1.8 hours (121, 122). Plasma protein binding of ceftazidime has been only 17%. The plasma clearance of the drug has been reported as 110 ml/min. Urinary recovery is 80 to 90% and there are no metabolites in the urine (121–123). By the IM route, mean peak values of 17.8 μg/ml and 37.2 μg/ml occur after 0.5 and 1 g, respectively. There has been no prolongation of half-life when probenecid was administered, indicating that the drug is cleared by glomerular filtration (123).

Ceftazidime has been shown to penetrate into blister fluid, bone, bile, and peritoneal fluid (124, 125). Levels in blister fluid are adequate to inhibit most *S. aureus* and *P. aeruginosa,* as well as other common gram negative bacilli (122).

There have been only a small number of clinical studies of ceftazidime, but it has proved effective in pneumonitis and other serious infections due to *Pseudomonas* (126, 127). No major adverse reactions have been reported.

CEFSULODIN

Cefsulodin (Figure 6) is 3-(4 carbamoyl-1-pyridinio-methyl-7-beta (D-α-β sulfophenylacetamido) -ceph-3em-4-carboxylate) as a sodium salt. It has many similarities to carbenicillin, with an acidic function at position 10. It also has a pyridinium group at position 3. The antibacterial activity of this

agent is fairly well limited to *Pseudomonas aeruginosa* and to some degree *S. aureus* (127–129). Inhibitory values have been widely different, ranging from 3.1 μg/ml and 50 μg/ml for 50% and 90% of strains to more recent reports of MIC_{50} of 32 μg/ml and MIC_{90} of 128 μg/ml. Cefsulodin has been usually four to eightfold more active against *Pseudomonas* than carbenicillin. It has activity similar to cefoperazone and moxalactam (130–132). Most of the *Enterobacteriaceae* have been resistant (MICs >50 μg/ml) as have streptococci. Some anaerobic bacteria and *S. aureus* have been inhibited at concentrations of 3 to 25 μg/ml (131). The compound is hydrolyzed by a number of β-lactamases present in *Pseudomonas,* but not by the Sabath-Abraham enzyme (Richmond type 1d), nor by the TEM (Richmond type III) enzyme. There is an increase in MIC and MBC values as the inoculum size is increased above 10^5 CFU. Although cefsulodin exhibits synergy when combined with aminoglycosides against *Pesudomonas,* this is not a consistent phenomenon (132).

The basis of the activity of cefsulodin against *P. aeruginosa* seems to be related to its ability to penetrate the outer wall of this species and to bind to the PBPs in *Pseudomonas* (133–135).

Pharmacology

The pharmacology of cefsulodin does not differ appreciably from those of other cephalosporins (136). The half-life of cefsulodin in individuals with normal renal function is 1.6 to 1.8 hours, and in patients with anuria $T_{½}$ is 9 to 10 hours (137). Following a 2 g IV bolus dose, serum levels of 121 μg/ml are present for the first hour and levels of 40 μg/ml for the second and third hours. Administration of cefsulodin at the same time as gentamicin or amikacin does not change the pharmacokinetics of either agent (139). About 70% of a dose is excreted in the urine. Studies in patients with cystic fibrosis show the $T_{½}$ is slightly shorter and total body clearance of the drug is greater (138). The compound enters interstitial fluid, producing levels of 15 μg/ml 2 hours after a 1 g IV dose (140).

Clinical studies so far have shown that cefsulodin is effective therapy of selected infections due to *Pseudomonas,* but much more data is needed to clarify the precise role of this agent and to determine whether it can be used as single therapy.

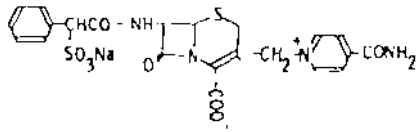

Figure 6 Cefsulodin.

CEFOPERAZONE

Following observations that penicillins with a 2,3 dioxopiperazinylcarbonyl group showed excellent antibacterial activity, the moiety was introduced into the cephalosporin nucleus. A variety of other chemical groups were introduced into the 3 position of the ring, and it was discovered that the compound which had the methyltetrazolythio group had the highest antibacterial activity and lowest toxicity. Further studies demonstrated that an ethyl group attached to the 4 position of the piperazine ring and a hydroxyl group to the benzyl group allowed optimal activity, thus giving the structure of cefoperazone (Figure 7) (141).

Antibacterial Activity

In the majority of studies cefoperazone has inhibited 90% of *S. aureus* at 3 to 4 μg/ml. It has been less active than cephalothin or cefamandole and generally comparable to the activity of cefoxitin. Methicillin-resistant *S. aureus* and *S. epidermis* are resistant to cefoperazone. Most *S. pyogenes, S. agalactiae,* and other streptococci, except for *S. faecalis,* have been inhibited by ≤0.4 μg/ml (142–145). *S. pneumoniae* are inhibited by ≤0.25 μg/ml (100%). *Neisseria meningitidis* have been inhibited (90%) by ≤0.015 μg/ml, 100% of *H. influenaze,* including β-lactamase strains, by 0.5 μg/ml, and 100% of *N. gonorrhoeae* by 0.12 μg/ml (142–145).

The activity of cefoperazone against the *Enterobacteriaceae* is markedly influenced by the type of β-lactamases present in the bacteria in the hospital. In some areas 98% of the isolates would be susceptible to ≤ 8 μg/ml (145), whereas in others 30% of isolates would be resistant (142, 143, 146, 147). The MIC_{90} for *E. coli* has ranged from 4 to >128 μg/ml, with most countries reporting 4 to 8 μg/ml. In most studies 4 to 12 μg/ml of cefoperazone will inhibit 90% of *K. pneumoniae,* but there are reports of organisms with cefoperazone MICs of >128 μg/ml (96). The aminothiazolyl cephalosporins and moxalactam are more active against *Klebsiella* and *E. coli* than cefoperazone. *P. mirabilis* generally have been inhibited by 1 to 8 μg/ml. *Morganella, P. vulgaris,* and *P. rettgeri* tend to have had higher

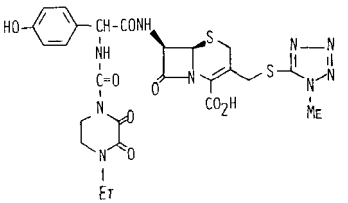

Figure 7 Cefoperazone.

cefoperazone MICs, but 16 μg/ml has inhibited most isolates. Cefoperazone has been less active than cefotaxime and moxalactam against these isolates.

The greatest variation in published cefoperazone MICs has been with *Enterobacter, Serratia,* and *Citrobacter* species. *E. aerogenes* and *C. diversus* generally have been susceptible, with 90% inhibited by 4 μg/ml. However, of *E. cloacae, C. freundii,* and *S. marcescens,* 20% could have cefoperazone MICs above 16 μg/ml.

Cefoperazone has been one of the most active new agents against *P. aeruginosa,* but here also the results depend upon the strains tested, since MIC_{90} of cefoperazone against *P. aeruginosa* range from 16 to > 128 μg/ml (142–147). Cefoperazone did not inhibit *Acinetobacter* and most of the other Pseudomonads, and did not inhibit *Campylobacter* nor *Legionella,* but was active against *Yersinia.*

Cefoperazone inhibited most *Bacteroides bivius, B. distatonis, B. oralis,* and *B. melaninogenicus* at concentrations below 8 μg/ml (51, 148, 149). It was less active than cefoxitin against *B. fragilis,* with 32 to 64 μg/ml required to inhibit 90% of isolates (51, 85, 148, 149). Cefoperazone at low concentrations inhibits *Clostridium* sp, *Eubacterium* sp., *Fusobacterium* sp., and peptostreptococci and peptococci.

Factors Affecting in Vitro Activity

The in vitro activity of cefoperazone is minimally affected by increases in inoculum below 10^6 CFU (142). However, at inocula of 10^7 CFU there has been marked differences between MIC and MBC values against *Enterobacter,* some *E. coli,* and *Pseudomonas.* Cefoperazone is active over a wide pH range, and activity is not influenced by type of medium.

Cefoperazone has acted synergistically with aminoglycosides against *Pseudomonas* and with clavulanic acid against *Klebsiella* and *B. fragilis,* which are resistant to cefoperazone (149).

Cefoperazone is less β-lactamase stable than the other compounds discussed in this article (142). It can be hydrolyzed by a variety of plasmid and chromosomal β-lactamases when the enzymes have been used as partially purified enzymes. The low level of enzyme present in some bacteria and the ability of cefoperazone to enter the bacterial cell and to bind the PBPs to some extent overcomes this β-lactamase instability and it inhibits many *Pseudomonas* (150). It binds very effectively to PBPs 3 and 1b. It is cefoperazone's ability to enter the bacterial cell and to bind to PBPs that explains its good activity against many bacteria. Nonetheless, cefoperazone cannot be considered to have the β-lactamase stability of agents such as ceftazidime or moxalactam.

Pharmacology

The pharmacology of cefoperazone has been reviewed in detail recently (151). In studies of the intramuscular (IM) administration of cefoperazone at doses of 0.25, 0.5, and 1 g, mean peak serum concentrations were 22, 33, and 67 μg/ml at 1 hour. At 8 hours, serum levels were 2.1 4.8, and 5.6 μg/ml, respectively, for the three doses. The mean half-life after intramuscular injection was 108–154 min (Table 4). Urinary recovery ranged from 14 to 18% of an administered dose. Intravenous (IV) administration of cefoperazone by rapid (3–5 min) infusion produced serum levels at 15 min of 76, 156, and 244 μg/ml after doses of 0.5,1, and 2 g, respectively. Concentrations of cefoperazone at 8 hours were 2.4, 6.5, and 11.8 μg/ml after these respective doses. Serum half-life was 115–120 min and urinary recovery, 29–33%. Levels determined at 5 min after bolus injection were 200 μg/ml for 1 g, 275 μg/ml for 2 g, and 518 μg/ml for 3 g. Intravenous infusion studies of cefoperazones in which 2 g of the drug has been infused over 15, 30, or 120 min have yielded levels of 250–260 μg/ml (152–164). At 12 hours, levels of 1–2 μg/ml were still present. The half-life found in these studies ranged from 1.6 to 2.38 hours. Urinary recovery was 25–30%. Serum clearances have been 80–90 ml/min and renal clearances, 18–30 ml/min. The apparent volume of distribution of the compound has ranged from 10 to 16 liters. Comparative studies have shown that cefoperazone produced higher serum levels than cefazolin, cefamandole, cefotaxime, and moxalactam. Biliary concentrations exceed 400 μg/ml and are two to four times the levels found with cefazolin or cefamandole. In the presence of renal failure there has been a minimal increase in serum half-life; but in the presence of biliary obstruction, serum half-life may reach 11 hours, depending on the degree of biliary obstruction. In the presence of biliary obstruction, the drug is 90% removed from the body by renal excretion (165).

