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MINIREVIEW

In Vitro and Pharmacokinetic Properties of the Carbapenems

RICHARD WISE

Department of Medical Microbiology, Dudley Road Hospital, Birmingham B18 7QH, United Kingdom

Over the past 20 years, many antibiotics have been synthesized by using the penam and cephem structures. When it was discovered, clavulanic acid was the first example of a novel, naturally occurring β-lactam with a different bicyclic ring structure. Since then, other bicyclic and, more recently, monocyclic semisynthetic and synthetic compounds have been described. The carbapenem group of compounds differs from the penicillins (penams) in that the 1-sulfur atom is replaced by carbon and there is a double bond at positions 2 to 3.

Carbapenems were discovered almost simultaneously by workers at Beecham Research Laboratories and Merck Sharp & Dohme Research Laboratories. The former identified three compounds, MM 4550, MM 13902, and MM 17880, from a culture of *Streptomyces olivaceus* (4, 5); such compounds were designated olivanic acids. Merck Sharp & Dohme Research Laboratories isolated thienamycin from "*Streptomyces cattleya*" (J. S. Kahan, F. M. Kahan, R. Goegelman, S. A. Currie, M. Jackson, E. O. Stapley, T. W. Miller, A. K. Miller, D. Hendlin, S. Mochales, S. Hernandez, and H. B. Woodruff, Program Abstr. 16th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 227, 1976). Since then, 40 or more compounds have been described.

STRUCTURE

The compounds are derived from 7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid; the more important agents are shown in Table 1 (R. Southgate and S. Elson, *Progress in the Chemistry of Organic Natural Products*, in press). Many compounds exist as stereoisomeric forms. In general, those compounds with an R_1 substituent and R_2 = H have *cis* (type 1) stereochemistry, and those with an R_2 substituent and R_1 = H have *trans* (type 2) stereochemistry (Fig. 1).

The presence of an exocyclic methylene-linked side chain at position −6, as occurs in the asparenomycins, destroys any stereochemistry at this site. Stereoisomerism can also occur at position −8; for example, epithienamycins D and C are stereoisomers of *N*-acetyl thienamycin and *N*-acetyl dehydrothienamycin, respectively. The major difference between the olivanic acids and the thienamycins is that the former tend to be type 1 and the latter tend to be type 2.

It has been suggested (8) that the configuration of the optically active side chains at C-8 influences intrinsic antimicrobial activity and the stereochemistry across C-5 to C-6 probably influences both activity and β-lactamase stability or inhibition. The presence of a sulfate at position −8 also appears to enhance β-lactamase stability. For example, olivanic acid MM 22380 is a potent antibiotic but lacks the β-lactamase stability of its stereoisomer *N*-acetyl thienamycin. It has been suggested that stereochemical differences at C-8 also affect β-lactamase inhibitory properties. For example, MM 4550 and MM 13902 (type 1 compounds) are potent inhibitors of many gram-negative bacteria as well as staphylococcal β-lactamase, whereas thienamycin and *N*-acetyl thienamycin (type 2 compounds), although potent antimicrobial agents, have poor β-lactamase inhibitory properties (3).

A serious problem of many carbapenems is chemical instability. A major contender for clinical use, thienamycin, is unstable both as a solid and in solution. The instability has been related to the terminal free amino group on the C-2 side chain, and derivatization to a less nucleophilic group such as the *N*-acetylimidoyl or *N*-formimidoyl group has improved stability (15). In the case of the latter compound, now known as imipenem, this has not led to any loss of antimicrobial activity. Other carbapenems shown to be unstable in solution are MM 4450 and MM 13902, their half-lives in broth at 37°C being 2 and 12 h, respectively (3). Alterations to the carboxy group at C-2 may affect the stability of certain carbapenems to the renal dehydropeptidases (T. Yoshioka, K. Isshiki, F. Nakamura, K. Yamamotto, Y. Shimauchi, M. Sakamoto, N. Shibamoto, Y. Fukagawa, and T. Ishikura, 24th ICAAC, abstr. no. 132, 1984).