Cefoperazone has not been metabolized in man. It has been widely distributed, achieving concentrations that would be therapeutic in most tissues. It is bound to plasma proteins about 90%. In rabbits with experimental meningitis it enters the CSF at 8% of the serum level, which is similar to the amount of cefotazime and ceftriaxone, but less than that of moxalactam (166). In another study using larger doses of cefoperazone and moxalactam, the CSF/serum ratio of cefoperazone and moxalactam were equal (167).

Clinical Use

Cefoperazone has been studied extensively in the treatment of upper and lower respiratory tract infections, urinary tract infection, gynecological infections, skin and skin-structure infection, as well as bacteremia (Table 5).

In general, the clinical and bacteriologic response has been excellent, ranging from 80 to 93% (168–176). A dose of 2 to 4 g a day has been used. Pathogens eliminated have been *E. coli, Klebsiella, Proteus,* and *Pseudomonas.* The cure rate for *Serratia* has been lower at 54%. Comparative trials of cefoperazone and other cephalosporins or aminoglycosides have shown comparable clinical results (H. Swarz, personal communication).

Adverse Effects

Cefoperazone has been well tolerated after IV or IM administration. Side effects have been few in Japanese studies, and were primarily fever and rash, both experienced by less than 2% of patients. Diarrhea has been seen in 7% of American patients. Disulfiram reactions occur in individuals who drink alcohol while receiving cefoperazone or drink up to 48 hours after receiving the drug. However, individuals already intoxicated who receive the drug do not develop any reaction. This is due to alcohol dehydrogenase reaction seen with all agents which have a methyltetrazolylthio group. Bleeding, which rarely occurs, is due to prolongation of the prothrombin time, which can be readily corrected with vitamin K administration.

MOXALACTAM

Oxa-cephems were first reported by Cama & Christensen in 1974 (177), who showed that a sulfur in position 1 of the dihydrothiazolidine ring could be replaced by an oxygen without loss of biologic activity. Studies of the structural-activity relations of derivatives of a 1-oxacephem led the Shiongi research group to the molecule moxalactam (Figure 8), also called 6059-S and LY127935 (178–180). The S → O shift, although increasing antibacterial activity, increases the relative rate of hydrolysis by certain β-lactamases, since it increases the acylating ability. Thus the enhanced reactivity of the ring causes both increased activity and lability. The oxygen cephalosporin has been shown to have an increased ability to penetrate bacteria, which probably is due to an increased hydrophilic nature of the compound. This has been shown to increase penetration (181). Another interesting change effected by the S → O shift is a decreased protein binding which correlates with better animal protection in infection models (178).

The other substituents on the molecule contribute to various factors. Studies with cefoxitin had shown that presence of a 7 α-methoxy group leads

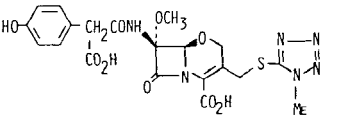

Figure 8 Moxalactam.

to great β-lactamase stability. An unsubstituted 1-oxacephem is hydrolyzed by every type of β-lactamase, but a 7 α-methoxy oxa-cephem is stabilized against the penicillinases such as TEM but not cephalosporinases. Addition of a carboxyl function in the malonyl side chain stabilized the molecule so that no β-lactamases attacked the molecule. The final aspect of the molecule relates not to antibacterial activity but to pharmacologic properties. Introduction of a *p*-hydroxyphenyl side chain produced high blood levels and changed the molecule to primarily excretion by filtration rather than secretion, as occurs with other cephalosporins.

Microbiologic Activity

Moxalactam has inhibited most commonly occuring gram positive, gram negative, and anaerobic bacteria (50, 182–194). It is not clear what should be the level used to define susceptibility, namely 8 μg/ml or 16 μg/ml. Moxalactam is much less active than earlier cephalosporins against *S. aureus,* 75% inhibited by 8 μg/ml and 95% by 32 μg/ml, in contrast to 95% inhibited by 0.4 μg/ml of cephalothin (182, 184, 185). It does not inhibit methicillin-resistant *S. aureus. S. epidermidis* have been slightly more resistant with MIC_{75}, 16 μg/ml. Streptococci such as *S. pyogenes* have required 1 to 8 μg/ml and the same is true of *S. agalactiae* (group B). *Enterococci* are completely resistant. The activity against *S. pneumoniae* is such that 60% require 1 μg/ml and 90% 2 μg/ml. Thus moxalactam, although able to inhibit gram positive species, has been much less active than older cephalosporins and the penicillins.

In contrast, activity against gram negative enteric bacteria is excellent. More than 90% of *E. coli, Klebsiella,* and *P. mirabilis* would be inhibited by < 0.2 μg/ml. Activity against *Enterobacter, Citrobacter,* and indole positive *Proteus, Providencia,* and *Morganella* have been excellent, with ≤ 1 μg/ml, inhibiting 85–90% of isolates. Some *Serratia* have required levels of 8 to 16 μg/ml, but 8 to 16 μg/ml would inhibit 95 to 98% of *Enterobacteriaceae* (184–196).

Moxalactam has been extremely active against *Haemophilis* and *Neisseria gonorrhoeae,* including β-lactamase-producing isolates of each species, with 98% inhibited by ≤ 0.5 μg/ml (189, 191, 192). The activity against *P. aeruginosa* is less significant, with 55% inhibited by 16 μg/ml, 75% by 32 μg/ml, and 85% by 64 μg/ml (184, 187, 196). It does not inhibit other *Pseudomonas* species (197) and activity against the uncommon nonfermenting organisms, such as *Acinetobacter,* is not remarkable: 50% inhibited by 16 μg/ml. It does not inhibit *Legionella* (198), but it does inhibit *Pasteurella, Vibrio,* and *Yersinia.*

The antianaerobic activity has been comparable to that of cefoxitin (148, 184, 186, 199). Most peptococci are inhibited by ≤ 2 μg/ml, but pepto-

streptococci may require levels of 32 to 64 μg/ml. Many *Clostridia* have been resistant, especially *C. difficile.* The *Bacteroides* have varied in susceptibility, with 8 μg/ml inhibiting 85%. Many *B. thetaiotamicron* have been resistant, as have some *B. distatonis.* Of *B. fragilis,* 90% would be inhibited by 16 μg/ml.

For most microorganisms the bactericidal concentration is identical or only twofold greater than the inhibitory level (184), with the exception of *P. aeruginosa.* Type of medium, presence of serum, and variations in pH or aerobic or anaerobic conditions have not affected the MIC or MBC values.

Moxalactam is extremely resistant to hydrolysis by all plasmid and chromosmal β-lactamases, whether they be of penicillinase or cephalosporinase affinity (39, 200, 201). It also has been shown to be an effective enzyme inhibitor of the Richmond type β-lactamases (39, 201). It also appears not to act as an inducer of some chromosmal β-lactamases, as occurs with cefoxitin.

Moxalactam acts synergistically with some aminoglycosides, but to a lesser degree than do penicillins. It does not act antagonistically with penicillins such as azlocillin, mezlocillin, and piperacillin (H. C. Neu, in preparation).

Pharmacology

Moxalactam is not absorbed from the intestine, but yields adequate serum and tissue levels after IV infusion or IM injection (202, 203). Mean peak serum concentrations after infusion of 500 mg are 48 μg/ml and 100 μg after 1 g. After a 1 g dose, serum levels of 1 to 2 μg/ml are present at 12 hours. A 30 min infusion of 2 g yields levels of 88 μg/ml at 1 hour and levels of 9 μg/ml at 8 hours. IM injection of 0.5 g yields levels at 1 hour of 24 μg/ml, with levels present at 8 hours. This is in contrast to cefotaxime, which is rapidly cleared, and similar to the kinetics of cefoperazone.

The mean half-life of moxalactam is 2 to 2.3 hours. The compound undergoes minimal metabolism in man, but this is probably of minimal significance (Table 4).

Most of the drug is excreted by the renal route, with recovery of 60 to 95%. The majority of the excretion occurs in the first 4 hours. Urine levels after a 500 mg dose have ranged from 450 μg/ml in the first two hours to 60 μg/ml in the 10 to 12 hour period. Probenecid does not affect renal excretion. In patients with renal impairment there is a prolongation of half-life and decrease in renal excretion (204–207). At creatinine clearances of 30 to 60 ml/min, the serum half-life is 4 hours, at creatinine clearances of 10–30 ml/min, $T_{½}$ is 8.5 hours, and in the anuric patient $T_{½}$ is 19 to 22 hours (205). Hemodialysis will reduce the half-life to 4 hours (205,

206–208). Peritoneal dialysis in contrast does not reduce the half-life of the drug (208).

The pharmacokinetics have been determined in newborn infants (209). Following a 10 min infusion of 50 mg/kg, mean peak levels have been 125 μg/ml. $T_{1/2}$ is 5 to 7.5 hours in neonates less than 7 days of age and 4.4 hours in those 1 to 4 weeks of age. In infants, the $T_{1/2}$ is 1.6 hours. In the infant, a level of 7 μg/ml is present 8 hours after a 50 mg/kg dose (209, 210).

Moxalactam is widely distributed to body fluids and has been found in bile, pleural fluid, interestitial fluid, and aqueous humor (211–214). Concentrations in CSF of infants have been 2.3 to 33.7 μg/ml 1 to 2 hours after a 50 mg/kg dose and represent 10% of CSF level at 2 hours and 20% at 5 to 6 hours. Levels in the CSF of adults have been in excess of 25 μg/ml 2 hours after a 2 g IV dose.

Clinical Efficacy

Clinical studies of moxalactam in the United States have yielded response rates of 83 to 94% (213, 215–217) (Table 5). Clinical cures of 77 to 80% have occurred in urinary tract infections due to *E. coli, K. pneumoniae, Enterobacter,* and *P. mirabilis,* but only 58% in those due to *P. aeruginosa.* Lower respiratory infections due to *S. pneumoniae, H. influenzae, Klebsiella, Enterobacter, E. coli* and *S. aureus* pneumonitis have been cured. But only 58% of *P. aeruginosa* pulmonary infections were cured. Satisfactory responses for intra-abdominal infections occured in 91% of patients, with excellent response in all the *Bacteroides* infections. Similarly, there was a 96% response rate in 106 patients with bacteremia. *E. coli, Klebsiella, Enterobacter, Serratia, P. mirabilis, S. aureus,* and *S. pneumoniae* responded, as did six *P. aeruginosa.* The response of 18 patients with meningitis, 5 due to *E. coli,* 3, to *K. pneumoniae,* 3 of 4, to *S. marcescens,* and 2 to *E. cloacae* (94%) was far better than reported for other classes of antibiotics (218).

Adverse Effects

The adverse effects in 3,558 patients have been small (217). Hematologic adverse effects included eosinophilia (2–6%), hypoprothrombinemia (0.7%), and leukopenia (0.4%). Rash was extremely uncommon, with all types of hypersensitivity occurring in only 2.9%. An antabuse reaction occurred infrequently. But this reaction can occur as much as 48 hours after the last dose of moxalactam, since the methyltetrazolythio group will inhibit the enzyme acetaldehyde dehydrogenase and cause accumulation of acetaldehyde (219, 220). Diarrhea occurred in only 2% of patients and there has been pseudomembranous colitis. Whether moxalactam actually

causes any renal toxicity is unclear, since only 1.8% of patients had any such reactions.

Overgrowth of enterococci with serious infection occurred in a small number of patients (221). *Candida* superinfection also was found in a small number of patients who were immunosuppressed and had received large doses of the compound.

CEFOTIAM AND CEFMETAZOLE

Cefamandole (222), cefuroxime (223), and cefoxitin (224) have seen extensive use in clinical medicine and reviews of their activity have been published. There are several other agents, such as cefotiam and cefmetazole (Figure 9), which are still in the process of clinical evaluation which I will not review in detail. Cefotiam has some properties which make it similar in some ways to cefamandole (225, 226). It has inhibited *S. aureus* at concentrations < 1 μg/ml and also most *S. pneumoniae* and *S. pyogenes.* Although it is poorly hydrolyzed by plasmid β-lactamases of *E. coli* and is active against *Klebsiella* and *P. mirabilis,* it has had MICS tenfold higher than for cefotaxime, ceftizoxime, cefoperazone, and moxalactam. Furthermore, most *Enterobacter,* indole-positive *Proteus, Morganella,* and *C. freundii* are resistant. Activity of cefotiam against gram positive anaerobes is good, but it has not inhibited *Bacteroides fragilis* and it has been inactive against *Pseudomonas.* It is somewhat more stable to β-lactamases of the Richmond Ia, II, and III types than is cefoperazone, but lacks the latter's ability to bind to receptor PBPs and to enter outer cell membranes. The pharmacology of the agent has shown it to have a relatively short half-life, 1 hour, and to have pharmacokinetics similar to agents such as cephalothin (227, 228). Clinical studies of its efficacy are in progress.

Cefmetazole in essence is similar to cefoxitin with better MICs against gram positive species and twofold lower MICs against *E. coli* and *Klebsiella* (229, 230). It has no *Enterobacter* or *Pseudomonas* activity. Its anaerobic activity is twofold less than that of cefoxitin against *Bacteroides.* It is as β-lactamase-stable as cefoxitin (230). Blood levels after 1 g given by intravenous infusion over 1 hour have been approximately 75 μg at 1 hour, and 2.4 μg/ml at 6 hours, with a half-life of 0.81 hours (231). The half-life increases in patients with anuria to 15 hours. In normals approximately

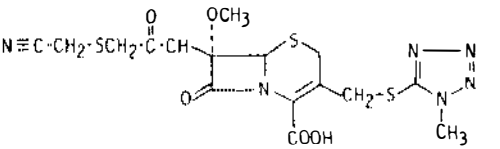

Figure 9 Cefmetazole (CS-1170).

70% of a dose is excreted in 6 hours. The presence of the methyl thiotetrazole side chain would suggest that it can cause antabuse reactions and bleeding.

OTHER β-LACTAM AGENTS

n-Formimidoyl Thienamycin

Thienamycin was a most promising antibacterial compound which unfortunately was not stable at high concentrations (232, 233). The development of *n*-formimidoyl thienamycin (Figure 10) yielded a derivative which retained the antibacterial activity of the parent compound and yet was stable (234–238). *n*-Formimidoyl thienamycin has shown remarkable gram positive activity, inhibiting not only β-lactamase positive isolates of *S. aureus,* but also methicillin-resistant isolates at concentrations below 2 μg/ml (236, 238). It has shown extremely excellent activity against streptococci and even inhibited 90% of *S. faecalis* at 2 μg/ml (234–238). Overall, with the exception of *Proteus* and *Providencia,* the compound had inhibited 90% of isolates at $\leq$ 1 μg/ml, and 50% at $\leq$ 0.2 μg/ml. *Proteus* species require 4 μg/ml to inhibit 90%. The compound also has shown remarkable activity against *P. aeruginosa,* inhibiting moxalactam and cefoperazone resistant strains, with 90% inhibited by 8 μg/ml (234–239). It has inhibited other *Pseudomonas* with the exception of *P. maltophilia.* It inhibited *Acinetobacter* resistant to all other β-lactams. Its anaerobic activity has been extensive, inhibiting 90% of *Bacteroides* at $\leq$ 1 μg/ml.

n-Formimidoyl thienamycin is β-lactamase-resistant and also acts as an effective inhibitor of selected β-lactamases. It is equivalent to clavulanic acid in some aspects, acting as a suicide molecule (237, 238).

n-Formimidoyl thienamycin is hydrolyzed in humans during excretion by a dipeptidase in the kidney (240). A series of specific enzyme inhibitors or the dipeptidase have been developed which can be administered to block peptidase activity and restore renal concentrations (241). To date no clinical studies of the use of the compound have been published.

Monobactams

Monobactams are a recently reported group of compounds which are synthetic analogues of a compound produced by a bacterium, *Chromobacterium violaceum* (242). The addition of an aminothiazoly group and the carboxy propyl oxyimino group have yielded a compound which has no activity against gram positive bacteria nor anaerobic bacteria, but which has

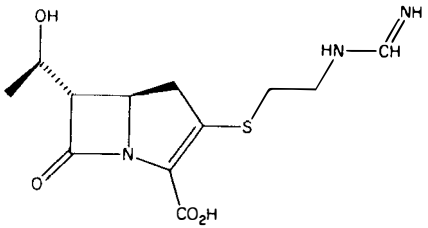

Figure 10 *n*-Formimidoyl thienamycin (MK0787).

remarkable activity against aerobic gram negative bacteria of the *Enterobacteriaceae* and *P. aeruginosa* (243–246).

The compound inhibited 90% of *Enterobacteriaceae* at concentrations below 1 μg/ml. Indeed, it inhibited 90% of *Serratia* at 3.1 μg/ml, where the concentration of cefoperazone was > 100 μg/ml and moxalactam and cefotaxime MIC_{90} was 25 μg/ml (243, 244, 246). It also inhibited cefsulodin- and cefoperazone-resistant *P. aeruginosa* (243–246). *H. influenzae* and *N. gonorrheae* were inhibited at ≤ 0.2 μg/ml.

Azthreonam is stable to all plasmid β-lactamases and acts as a competitive inhibitor of some type I β-lactamases (243–245). Only the K1 β-lactamase of some *Klebsiella* and *Enterobacter* will cause partial hydrolysis.

Combination of Azthreonam with other β-lactams such as nafcillin, clindamycin, and metronidazole, and with other agents such as aminoglycosides did not affect MIC values (H. C. Neu, in preparation). Different media and serum do not alter MIC nor MBC values. There is no appreciable difference between MIC and MBC values. The compound binds preferentially to PBP 3 so that long filaments which are unable to grow develop. Azthreonam lacks activity against gram positive bacteria because of failure to bind to PBPs.

Preliminary pharmacologic data have shown that mean blood levels of 58 μg/ml occur after a 500 mg bolus injection and 242 μg/ml after a 2 g injection. The half-life is 1.5–1.8 hours (247). Urine levels are > 140 μg/ml for 8 hours after a 500 mg dose. Clinical studies are in progress.

SUMMARY

A number of new β-lactam agents have become available in the past several years. Most of the agents discussed are still undergoing clinical investigation. Major advances in the antibacterial activity and clinical pharmacology has been achieved by molecular modifications. Fortunately, toxicity has rarely accompanied these changes and β-lactam would appear to be the antibacterial agents for the 1980s.

Literature Cited

1. Finland, M. 1979. Emergence of antibiotic resistance in hospitals, 1935–1975. *Rev. Infect. Dis.* 1:4–21
2. O Brien, T. F., Acar, J. F., Mederios, A. A., Norton, R. A., Goldstein, F., Kent, R. L. 1978. International comparison of prevalence of resistance to antibiotics. *J. Am. Med. Assoc.* 239:1518–23
3. Williams, J. D. 1977. Changing antibiotic susceptibility of common bacteria. *Practitioner* 11:102–8
4. Neu, H. C. 1981. The pharmacology and toxicology of antimicrobial agents. In *Medical Microbiology Infectious Diseases,* ed. A. Braude, pp. 257–74. Philadelphia: Saunders
5. Aoki, H., Okuhura, M. 1980. Natural β-lactam antibiotics. *Ann. Rev. Microbiol.* 34:159–81
6. Bryan, L. E. 1979. Resistance to antimicrobial agents: the general nature of the problem and the basis of resistance in *Pseudomonas aeruginosa.* In *Pseudomonas aeruginosa: Clinical Manifestations of Infection and Therapy,* ed. R. G. Doggett, pp. 219–70 New York: Academic. 504 pp.
7. Nikaido, H. 1979. Nonspecific transport through the outer membrane. In *Bacterial Outer Membrane,* ed. M. Inovye, pp. 361–407. New York: Wiley
8. Ghuysen, J.-M., Frère, J.-M., Leyh-Bouille, M., Coyette, J., Dusart, J. Nguyen-Distèche, M. 1979. Use of model enzymes in the determination of the mode of action of penicillins and Δ^3-cephalosporins. *Ann. Rev. Biochem.* 48:73–101
9. Neu, N. C. 1981. Mechanisms of bacterial resistance of antimicrobial agents with particular reference to β-lactam compounds. *Rev. Infect. Dis.* In press
10. Curtis, N. A. C., Orr, D., Ross, G. W., Boulton, M. G. 1979. Affinities of penicillins and cephalosporins for the penicillin-binding proteins of *Escherichia coli* K-12 and their antibacterial activity. *Antimicrob. Agents Chemother.* 16:533–39
11. Spratt, B. G. 1975. Distinct penicillin binding proteins involved in division, elongation and shape of *Escherichia coli* K-12. *Proc. Natl. Acad. Sci. USA* 72:2999–3003
12. Sykes, R. B., Matthew, M. 1976. The beta-lactamases of gram-negative bacteria and their role in resistance to beta-lactam antibiotics. *J. Antimicrob. Chemother.* 2:115–17
13. Spratt, B. G. 1980. Biochemical and genetical approaches to the mechanism of action of penicillin. *Philos. Trans. R. Soc. London* 289:273–83
14. Nakano, H. 1981. Structure-activity relationships related to ceftizoxime (FK 749). *Med. Res. Rev.* 2:127–57
15. Bucourt, R., Bormann, D., Heymes, R., Perronnet, M. 1980. Chemistry of cefotaxime. *J. Antimicrob. Chemother.* 6(S): 63–67
16. O'Callaghan, C. H. 1980. Structure-activity relations and β-lactamase resistance. *Philos. Trans. R. Soc. London* 289:197–205
17. Jones, R. N., Thornsberry, C. 1981. Cefotaxime (HR 756): A review of the in vitro antimicrobial properties and spectrum of activity. *Rev. Infect. Dis.* In press
18. Neu, H. C., Aswapokee, N., Aswapokee, P., Fu, K. P. 1979. HR 756, a new cephalosporin active against gram-positive and gram-negative aerobic and anaerobic bacteria. *Antimicrob. Agents Chemother.* 15:273–81
19. Sosna, J. P., Murray, P. R., Medoff, G. 1978. Comparison of the in vitro activities of HR 756 with cephalothin, cefoxitin and cefamandole. *Antimicrob. Agents Chemother.* 14:876–79
20. Hamilton-Miller, J. M. T., Brumfitt, W., Reynolds, A. V. 1978. Cefotaxime (HR 756), a new cephalosporin with exceptional broad-spectrum activity in vitro. *J. Antimicrob. Chemother.* 4: 437–44
21. Wise, R., Rollason, T., Logan, M., Andrews, J. M., Bedford, K. A. 1978. HR 756, a highly active cephalosporin: Comparison with cefazolin and carbenicillin. *Antimicrob. Agents Chemother.* 14:807–11
22. Yourassowsky, E., VanDerLinden, M. P., Lismont, M. J., Crokaert, F. 1980. Activity of ten cephalosporins on biomass of methicillin-susceptible and resistant *Staphylococcus aureus. Antimicrob. Agents Chemother.* 17:856–60
23. Mouton, R. P., Bongaerts, G. P., vanGestel, M. 1979. Comparison of activity and beta-lactamase stability of cefotaxime with those of six other cephalosporins. *Antimicrob. Agents Chemother.* 16:757–60
24. Masuyoshi, S., Arai, S., Miyamoto, M., Mitsuhashi, S. 1980. In vitro antimicrobial activity of cefotaxime, a new cephalopsorin. *Antimicrob. Agents Chemother.* 18:1–8
25. Lang, S. D. R., Edwards, D. J., Durack, D. T. 1980. Comparison of cefoperazone, cefotaxime and moxalactam (LY