MICROBIOLOGICAL ACTIVITY AND CHEMICAL STABILITY

In this section, the activity of the major groups of carbapenems is described, with emphasis on those few agents which have been studied in humans. The activity of the agents most studied is shown in Table 2.

(i) Olivanic acids. Olivanic acids were isolated from *S. olivaceus* and developed mainly by Beecham Research Laboratories in a search for β-lactamase inhibitors (1). However, it was realized that many were potent broad-spectrum antibiotics. It was found that compounds MM 4550, MM 13902, and MM 17880 were effective inhibitors in cell-free

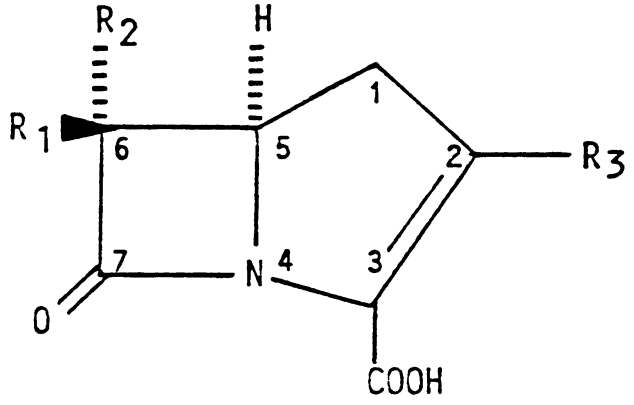


FIG. 1. R_1 = substituent, R_2 = H = *cis* (type 1) compounds. R_2 = substituent, R_1 = H = *trans* (type 2) compounds.

TABLE 1. Structure of the carbapenems[a]

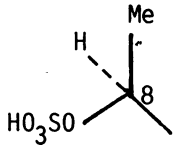
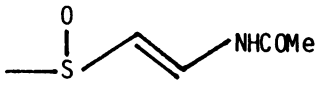
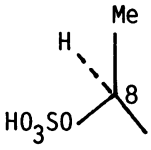
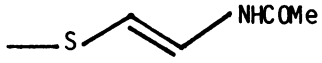
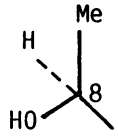
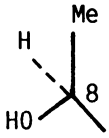
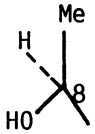
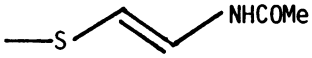
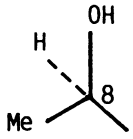
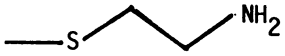
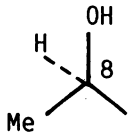
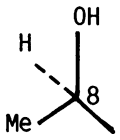
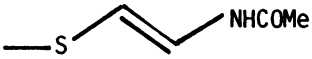
Name	R^1	R^2	R^3
MM 4550		H	
MM 13902 or Epithienamycin E		H	
MM 22380 or Epithienamycin A		H	
MM 22381 or Epithienamycin C	H		
M 22383 or Epithienamycin D	H		
Thienamycin	H		
N-Acetyl-thienamycin	H		
N-Acetylde-hydrothienamycin	H		

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TABLE 1—*Continued*

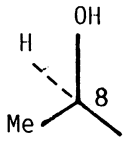
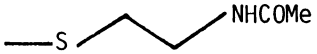
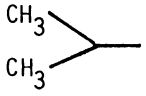
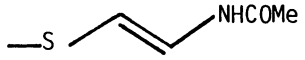
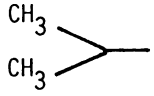
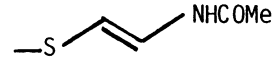
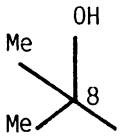
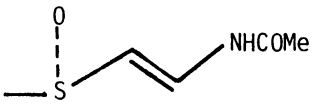
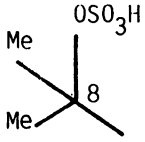
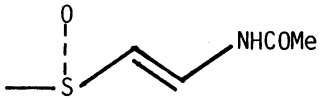
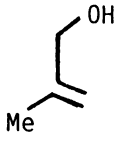
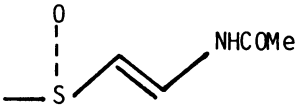
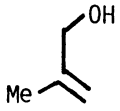
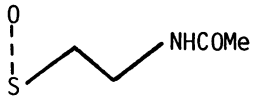
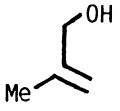
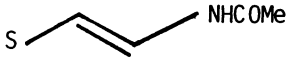
Name	R^1	R^2	R^3
N-formimidoyl thienamycin (MK 0787, imipenem)	H		
PS-5 MM 22744	H	CH_3CH_2-	
PS-6	H		
PS-7	H	CH_3CH_2—	
PS-8	H		
Carpetimycin A		H	
Carpetimycin B		H	
Asparenomycin A	R^1, R^2 =		
Asparenomycin B	R^1R^2 =		
Asparenomycin C	R^1R^2 =		

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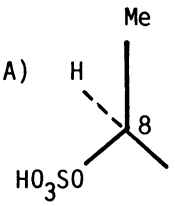
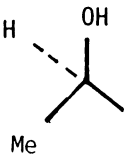
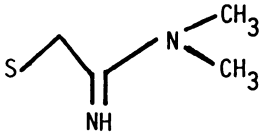
TABLE 1—*Continued*

Name	R_1	R_2	R_3
SF-2103A (Pluracidomycin A)		H	$-SO_3H$
L646,591	H		
SQ 27,860	H	H	H

[a] See Fig. 1 for R_1, R_2, and R_3.

β-lactamase preparations from *Escherichia coli*, *Klebsiella aerogenes*, *Proteus mirabilis*, *Enterobacter cloacae*, and *Staphylococcus aureus* (7). However, when I_{50} (the amount of drug that inhibits 50% of β-lactamase production) values were compared with those of clavulanic acid (23), MM 4550 was, for example, only one tenth as potent an inhibitor of the TEM-1 enzyme. Compound MM 4550 (which was the most potent β-lactamase inhibitor) was less active than MM 13902 against a wide range of bacterial pathogens (Table 2). As has already been mentioned, the olivanic acids share a problem common to other carbapenems, that of chemical instability. MM 13902, the most promising olivanic acid, has a half-life of 12 h in aqueous solution at 25°C, reduced to 4 h at pH 6.

(ii) Carpetimycins. The carpetimycin compounds were isolated from a filtrate of *Streptomyces* spp. KC-6643 (16). The two more important compounds described differ in that carpetimycin B is sulfated at position 8 and carpetimycin A is not sulfated. Carpetimycin C and D differ from A and B, respectively, by having an unsaturated side chain at position −2. Carpetimycin A is 5- to 20-fold more active than carpetimycin B against a wide range of bacteria (including *Pseudomonas aeruginosa*). Based on the limited data on β-lactamase inhibitory properties, carpetimycins A and B appear to possess β-lactamase inhibitory potency similar to that of MM 4550, that is, about one tenth that of clavulanic acid. Carpetimycins A and B are more stable than the olivanic acids, at pH 7 in aqueous buffer at 25°C their half-lives being 187 and 170 h, respectively.

(iii) Asparenomycins. The asparenomycins were isolated from cultures of "*Streptomyces tokunonesis*" and *Streptomyces argenteolus* (17, 31) and are unique in having a substituted ethylidene side chain at position −6. Information is sparse, except for asparenomycin A, with a spectrum of activity similar to that of carpetimycin A, being generally half as active as the latter. Compared with clavulanic acid, it is a potent β-lactamase inhibitor, especially of Richmond and Sykes group I a, b, and c enzymes (24), for which it is 100 times more potent (31). Against other bacterial β-lactamases, it has a potency similar to that of clavulanic acid. Little information on stability is available; however, at pH 4 at room temperature, asparenomycin A is hydrolyzed to a non-β-lactam compound within 6 h. Oxidation followed by hydrolysis of asparenomycin A yields significant amounts of aspartic acid.