127935) against aerobic gramnegative bacilli. *Antimicrob. Agents Chemother.* 17:488–93

26. VanLanduyt, H. W., Pyckavet, M. 1979. In vitro activity of cefotaxime against cephalothin-resistant clinical isolates. *Antimicrob. Agents Chemother.* 16:109–11
27. Counts, G. W., Turck, M. 1979. Antibacterial activity of a new parenteral cephalosporin—HR 756. Comparison with cefamandole and ceforanide. *Antimicrob. Agents Chemother.* 16:64–68
28. Heymes, R., Lutz, A., Schrinner, E. 1977. Experimental evaluation of HR 756, a new cephalosporin derivative: pre-clinical study. *Infection* 5:259–60
29. Drasar, F. A., Farrell, W., Howard, A. J., Hince, C., Leung, T., Williams, J. D. 1978. Activity of HR 756 against *Haemophilus influenzae,* Bacteroides fragilis and gram-negative rods. *J. Antimicrob. Chemother.* 4:445–50
30. Heymes, R., Bucourt, R., Lutz, A., Penasse, L., Perronnet, J. 1979. Considerable magnification of the antibacterial activity of cephalosporin derivatives with 3-amino-4-thiazolyl acetyl side chain by introduction of a syn alkoxy imino group (HR 756). *Drugs Exp. Clin. Res.* 5:23–30
31. Chabbert, Y. A., Lutz, A. J. 1978. HR 756, the syn isomer of the new methoxy imino cephalosporin with unusual antibacterial activity. *Antimicrob. Agents Chemother.* 14:749–54
32. Dabernat, H. J., Buu-Hoi-Dang Van, A., Delmas, C., Bauriaud, R. 1979. Comparative activities of cefotaxime, a new cephalosporin derivative and of selected beta-lactam antibiotics against *Haemophilus* species. *Ann. Microbiol.* 130:461–67
33. Howard, A. J., Hince, C., Williams, J. D. 1979. The susceptibility of *Haemophilus influenzae* to HR 756 compared with four other cephalosporins and cefoxitin and the influence of a new compound CP-45, 899 on the inhibitory activity of ampicillin on beta-lactamase producing strains. *Drug Exp. Clin. Res.* 5:7–11
34. Jorgensen, J. H., Crawford, S. A., Alexander, G. A. 1980. In vitro activities of cefotaxime and moxalactam (LY 127935), against *Haemophilus influenzae. Antimicrob. Agents Chemother. 17:516–17*
35. Baker, C. N., Thornsberry, C., Jones, R. N. 1980. In vitro antimicrobial activity of cefoperazone, cefotaxime, moxalactam (LY 127935), azlocillin, mezlocillin and other beta-lactam antibiotics against *N. gonorrhoeae* and *H. influenzae,* including beta-lactamase-producing strains. *Antimicrob. Agents Chemother.* 17:757–61
36. Piot, P., vanDyck, E., Colaert, J., Ursi, J. P., Bosmans, E., Meheus, A. 1979. Antibiotic susceptibility of *Neisseria gonorrhoeae* strains from Europe and Africa. *Antimicrob. Agents Chemother.* 15:535–39
37. Milatovic, D., Machka, K., Galla, O., Braveny, I. 1978. Beta-lactamase producing gonococci in Munich. *Infection* 6:242–43
38. Tan, R. J. S., Sng, E. H., Rajan, V. S., Lim, A. L., Yeo, K. L., Lim, E. W. 1978. Evaluation of cefotaxime (HR 756)—a new cephalosporin—against penicillinase producing strains of *Neisseria gonorrhoeae. Asian J. Infect. Dis.* 2:239–41
39. Fu, K. P., Neu, H. C. 1979. The comparative beta-lactamase resistance and inhibitory activity of 1-oxa cephalosporin, cefoxitin and cefotaxime. *J. Antibiot.* 32:909–14
40. Minami, S., Yotsuji, A., Inoue, M., Mitsuhashi, S. 1980. Induction of beta-lactamase by various beta-lactam antibiotics in *Enterobacter cloacae. Antimicrob. Agents Chemother.* 18:382–85
41. Lang, S. D. R., Durack, D. T. 1980. In vitro efficacy of cefoperazone compared with cefotaxime, LY 127935, and thienamycin. *Clin. Ther. 3(S):112–16*
42. Legakis, N. J., Kafetzia, A., Papadatos, C. J., Papavassiliou, J. T. 1980. Antibacterial activity of HR 756, cefoxitin and cefuroxime against multiple antibiotic resistant strains of *Enterobacteriaceae* and *Pseudomonas aeruginosa. Chemotherapy* 26:334–43
43. Hall, W. H., Opfer, B. J., Gerding, D. N. 1980. Comparative activities of the oxa-beta-lactam LY 127935, cefotaxime, cefoperazone, cefamandole, and ticarcillin against multiply resistant gram-negative bacilli. *Antimicrob. Agents Chemother.* 17:273–97
44. Jorgensen, J. H., Crawford, S. A., Alexander, G. A. 1980. In vitro activities of moxalactam and cefotaxime against aerobic gram-negative bacilli. *Antimicrob. Agents Chemother.* 17:937–42
45. Goldstein, E. J. C., Gombert, M. E., Agyare, E. O. 1980. Susceptibility of *Eikenella corrodens* to newer beta-lactam antibiotics. *Antimicrob. Agents Chemother.* 18:832–33
46. Hoffler, U., Niederau, W., Pulverer, G. 1980. Susceptibility of *Bacterium ac-*

tinomycetem comitans to 45 antibiotics. *Antimicrob. Agents Chemother.* 17: 943–46
47. Stephens, M., Potten, M., Bint, A. J. 1979. The sensitivity of gentamicin-resistant gram-negative bacilli to cefotaxime, other cephalosporins and aminoglycosides. *Infection* 7:109–12
48. Walder, M. 1979. Susceptibility of *Campylobacter* fetus *subsp. jejuni* to twenty antimicrobial agents. *Antimicrob. Agents Chemother.* 16:37–39
49. Yourassowsky, E., VanDerLinden, M. P., Lismont, M. J., Crokaert, F. 1980. The antimicrobial activity of the cephalosporin CGP 7174/E against *Pseudomonas aeruginosa* in comparison to carbenicillin, piperacillin and cefotaxime. *Curr. Ther. Res. Clin. Exp.* 28:203–7
50. Barza, M., Tally, F. P., Jacobus, N. V., Gorbach, S. L. 1979. In vitro activity of LY 127935. *Antimicrob. Agents Chemother.* 16:287–92
51. Jacobus, N. V., Tally, F. P., Barza, M., Gorbach, S. L. 1980. Susceptibility of anerobic bacteria to cefoperazone and other beta-lactam antibiotics. *Clin. Ther.* 3(S):34–38
52. Jorgensen, J. H., Crawford, S. A., Alexander, G. A. 1980. Comparison of moxalactam (LY 127935) and cefotaxime against anaerobic bacteria. *Antimicrob. Agents Chemother.* 17:901–4
53. Borobio, M. V., Aznar, J., Jimenez, R., Garcia, F., Perea, E. J. 1980. Comparative in vitro activity of l-oxa beta-lactam (LY 127935) and cefoperazone with other beta-lactam antibiotics against anaerobic bacteria. *Antimicrob. Agents Chemother.* 17:129–31
54. Dornbush, K., Nord, C. E., Olsson-Liljeqvist, B. 1970. Antibiotic susceptibility of anaerobic bacteria with special reference to *Bacteroides fragilis. Scand. J. Infect. Dis.* 19:17–25
55. Pechere, J. C., Guay, R., Dubois, J., Letarte, R. 1980. Hydrolysis of cefotaxime by a beta-lactamase from *Bacteroides fragilis. Antimicrob. Agents Chemother.* 17:1001–3
56. Wise, R., Wills, P. J., Andrews, J. M., Bedford, K. A. 1980. Activity of the cefotaxime (HR 756) desacetyl metabolite compared with those of cefotaxime and other cephalosporins. *Antimicrob. Agents Chemother.* 17:84–86
57. Neu, H. C. 1981. Activity of desacetyl cefotaxime and its synergy with cefotaxime. *Rev. Infect. Dis.* In press
58. Shah, P. M., Troche, G., Stille, W. 1979. Effect of concentration on bactericidal activity of cefotaxime. *J. Antimicrob. Chemother.* 5:419–22
59. Aswapokee, N., Aswapokee, P., Neu, H. C., Fu, K. P. 1979. Diffusion disk susceptibility testing with cefotaxime. *Antimicrob. Agents Chemother.* 16: 164–66
60. Fuchs, P. C., Barry, A. L., Thornsberry, C., Jones, R. N., Gavan, T. L., Gerlach, E. H., Sommers, H. M. 1980. Cefotaxime: in vitro activity and tentative interpretive standards for disk susceptibility testing. *Antimicrob. Agents Chemother.* 18:88–93
61. Fu, K. P., Neu, H. C. 1978. Beta-lactamase stability of HR 756, a novel cephalosporin, compared to that of cefuroxime and cefoxitin. *Antimicrob. Agents Chemother.* 14:322–26
62. Waterworth, P. M., Emmerson, A. M. 1979. Dissociated resistance among cephalosporins. *Antimicrob. Agents Chemother.* 15:497–503
63. Kojo, H., Shigi, Y., Nishida, M. 1979. *Enterobacter cloacae* outer membrane permeability to ceftizoxime (FK 749) and five other new cephalosporin derivatives. *J. Antibiot.* 33:317–21
64. Georgopapadakou, N. H., Liu, F. Y. 1980. Binding of beta-lactam antibiotics to penicillin-binding proteins of *Staphylococcus aureus* and *Streptococcus faecalis:* relation to antibacterial activity. *Antimicrob. Agents Chemother.* 18:834–36
65. Murray, P. R. 1980. Activity of cefotaxime-aminoglycoside combinations against aminoglycoside-resistant *Pseudomonas. Antimicrob. Agents Chemother.* 17:474–76
66. Fu, K. P., Aswapokee, P., Ho, I., Matthijssen, C., Neu, H. C. 1979. Pharmacokinetics of cefotaxime. *Antimicrob. Agents Chemother.* 16:572–97
67. Neu, H. C., Aswapokee, P., Fu, K. P., Ho, I., Matthijssen, C. 1980. Cefotaxime kinetics after intravenous and intramuscular injection of single and multiple doses. *Clin. Pharm. Ther.* 27: 677–85
68. Luthy, R., Munch, R., Blaser, J., Blend, H., Segenthaler, W. 1979. Human pharmacology of cefotaxime (HR 756), a new cephalosporin. *Antimicrob. Agents Chemother.* 16:127–33
69. Fillaste, J. P., Leroy, A., Humbert, G., Godin, M. 1981. Pharmacokinetics of cefotaxime in subjects with normal and impaired renal function. *J. Antimicrob. Chemother.* 6(S):103–11
70. Esmieu, F., Guibert, J., Rosenkilde, H. C., Ho, I., LeGo, M. 1980. Pharmacoki-

netics of cefotaxime in normal subjects. *J. Antimicrob. Chemother.* 6(S):83–92
71. Reeves, D. S., White, L. O., Holt, H. A., Bahari, D., Bywater, M. J., Bax, R. P. 1980. Human metabolism of cefotaxime. *J. Antimicrob. Chemother.* 6(S): 93–101
72. Soussy, C. J., Deforges, L. P., VanThoi, J., Feghali, W., Duval, J. R. 1980. Cefotaxime concentration in the bile and wall of the gallbladder. *J. Antimicrob. Chemother.* 6(S):125–30
73. Novick, W. J. 1981. Tissue levels of cefotaxime sodium: a review. *Rev. Infect. Dis.* In press
74. Kosmidis, J., Stathakis, C., Mantopoulos, K., Pouriezi, T., Papathanassiou, B., Daikos, G. K. 1980. Clinical pharmacology of cefotaxime penetration into bile, sputum, bone and including cerebrospinal fluid. *J. Antimicrob. Chemother.* 6(S):145–52
75. Handsfield, H. H. 1981. Treatment of uncomplicated gonorrhoea with cefotaxime. Summary of United States studies. *Rev. Infect. Dis.* In press
76. Cherubin, C. E., Corrado, M., Nair, S. R., Landesman, S., Humbert, G. 1981. The treatment of gram-negative bacillary meningitis. *Rev. Infect. Dis.* In press
77. Doerr, I. M., Glomot, R., Kieff, H., Kramer, M., Sakaguchi, T. 1981. Toxicity studies: a review of preclinical studies and some clinical reports. *Rev. Infect. Dis.* In press
78. Nakano, H., Kumiya, T. 1981. The development of ceftizoxime, a new parenteral cephalosporin. In *β-lactam Antibiotics,* ed. M. Salton, G. D. Shockman, pp. 415–28 604 pp.
79. Fu, K. P., Neu, H. C. 1980. Antibacterial activity of ceftizoxime a β-lactamase-stable cephalosporin. *Antimicrob. Agents Chemother.* 17:583–90
80. Kamimura, T., Matsumoto, Y., Okada, N., Mine, Y., Nishida, M., Gotto S., Kuwahara, S. 1979. Ceftizoxime (FK 749), a new parenteral cephalosporin: in vitro and in vivo antibacterial activities. *Antimicrob. Agents Chemother.* 16: 540–48
81. Greenwood, D., Pearson, N., Eley, A., O'Grady, F. 1980. Comparative in vitro activities of cefotaxime and ceftizoxime (FK 749): new cephalosporins with exceptional potency. *Antimicrob. Agents Chemother.* 17:397–401
82. Ogawa, M., Hama, M., Takata, N., Kosaki, G. 1981. Ceftizoxime (FK 749) a new cephalosporin with potent in vitro activity against gram-negative bacilli. *J. Antimicrob. Chemother.* 7: 673–76
83. Takata, N., Suginaka, H., Kotani, S., Ogawa, M., Kosaki, G. 1981. β-lactam resistance in *Serratia marcescens*—comparison of action of benzylpenicillin, apalcillin, cefazolin and ceftizoxime. *Antimicrob. Agents Chemother.* 19:397–401
84. Yabucchi, E., Ito, T., Tanimura, E., Yamamato, N., Ohyama, A. 1981. In vitro antimicrobial activity of ceftizoxime against glucose non-fermenting gram-negative rods. *Antimicrob. Agents Chemother.* 20:136–39
85. George, W. L., Sutter, V. L., Finegold, S. M. 1981. β-lactam antimicrobials for treatment of anaerobic infections—a review of in vitro activity and therapeutic efficacy. See Ref. 78, pp. 493–530
86. Shigi, Y., Kojo, H., Wakasugi, M., Nishida, M. 1981. Differences between ceftizoxime and its steroisomer in antibacterial activity and affinity for penicillin-binding proteins. *Antimicrob. Agents Chemother.* 19:303–6
87. Neu, H. C., Srinivasan, S. 1981. Human pharmacology of ceftizoxime. *Antimicrob. Agents Chemother.* 20:366–69
88. Yamasuku, F., Suzuki, Y., Takeda, H., Sekine, O., Usuda, Y. 1981. Pharmacokinetics of ceftizoxime (single dose) in adult volunteers and patients with renal dysfunction. *Int. Congr. Chemother., 12th, Florence, 1981.* (Abstr.)
89. Takii, M., Rikitake, O., Otonari, T., Sawae, Y., Okada, K. 1981. Pharmacokinetics of ceftizoxime and its clinical applications in patients undergoing dialysis. See Ref. 88 (Abstr.)
90. Cho, N., Takase, Z. 1981. Pharmacokinetics and clinical evaluation of ceftizoxime in obstetrics and gynecology. See Ref. 88 (Abstr.)
91. Nakatomi, M., Saito, A., Naso, M., Yamaguchi, K., Shigono, Y., Hara, K. 1981. In vitro activity, serum and sputum level and clinical effectiveness of ceftizoxime, a new parenteral cephalosporin. See Ref. 88 (Abstr.)
92. Counts, G., Hill, C. D., Turck, M. 1981. Clinical studies with ceftizoxime. See Ref. 88 (Abstr.)
93. Holloway, W. J. 1981. Ceftizoxime in the treatment of complicated urinary tract infections. See Ref. 88 (Abstr.)
94. Tsuchya, K., Kondo, M., Kida, M., Nakao, M., Iwahi, T., Nishi, T., Noji, Y., Takeuchi, M., Nozaki, Y. 1981. Cefmanoxime (SCE-1365), a novel broad spectrum cephalosporin: in vitro and in

vivo antibacterial activities. *Antimicrob. Agents Chemother.* 19:56–65
95. Stamm, J. M., Girolami, R. L., Shipkowitz, N. L., Bower, R. R. 1981. Antibacterial activity of cefmenoxime (SCE-1365). *Antimicrob. Agents Chemother.* 19:454–60
96. Verbist, L. 1981. Comparison of in vitro activities of eight β-lactamase stable cephalosporins against β-lactamase producing gram-negative bacilli. *Antimicrob. Agents Chemother.* 19:407–13
97. Neu, H. C., Labathavikul, P. 1981. The in vitro activity and β-lactamase stability of cefmenoxime compared to that of other β-lactams and aminoglycosides. *Antimicrob. Agents Chemother.* In press
98. Fuchs, P. C., Jones, R. N., Thornsberry, C., Barry, A. L., Gerlach, E. H., Sommers, H. M. 1981. Cefmenoxime (SCE 1365), a new cephalosporin, in vitro activity comparison with other antimicrobics, beta-lactamase stability and disk diffusion testing with tentative interpretive criteria. *Antimicrob. Agents Chemother.* In press
99. Angehrin, P., Probst, P. J., Reiner, R., Then, R. L. 1980. Ro 13-9904, a long-acting broad spectrum cephalosporin: in vitro and in vivo studies. *Antimicrob. Agents Chemother.* 18:913–21
100. Shannon, K., King, A., Warren, C., Phillips, I. 1980. In vitro antibacterial activity and susceptibility of the cephalosporin Ro 13-9904 to beta-lactamases. *Antimicrob. Agents Chemother.* 18:292–98
101. Hinkle, A. M., Bodey, G. P. 1980. In vitro evaluation of Ro 13-9904. *Antimicrob. Agents Chemother.* 18:577–78
102. Neu, H. C., Meropol, N. J., Fu, K. P. 1981. Antibacterial activity of ceftriaxone (Ro 13-9904), a β-lactamase stable cephalosporin. *Antimicrob. Agents Chemother.* 19:414–23
103. Greenwood, D., Eley, A. 1981. Activity of a new cephalosporin antibiotic, Ro 13-9904, against dense populations of selected Enterobacteria. *Antimicrob. Agents Chemother.* 19:66–71
104. Wise, R., Gillett, A. P., Andrew, J. M., Bedford, K. A. 1981. Ro 13-9904: a cephalosporin with a high degree of activity and broad antibacterial activity: an in vitro comparative study. *J. Antimicrob. Chemother.* 6:595–600
105. Clarke, A. M., Zencov, S. J. V. 1981. Ro 13-9904 and GR 20263, two new cephalosporins with broad-spectrum activity, an in vitro comparison with other β-lactam antibiotics. *J. Antimicrob. Chemother.* 7:515–20
106. Stoeckel, K. 1981. Pharmacokinetics of rocephin, a highly active new cephalosporin with an exceptionally long biological half-life. *Chemotherapy* 27(S):42–46
107. Patel, I. H., Miller, K., Weinfeld, R., Spicehandler, J. 1981. Multiple intravenous dose pharmacokinetics of ceftriaxone in man. *Chemotherapy* 27(S):47–56
108. Seddon, M., Wise, R., Gillett, A. P., Livingston, R. 1980. Pharmacokinetics of Ro 13-9904, a broad-spectrum cephalosporin. *Antimicrob. Agents Chemother.* 18:240–42
109. Stoeckel, K., McNamara, P. J., Brandt, R., Plozza-Nottebrock, H., Ziegler, W. H. 1981. Effects of concentration-dependent plasma protein binding on ceftriaxone kinetics. *Clin. Pharmacol. Ther.* 29:650–57
110. Henning, C., Holm, S. E. 1981. Penetration of ^{14}C Ro 13-9904 into tissue cage fluid in rabbits. *Chemotherapy* 27(S): 32–36
111. Marchow, B., Tran Van Thou, A., Armengaud, M. 1981. Diffusion of cefriaxone (RO 13-9904) in the cerebrospinal fluid. Comparison with other β-lactam antibiotics in dogs with healthy meninges and in dogs with experimental meningitis. *Chemotherapy* 27(S):37–41
112. Giamarellou, H., Poulopoulos, B., Katsabas, A., Petrikkos, G., Papapetropoulou, M., Daikos, G. K. 1981. Antibacterial activity of Ro 13-9904 and preliminary experience in gonorrhoea and chronic urinary tract infections. *Chemotherapy* 27(S):70–74
113. Keller, R., Humair, L. 1981. Treatment of severe lower respiratory tract infections with ceftriaxone (Ro 13-9904): a pilot study. *Chemotherapy* 27(S):93–99
114. Cadoz, M., Denis, F., Felix, H., Diop Mar, I. 1981. Treatment of purulent meningitis with a new cephalosporin—Rocephin (Ro 13-9904)—clinical bacteriological and pharmacological observations in 24 cases. *Chemotherapy* 27(S):57–61
115. O'Callaghan, C. H., Acred, P., Harper, P. B., Ryan, D. M., Kirby, S. M., Harding, S. M. 1980. GR 20263, a new broad-spectrum cephalosporin with anti-pseudomonal activity. *Antimicrob. Agents Chemother.* 17:876–83
116. Hamilton-Miller, J. M. T., Brumfitt, W. 1981. Activity of ceftazidime (GR 20263) against nosocomially important pathogens. *Antimicrob. Agents Chemother.* 19:1067–69
117. Verbist, L., Verhaegen, J. 1981. In vitro activity of *n*-formimidoyl thienamycin