(iv) Pluracidomycins. Pluracidomycin A (SF 2103A) was isolated from a strain of *Streptomyces sulfonofaciens*. It appears to have only weak antimicrobial activity (32), yet it inhibits completely, in a progressive manner, a wider range of β-lactamases than clavulanic-acid-inactivating (9, 36) types Ib and II plasmid-mediated enzymes. Against a *Citrobacter freundii* cephalosporinase, pluracidomycin A acts as a poor substrate, the inactivation being reversible. Synergy between SF 2103A and ceftizoxime, cefoperazone, cefotaxime, and cefmetazole has been described as tested in checkerboard titrations against members of the family *Enterobacteriaceae* (T. Niwa, T. Ito, T. Yoshida, T. Niida, and M. Kojima, 22nd ICAAC, abstr. no. 298, 1982). The compound is said to be "relatively stable in aqueous solution."

(v) PS series. PS 5, 6, 7, and 8 differ in the 2-carbon substituent at C-6 and the saturated (PS-5, PS-6) or unsaturated (PS-7, PS-8) side chain at C-2. These have been isolated from *Streptomyces cremeus* subsp. *auratilis* admixed with olivanic acids and epithenamycins (26). Information on the microbiological activity of PS-5 and PS-8 only is available, with PS-8 being 2- to 10-fold less active than PS-5 (21, 27). PS-5 was found to be a potent antibiotic with activity similar to that of MM 13902 but lacks good activity against *P. aeruginosa*. In a crude test of β-lactamase inhibition, PS-5 at a concentration of 2.5 μg/ml against a β-lactamase-producing strain of *Proteus vulgaris* reduced the ampicillin MIC from

TABLE 2. In vitro activity of representative carbapenems

Group and agent(s)	MIC (μg/ml) for: *Escherichia coli*	*Escherichia coli* (TEM+)	*Klebsiella* spp.	*Proteus mirabilis*	*Serratia marcescens*	*Enterobacter aerogenes*	*Enterobacter cloacae*	*Pseudomonas aeruginosa*	*Bacteroides fragilis*	*Staphylococcus aureus* (β+)	*Streptococcus pyogenes*	*Streptococcus faecalis*	*Haemophilus influenzae* (β−)	*Neisseria gonorrhoeae*	Reference(s)
Olivanic acids															
MM 4550	12.5	2.5	12.5	12.5	25	25	100	>100	3.1	50	6.2	50	6.2		3, 7
MM 13902	0.2	1.6	0.4	0.2	3.1	3.1	12.5	50	0.4	1.6	0.2	6.2	0.1		3, 7
Thienamycins															14, 29, 35
Thienamycin	0.16	0.32	0.63	5.0	16	1.3		2.5	1.0	0.04		1.3			
Imipenem	0.08	0.32	0.63	2.5	2	0.6		5.0	0.12	0.02		2.5	0.5	0.03	8
Carpetimycins															
Carpetimycin A	0.05	0.2	0.78	1.6	3.1	0.1	3.1	6.25	3.1	0.39			0.8		16
Asparenomycins															
Asparenomycin A	1.6	0.4	0.8	3.1	12.5		1.6	25		1.6	1.6				31
Pluracidomycins															
Pluracidomycin A (SF 2103A)	6.3	12.5	50		100			>100		25		50			32
PS series															
PS-5 (MM 22744)	3.1	3.1	3.1	12.5	6.3		12.5	25		0.16	0.08	0.39			21

1,250 to 1.2 μg/ml. There is no information on chemical stability.

A number of PS series analogs have been produced. Starting with PS-5, different C-3 substituents have been produced (Yoshioka et al., 24th ICAAC, abstr. no. 132, 1984). 4-Pyridylthio side chains show the highest activity against gram-positive bacteria, and D-cysteinyl side chains show greater activity against gram-negative bacteria.