in comparison with cefotaxime, moxalactam and ceftazidime. *Antimicrob. Agents Chemother.* 19:402–6

118. Verbist, L., Verhaegen, J. 1980. GR 20263: a new aminothiazolyl cephalosporin with high activity against *Pseudomonas* and *Enterobacteriaceae. Antimicrob. Agents Chemother.* 17: 807–12
119. Wise, R., Andrews, J. M., Bedford, K. A. 1980. Comparison of in vitro activity of GR 20263, a novel cephalosporin derivative with activities of other beta-lactam compounds. *Antimicrob. Agents Chemother.* 17:B884–89
120. Neu, H. C., Labthavikul, P. 1982. Ceftazidime, activity and beta-lactamase stability compared to other β-lactam antibiotics. *Antimicrob. Agents Chemother.* 21:11–18
121. Harding, S. M., Muro, A. J., Thorton, J. E., Ayrton, J., Hogg, M. T. J. 1981. The comparative pharmacokinetics of ceftazidime and cefotaxime in healthy volunteers. *J. Antimicrob. Chemother.* 8(Suppl. B):263–72
122. Wise, R., Armstrong, G. C., Andrews, J. M., Brown, R. M. 1981. The pharmacokinetics and tissue penetration of ceftadime and cefamandole in healthy volunteers. See Ref. 121, pp. 277–82
123. Luthy, R., Blaser, J., Bonnetti, A., Simmer, H. R., Wise, R., Siegenthaler, W. 1981. Human pharmacokinetics of ceftazidime in comparison to moxalactam and cefotaxime. See Ref. 121, pp. 273–76
124. Ryan, D. M., Mason, U., Harding, S. M. 1981. The penetration of ceftazidime into extravascular fluid. See Ref. 121, pp. 283–88
125. Wittman, D. H., Schassan, H. H., Koshler, F. 1981. The penetration of ceftazidime into bone, bile, tissue fluid and peritoneal fluid. See Ref. 121, pp. 293–98
126. Daikos, G. K., Kosmidis, J., Stathakis, C., Gimarellou, H., Douzinas, E., Kastanakis, S., Eliades, K. 1981. Ceftazidime: Therapeutic results in various infections and studies. See Ref. 121, pp. 331–38
127. DeSande, G., Corrocher, R., Gabrielli, G. B., Ho, I. 1981. Clinical experience on the use of ceftazidime in lower respiratory tract infections. See Ref. 121, pp. 307–10
128. Neu, H. C., Fu, K. P. 1979. In vitro antibacterial activity and β-lactamase stability of SCE-129, a new cephalosporin. *Antimicrob. Agents Chemother.* 15:646–50
129. Tsuchiya, K., Kondo, M. 1978. Comparative in vitro activity of SCE-129, sulbenicillin, gentamicin and dibekacin against *Pseudomonas. Antimicrob. Agents Chemother.* 13:536–39
130. King, A., Shannon, K., Phillips, I. 1980. In vitro antibacterial activity and susceptibility of cefsulodin, an antipseudomonal cephalosporin to beta-lactamases. *Antimicrob. Agents Chemother.* 17:165–69
131. Watt, B., Brown, F. V. 1981. The comparative activity of cefsulodin against anaerobic bacteria of clinical interest: synergy with cefoxitin. *J. Antimicrob. Chemother.* 7:269–78
132. Slack, M. P. E., Whedon, D. B., Swann, R. A., Perks, E. 1979. Cefsulodin, a new cephalosporin with specific antipseudomonal activity: in vitro studies of the drug alone and in combination. *J. Antimicrob. Chemother.* 5:687–91
133. Zak, O. 1980. *Antibiotics and Pseudomonas aeruginosa in Pseudomonas aeruginosa. ed.* L. D. Sabath, pp. 133–59. Bern: Hans Huber 264 pp.
134. Zimmerman, W. 1979. Penetration through the gram-negative cell wall: a co-determinant of the efficacy of beta-lactam antibiotics. *Int. J. Clin. Pharmacol. Biopharmacol.* 17:131–34
135. Suginaka, H., Shimatani, M., Kotani, S., Ogawa, M., Hama, M., Kosaki, G. 1979. Antibacterial mechanisms of cefsulodin against *Pseudomonas aeruginosa* and *Escherchia coli. FEMS Microbiol. Lett.* 5:177–79
136. Mashimoto, K., Tuguchi, T., Nakano, Y., Yamamoto, T., Yamaguchi, N. 1977. Pharmacology of SCE-129, a new cephalosporin antibiotic in human volunteers. *Curr. Chemother.* 1:841–42
137. Schoeller, J. P., Fillastre, J. P., Humbert, G., Lecaillon, J. B. 1981. Pharmacokinetics of cefsulodin in patients with renal insufficiency. See Ref. 88 (Abstr.)
138. Michalson, M., Bergan, T. 1981. Effect of cystic fibrosis on the pharmacokinetics of cefsulodine (CGP 7174/E). See Ref. 88 (Abstr.)
139. Lecaillon, J. B., Humbert, G., Schoeller, J. P. 1981. Pharmacokinetics of cefsulodin, gentamicin, amikacin after concomittant single IV administration of cefsulodin and one of the two aminoglycosides. See Ref. 88 (Abstr.)
140. Findlay, C. D., Wise, R., Allcock, J. E., Durham, S. R. 1981. The tissue penetration as measured by a blister technique, and pharmacokinetics of cefsulodin compared with carbenicillin and ticar-

cillin. *J. Antimicrob. Chemother.* 7: 637–42
141. Saikawa, I., Mitsuhashi, S. 1981. Studies on new beta-lactam antibiotics having 2,3-diox piperazine group in *β-lactam Antibiotics.* See Ref. 78, pp. 353–60
142. Neu, H. C., Fu, K. P., Aswapokee, N., Aswapokee, P., Kung, K. 1979. Comparative activity and beta-lactamase stability of cefoperazone, a piperazine cephalosporin. *Antimicrob. Agents Chemother.* 16:150–57
143. Wise, R., Gillett, A. P., Andrews, J. M. 1980. A study of the in vitro activity of cefoperazone: a comparison with other beta-lactam antibiotics. *Clin. Ther.* 3(S):149–55
144. Chabbert, Y. A., Collatz, E. 1980. Comparative activity of cefoperazone against selected cephalosporinase-producing enteric bacteria. *Clin. Ther.* 3(S):98–102
145. Jones, R. N., Fuchs, P. C., Barry, A. L., Gavan, T. L., Gerlach, E. H., Sommers, M. S. 1980. Antimicrobial activity and spectrum of cefoperazone against recent clinical isolates. *Clin. Ther.* 3(S):14–23
146. Verbist, L., Verhaegen, J. 1980. GR-20263: A new aminothiazolyl cephalosporin with high activity against *Pseudomonas* and *Enterobacteriaceae. Antimicrob. Agents Chemother.* 17: 807–12
147. Kaye, D., Kobasa, W., Kaye, K. 1980. Susceptibilities of anaerobic bacteria to cefoperazone and other antibiotics. *Antimicrob. Agents Chemother.* 17:957–60
148. Borobio, M. V., Aznar, J., Jimenez, R., Garcia, F., Perea, E. J. 1980. Comparative in vitro activity of 1-oxa-β-lactam (LY 127935) and cefoperazone with other β-lactam antibiotics against anaerobic bacteria. *Antimicrob. Agents Chemother.* 17:129–31
149. Fu, K. P., Neu, H. C. 1981. Synergistic activity of cefoperazone in combination with β-lactamase inhibitors. *J. Antimicrob. Chemother.* 7:287–92
150. Matsubara, N., Minami, S., Matsuhashi, M., Takaoka, M., Mitsuhashi, S. 1980. Affinity of cefoperazone for penicillin-binding proteins. *Antimicrob. Agents Chemother.* 18:195–99
151. Neu, H. C. 1981. A review and summary of the pharmacokinetics of cefoperazone: a new extended spectrum β-lactam antibiotic. *Ther. Drug Mon.* 3: 121–28
152. Shimizu, K. 1980. Cefoperazone: absorption, excretion, distribution and metabolism. *Clin. Ther.* 3(S):60–79
153. *Gen. Cong. Jpn. Soc.* Chemother., *New Drug Symp. I, 27th Fukuoka City, 1979.* pp. 57–95
154. Reeves, D. S., Bywater, M. J., Holt, H. A., White, L. O., Davies, A. J., Elliott, P. J., Foulds, G. 1980. Pharmacokinetics of cefoperazone in man. *Intersci. Conf. Antimicrob. Agents Chemother., 20th, New Orleans, 1980.* (Abstr.)
155. Foster, T. S., Batenhorst, R. L., Raehl, C. L., Wilson, H. D., Goodman, N. L., Haack, D. G., McKean, H. E. 1980. Pharmacokinetics of cefoperazone and the effect on bowel function and flora. *Cefoperazone Symp., New Orleans, 1980*
156. Balant, L., Dayer, P., Rudhardt, M., Allaz, A. F., Fabre, J. 1980. Cefoperazone: pharmacokinetics in humans with normal and impaired renal function and pharmacokinetics in rats. *Clin. Ther.* 3(S):50–59
157. Craig, W. A. 1980. Single-dose pharmacokinetics of cefoperazone following intravenous administration. *Clin. Ther.* 3(S):46-49
158. Lode, H., Kemmerich, B., Koeppe, P., Belmega, D., Jendroschek, H. 1980. Comparative pharmacokinetics of cefoperazone and cefotaxime. *Clin. Ther.* 3(S):80–88
159. Srinivasan, S., Francke, E. L., Neu, H. C. 1980. Comparative pharmacokinetics of moxalactam, cefoperazone, cefotaxime, cefamandole, and cefazolin in normal individuals. See Ref. 154 (Abstr.)
160. Bolton, W. K., Michael, W. M., Merle, M. A. 1980. Pharmacokinetics of cefoperazone in patients with renal insufficiency. See Ref. 155
161. Rosenfeld, M. B., Ratzan, K. R., Lauredo, I. 1980. A comparison of the biliary tract excretion of cefoperazone and cefamandole. See Ref. 154 (Abstr.)
162. Ducroux, A., Pothier, P., Potier, H. 1980. Cefoperazone levels in the human biliary tract. See Ref. 154 (Abstr.)
163. Srinivasan, S., Francke, E. L., Appel, G. B., Saltzman, M., Neu, H. C. 1980. Pharmacokinetics of moxalactam, cefotaxime, cefoperazone in patients with renal insufficiency and undergoing hemodialysis. See Ref. 154 (Abstr.)
164. Bailey, R. R., Peddie, B., Blake, E. 1980. Serum and urine levels of cefoperazone in severe chronic renal failure: single and multiple doses studies. *Int. Conf. Intern. Med., 25th, Hamburg, 1980*
165. Craig, W. A., Gerber, A. U., Barbhaiya, R. H., Welling, P. G. 1980. Pharmacokinetics of cefoperazone in pa-

tients with hepatic dysfunction. See Ref. 155

166. Schaad, U. B., McCracken, G. H. Jr., Loock, C. A., Thomas, M. L. 1981. Pharmacokinetics and bacteriologic efficacy of moxalactam, cefotaxime, cefoperazone, and rocephin in experimental bacterial miningitis. *J. Infect. Dis.* 143: 156-63
167. Perfect, J. R., Durack, D. T. 1981. Pharmacokinetics of cefoperazone, moxalactam, cefotaxime, trimethroprim and sulfamethoxazole in experimental meningitis. *J. Antimicrob. Chemother.* 8:49–58
168. Kamiya, H., Kawamura, Y., Inoue, M., Tanimoto, Y., Sakurai, M., Izawa, T. 1980. Fundamental and clinical studies of cefoperazone in pediatric patients. *Jpn. J. Antibiot.* 33:891–98
169. Kanao, M., Okada, H., Iwasaki, T., Oshima, K., Furuta, N. 1981. Clinical studies on cefoperazone in gynecological and obstetrical field. *Jpn. J. Antibiot.* 34:1–6
170. Kanda, S., Kato, M., Hasegawa, M. 1980. Fundamental and clinical studies on cefoperazone (T-1551) in urinary tract infections. *Chemotherapy* 28(S-6):701–18
171. Kaplowitz, L. G., Sparling, P. L. 1980. Cefoperazone in the treatment of lower respiratory tract infections. Cefoperazone: a clinical review. Program & Abstracts, *Excerpta Med.* p. 11
172. Kawabata, T., Ohi, Y., Obata, M., Goro, T., Naganuma, K., Okamoto, K. 1980. Experimental and clinical studies on cefoperazone (T-1551) in urinary tract infection. *Chemotherapy* 28(S-6):768–78
173. Kawamura, S. 1980. Clinical studies on cefoperazone (T-1551) in various infections of otorhinolargyngological field. *Chemotherapy* 28(S-6):879–82
174. Kawamura, S. 1980. Clinical studies on cefoperazone in otorhinolaryngological field. *Jpn. J. Antibiot.* 33:1313–17
175. Ueda, Y. 1980. Clinical studies on cefoperazone (T-1551). *Chemotherapy Jpn. J. Antibiot.* 28(S-6):369–84
176. Furukawa, S., Okada, T., Hirao, F. 1980. Results of application of cefoperazone to pediatric infections. *Jpn. J. Antibiot.* 33:925–30
177. Cama, L. D., Christensen, B. G. 1974. Total synthesis of β-lactam antibiotics. VII. Total synthesis of (±) oxa-cephalosporin. *J. Am. Chem. Soc.* 96: 7582–84
178. Yoshida, T. 1981. Structure-activity relationships leading to the development of 1-oxacephem 6059-S moxalactam. See Ref. 78, pp. 403–14
179. Murakami, K., Yoshida, T. 1981. Role of the 7α-methoxy and side chain carboxyl of moxalactam in β-lactamase stability and antibacterial activity. *Antimicrob. Agents Chemother.* 19:1–7
180. Yoshida, Y. 1980. Structural requirements for antibacterial activity and β-lactamase stability of 7α-arylmalonylamino-7α-methoxy-1-oxa cephems. *Philos. Trans. R. Soc. London* 289:231–37
181. Sawai, T., Matsuba, K., Tamura, A., Yamagishi, S. 1979. The bacterial outer membrane permeability of β-lactam antibiotics. *J. Antibiot.* 32:59–65
182. Neu, H. C., Aswapokee, N., Fu, K. P., Aswapokee, P. 1979. Antibacterial activity of a new 1-oxa cephalosporin compared with that of other beta-lactam compounds. *Antimicrob. Agents Chemother.* 16:141–49
183. Delgado, D. G., Brau, C. J., Cobbs, C. G., Dismukes, W. E. 1979. In vitro activity of LY 127935, a new 1-oxa cephalosporin, against aerobic gram-negative bacilli. *Antimicrob. Agents Chemother.* 16:864–68
184. Jones, R. N., Fuchs, P. C., Sommers, H. M., Gavan, T. L., Barry, A. L., Gerlach, E. H. 1980. Moxalactam (LY 127935), a new semisynthetic 1-oxa beta-lactam antibiotic with remarkable antimicrobial activity: in vitro comparison with cefamandole and tobramycin. *Antimicrob. Agents Chemother.* 17: 750–56
185. Yoshida, T., Matsuura, S., Mayama, M., Kameda, Y., Kuwahara, S. 1980. Moxalactam (6059-S), a novel 1-oxa-β-lactam with an expanded antibacterial spectrum: laboratory evaluation. *Antimicrob. Agents Chemother.* 17:302–12
186. Trager, G. M., White, G. W., Zimelis, V. M., Panwalker, A. P. 1979. LY 127935: a novel beta-lactam antibiotic with unusual antibacterial activity. *Antimicrob. Agents Chemother.* 16:297–300
187. Reimer, L. G., Mirrett, S., Reller, L. B. 1980. Comparison of in vitro activity of moxalactam (LY 127935) with cefazolin, amikacin, tobramycin, carbenicillin, piperacillin, and ticarcillin against 420 blood culture isolates. *Antimicrob. Agents Chemother.* 17:412–16
188. Jorgensen, J. H., Crawford, S. A., Alexander, G. A. 1980. In vitro activities of moxalactam and cefotaxime against

aerobic gram-negative bacilli. *Antimicrob. Agents Chemother.* 17:937–42

189. Mason, E. O. Jr., Kaplan, S. L., Anderson, D. C., Hinds, D. B., Feigin, R. D. 1980. In vitro susceptibility of 104 clinical isolates of *Haemophilus influenzae* to moxalactam (LY 127935), ampicillin, chloramphenicol, and ticarcillin. *Antimicrob. Agents Chemother.* 17: 470–73
190. Wise, R., Andrews, J. M., Bedford, K. A. 1979. LY 127935, a novel oxa-β-lactam: an in vitro comparison with other β-lactam antibiotics. *Antimicrob. Agents Chemother.* 16:341–45
191. Louie, M. H., Meyer, R. D., Pasiecznik, K. A. 1980. In vitro susceptibility of cephalothin-resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa* to a one-oxa cephalosporin (LY 127935 or moxalactam), amikacin, and selected cephalosporins. *Curr. Microbiol.* 3:301–4
192. Markowitz, S. M., Sibilla, D. J. 1980. Comparative susceptibilities of clinical isolates of *Serratia marcescens* to newer cephalosporins, alone and in combination with various aminoglycosides. *Antimicrob. Agents Chemother.* 18:651–55
193. Baker, C. N., Thornsberry, C., Jones, R. N. 1980. In vitro antimicrobial activity of cefoperazone, cefotaxime, moxalactam (LY 127935), azlocillin, mezlocillin, and other β-lactam antibiotics against *Neisseria gonorrhoeae* and *Haemophilus influenzae,* including β-lactamase-producing strains. *Antimicrob. Agents Chemother.* 17:757–61
194. Jorgensen, J. H., Crawford, S. A., Alexander, G. A. 1980. In vitro activities of cefotaxime and moxalactam (LY 127935) against *Haemophilus influenaze. Antimicrob. Agents Chemother.* 17:516–17
195. Flournoy, D. J., Perryman, F. A. 1979. LY 127935, a new beta-lactam antibiotic, versus *Proteus, Klebsiella, Serratia,* and *Pseudomonas. Antimicrob. Agents Chemother.* 16:641–43
196. Yu, V. L., Vickers, R. M., Zuravleff, J. J. 1980. Comparative susceptibilities of *Pseudomonas aeruginosa* to 1-oxa cephalosporin (LY 127935) and eight other antipseudomonal antimicrobial agents (old and new). *Antimicrob. Agents Chemother.* 17:96–98
197. Felegie, T. P., Yu, V. L., Rumans, L. W., Yee, R. B. 1979. Susceptibility of *Pseudomonas maltophilia* to antimicrobial agents, singly and in combination. *Antimicrob. Agents Chemother.* 16:833–37
198. Edelstein, P. H., Meyer, R. D. 1980. Susceptibility of *Legionella pneumophila* to twenty antimicrobial agents. *Antimicrob. Agents Chemother.* 18: 403–8
199. Brown, J. E., Del Bene, V., Collins, C. D. 1981. In vitro activity of *n*-formimidoyl thienamycin, moxalactam, and other new beta-lactam agents against *Bacteroides fragilis. Antimicrob. Agents Chemother.* 19:248–52
200. Sato, K., Inoue, M., Mitsuhashi, S. 1980. Activity of β-lactamase produced by *Bacteroides fragilis* against newly introduced cephalosporins. *Antimicrob. Agents Chemother.* 17:736–37
201. Richmond, M. H. 1980. The β-lactamase stability of a novel β-lactam antibiotic containing a 7α-methoxyoxacephem nucleus. *J. Antimicrob. Chemother.* 6:445-53
202. Parsons, J. N., Romano, J. M., Levison, M. E. 1980. Pharmacology of a new 1-oxa-β-lactam (LY 127935) in normal volunteers. *Antimicrob. Agents Chemother.* 17:226–28
203. Srinivasan, S., Fu, K. P., Neu, H. C. 1981. Pharmacokinetics of moxalactam and cefazolin compared in normal volunteers. *Antimicrob. Agents Chemother.* 19:302–5
204. Lam, M., Manion, C. V., Czerwinski, A. W. 1981. Pharmacokinetics of moxalactam in patients with renal insufficiency. *Antimicrob. Agents Chemother.* 19:461–64
205. Leroy, A., Humbert, G., Fillastre, J. P. 1981. Pharmacokinetics of moxalactam in subjects with normal and impaired renal function. *Antimicrob. Agents Chemother.* 19:965–71
206. Srinivasan, S., Neu, H. C. 1981. Pharmacokinetics of moxalactam in patients with renal failure and during dialysis. *Antimicrob. Agents Chemother.* 19:302–5
207. Bolton, W. K., Scheld, W. M., Spyker, D. A., Overby, T. L., Sande, M. A. 1981. Pharmacokinetics of moxalactam in subjects with varying degrees of renal dysfunction. *Antimicrob. Agents Chemother.* 19:613–19
208. Arnoff, G. R., Sloan, R. S., Mong, S. A., Luft, F. C., Kleit, S. A. 1981. Moxalactam pharmacokinetics during hemodialysis. *Antimicrob. Agents Chemother.* 19:575–77
209. Schaad, U. B., McCracken, G. H. Jr., Threlkeld, N., Thomas, M. L. 1981. Clinical evaluation of a new broad-spectrum oxa-beta-lactam antibiotic, mox-

alactam, in neonates and infants. *J. Pediatr.* 98:129–36
210. Kaplan, S. L., Mason, E. O. Jr., Garcia, H., Kvernland, S. J., Loiselle, E. M., Anderson, D. C., Mintz, A. A., Feigin, R. D. 1981. Pharmacokinetics and cerebrospinal fluid penetration of moxalactam in children with bacterial meningitis. *J. Pediatr.* 98:152–57
211. Wise, R., Baker, S., Livingston, R. 1980. Comparson of cefotaxime and moxalactam pharmacokinetics and tissue levels. *Antimicrob. Agents Chemother.* 18:369–71
212. Landesman, S. H., Corrado, M. L., Cherubin, C. C., Gombert, M., Cleri, D. 1980. Diffusion of a new beta-lactam (LY 127935) into cerebrospinal fluid. *Am. J. Med.* 69:92–98
213. McKee, K. T. Jr., Wright, P. F., Gregg, C. R., Stratton, C. W. 1980. Initial evaluation of kinetics and efficacy of moxalactam (LY 127935) in neonatal systemic gram-negative bacterial disease. *Curr. Ther. Res.* 28:603–10
214. Axelrod, J. L., Kochman, R. S. 1980. Moxalactam (LY 127935) penetration into human aqueous humor. See Ref. 154 (Abstr.)
215. Livingston, W. K., Elliott, A. M., Desmukes, W. E., Avent, C. K., Cobbs, C. G. 1981. Clinical evaluation of moxalactam. *Antimicrob. Agents Chemother.* 20:88–97
216. Tofte, R.W., Rotschafer, J., Solliday, J., Crossley, K. B. 1981. Moxalactam therapy for a wide spectrum of bacterial infections in adults. *Antimicrob. Agents Chemother.* 19:740–44
217. Kammer, R. 1981. Moxalactam clinical summary: efficacy and safety. *Symp. New Generation Beta-lactam Antibiot., London*
218. Rahal, J. J. 1981. Accumulated experience with moxalactam therapy of gram-negative bacillary meningitis. See Ref. 217
219. Neu, H. C., Prince, A. 1981. Activities of new beta-lactam antibiotics against isolates of *Pseudomonas aeruginosa* from patients with cystic fibrosis. *Antimicrob. Agents Chemother.* 20:545–46
220. Wold, J. S., Buening, M. K. 1981. Alcohol-moxalactam interactions in vivo. See Ref. 217
221. Yu, V. L. 1981. Enterococcal superinfection and colonization after therapy with moxalactam, a new broad-spectrum antibiotic. *Ann. Intern. Med.* 94:784
222. Moellering, R. C., ed. 1978. Symposium on cefamandole. *J. Infect. Dis.* 137:1–194
223. Cefuroxime. 1977. *Proc. R. Soc. Med.* 70(S-9):1–214
224. Kass, E. H., Evans, D. A., eds. 1979. Future prospects and past problems in antimicrobial therapy: the role of cefoxitin. *Rev. Infect. Dis.* 1:1–239
225. Sugawara, S., Tajima, M., Igarashi, I., Utsui, Y., Ohya, S., Nakahara, M. 1978. CS-1170, a new cephamycin antibiotic: in vitro and in vivo antibacterial activities. *Chemotherapy* 26(S-5):81–98
226. Tsuchiya, K., Kida, M., Kondon, M., Ono, H., Takeuchi, M., Nishi, T. 1978. SCE-963, a new broad spectrum cephalosporin: in vitro and in vivo antibacterial activities. *Antimicrob. Agents Chemother.* 14:557–68
227. Tsuchiya, K., Kondo, M., Kita, Y., Noji, Y., Takeuchi, M., Fugono, T. 1978. Absorption, distribution and excretion of SCE-963, a new broad spectrum cephalosporin, in mice, rats, rabbits and dogs. *J. Antibiot.* 31:1272–82
228. Yamamoto, T., Kuwahara, I., Adachi, Y., Yamaguchi, N. 1979. Phase 1 clinical studies on cefotiam (SCE-963). *Chemotherapy* 27(S 3):172–80
229. Goto, S. M., Ogawa, M., Tsuji, A., Kaneko, Y., Kuwahara, S. 1978. Bacteriological evaluation of a new cephamycin substance, CS-1170: comparison with antibacterial action of cephalosporins and cefoxitin. *Chemotherapy* 26(S):1–20
230. Tajima, M., Mitsuhashi, S. 1978. CS-1170, antibacterial activity and resistance to hydrolysis by -lactamases. *Chemotherapy* 26(S):21–26
231. Ohkawa, M., Orito, M., Sugata, T., Shimamura, M., Sawaki, M., Nakashita, E., Kuroda, R., Sasahara, K. 1980. Pharmacokinetics of cefmetazole in normal subjects and in patients with impaired renal function. *Antimicrob. Agents Chemother.* 18:386–89
232. Weaver, S. S., Bodey, G. P., LeBlanc, B. M. 1979. Thienamycin, a new beta-lactam antibiotic with potent broad-spectrum activity. *Antimicrob. Agents Chemother.* 15:518–21
233. Tally, F. P., Jacobs, N. V., Gorbach, S. L. 1978. In vitro activity of thienamycin. *Antimicrob. Agents Chemother.* 14:436–38
234. Kesado, T., Hashizume, T., Asahi, Y. 1980. Antibacterial activities of a new stabilized thienamycin, *n*-formimidoyl thienamycin, in comparison with other antibiotics. *Antimicrob. Agents Chemother.* 17:912–17

235. Kropp, H., Sundelof, J. G., Kahan, J. S., Kahan, F. M., Birnbaum, J. 1980. MR 7087 (*n*-formimidoyl thienamycin) evaluation of in vitro and in vivo activities. *Antimicrob. Agents Chemother.* 17:993–1000
236. Verbist, L., Verhaegen, J. 1981. In vitro comparison of *n*-formimidoyl thienamycin in comparison with cefotaxime, moxalactam and ceftazidime. *Antimicrob. Agents Chemother.* 19:402–6
237. Toda, M., Sato, K., Nakazawa, H., Inoue, M., Mitsuhashi, S. 1980. Effect of *n*-formimidoyl thienamycin (MK 0787) on β-lactamases and activity against β-lactamase producing strains. *Antimicrob. Agents Chemother.* 18:837–39
238. Neu, H. C., Labthavikul, P. 1981. The comparative activity of *n*-formimidoyl thienamycin against gram-positive and gram-negative aerobic and anaerobic species and its β-lactamase stability. *Antimicrob. Agents Chemother.* 28:180–87
239. Martinez-Beltran, J., Lorza, E., Jimero, J., Bouza, E., Baquero, F. 1981. Evaluation of *n*-formimidoyl thienamycin and thirteen cephalosporins on gentamicin-resistant gram-negative bacilli. See Ref. 88 (Abstr.)
240. Kropp, R., Sundelof, J. G., Hardu, R., Kahan, F. M. 1980. Metabolism of thienamycin and related carbapenem antibiotics by the renal dipeptidase—dihydropeptidase I. See Ref. 154 (Abstr.)
241. Norby, R., Alestig, K., Kahan, F., Kahan, J., Knopp, R., Ferber, F., Meisinger, M. 1981. Enhanced urinary recovery of *n*-formimidoyl thienamycin (MK 0787) on administering an inhibitor of the renal dipeptidase responsible for antibiotic metabolism. See Ref. 88 (Abstr.)
242. Sykes, R. B., Cimarusti, C. M., Bonner, D. P., Bush, K., Floyd, D. M., Georgopapadakou, N. H., Koster, W. H., Liu, W. C., Parker, W. L., Principe, A., Rathnum, M. L., Slusarchyk, W. A., Trejo, W. H., Wells, J. S. 1981. Monocyclic β-lactam antibiotics produced by bacteria. *Nature* 291:490–92
243. Neu, H. C., Labthavikul, P. 1981. Antibacterial activity of a monocyclic β-lactam. *J. Antimicrob. Chemother.* 8:111–22
244. Sykes, R. B., Bonner, D. P., Bush, K., Georgopapadakou, N. H., Wells, J. S. 1981. Monobactams, monocyclic antibiotics produced by bacteria. *J. Antimicrob. Chemother.* 8:1–16
245. Livermore, D. M., Williams, J. D. 1981. Activity of SQ 26,667 against *Pseudomonas aeruginosa* and its stability to β-lactamases. *J. Antimicrob. Chemother.* 8:29–38
246. Reeves, D. 1981. Antibacterial activity of the monobactam SQ 26,776 against antibiotic resistant *Enterobacteriaceae* including *Serratia*. *J. Antimicrob. Chemother.* 8:57–68
247. Swabb, E. A. 1981. Human pharmacology of SQ 26,776, *J. Antimicrob. Chemother.* 8:131–40