(vi) Thienamycins. There is considerable information on a wide range of thienamycin derivatives. The original compound, thienamycin, was isolated from "*S. cattelya*" (11), together with *N*-acetyl thienamycin. Thienamycin has a very broad antibacterial spectrum, including *P. aeruginosa*. Members of the family *Enterobacteriaceae* (including many isolates resistant to other β-lactams), *S. aureus*, and *Bacteroides fragilis*. An early observation (11) was the concentration-dependent chemical instability of this compound; the rate of breakdown accelerates above 10 μg/ml regardless of the buffer used. For example, at pH 7 and 25°C, the time for 30% of the initial activity to disappear varied from 13 to 3 h in a 60- or 600-mM solution, respectively. A search for chemically stable derivatives was undertaken, investigating several hundred analogs. *N*-Formimidoyl thienamycin (imipenem) was finally selected for studies in humans. Imipenem has good stability to the β-lactamases from *S. aureus*, *B. fragilis*, and Richmond and Sykes types Ia, III, and IVc enzymes (24). The compound is also a potent inhibitor of type Ia and *B. fragilis* enzymes. Imipenem is active against strains possessing the constitutively produced P99 cephalosporinases (although a good inducer of these enzymes), and this activity is considered to be the result of the high rate of penetration of the outer cell membranes of bacteria producing the enzymes (33). In *P. aeruginosa*, it has been shown (30) that imipenem induces significantly elevated levels of β-lactamase which cause in vitro antagonism with nine antipseudomonal β-lactams. Imipenem MICs are little affected by the higher β-lactamase production. However, there is some lability to chromosomal type 1d β-lactamase (D. M. Livermore, Proc. 14th Int. Congr. Chemother., abstr. no. S 78-3, p. 253). In addition, *Pseudomonas maltophilia* (12) and *Aeromonas hydrophila* (25) may be resistant to imipenem by virtue of β-lactamases that can hydrolyze the compound. The high bacterial cell penetrability of imipenem may be the reason that little cross resistance exists between imipenem and other β-lactams. This good penetrability may be related to the zwitterionic nature of the compound. Imipenem binds preferentially to penicillin-binding protein (PBP) 2 in *E. coli*, and the initial morphological response is cell rounding. Higher concentrations bind to PBP-1 a/b, and even higher concentrations bind to PBP-3. The microbiological properties of imipenem are well reviewed elsewhere (10, 12). Briefly, the spectrum includes *S. aureus* (including β-lactamase producers), *Streptococcus pyogenes*, *Streptococcus pneumoniae*, and *Neisseria* sp., all of which are exquisitely susceptible. *Streptococcus faecalis* is susceptible to 1 to 4 μg/ml, and *Haemophilus influenzae* is interesting in that it is less susceptible to imipenem (MIC, 0.2 to 1 μg/ml) than, e.g., cefotaxime (MIC, 0.01 to 0.06 μg/ml). The MIC_{90}s (MICs for 90% of strains tested) for members of the family *Enterobacteriaceae* and *P. aeruginosa* generally are ≤4 μg/ml. Imipenem has considerable activity against anaerobes, the MIC_{90} for the *B. fragilis* group being 1 μg/ml and the MIC_{90} for *Clostridium* sp. being 0.25 μg/ml.

vii. Other compounds. Structurally, the simplest carbapenem is the unsubstituted compound SQ 2,860 (22). This highly unstable compound, isolated from *Serratia* and *Erwinia* spp., has activity possibly slightly superior to that of ampicillin against staphylococci, *E. coli*, and *E. cloacae*. Although it was active against strains containing the P99 β-lactamase, it had no activity against TEM-producing strains. The high instability makes further development unlikely.

TABLE 3. Pharmacokinetic parameters of imipenem after 500 to 1,000 mg intravenously[a]

Parameter	Unit	Value
Slope of distribution curve	h^{-1}	4.13
Slope of elimination curve	h^{-1}	0.76
K_{21} (Redistribution rate constant)	h^{-1}	2.36
K_{12} (Distribution rate constant)	h^{-1}	1.2
K_{10} (Overall elimination rate constant)	h^{-1}	1.3
$t_{1/2\alpha}$ (Distribution half-life)	h	0.23
$t_{1/2\beta}$ (Elimination half-life)	h	0.93
Plasma clearance (with cilastatin)	liters/h per 1.73 m^2	12.1
Renal clearance (with cilastatin)	liters/h per 1.73 m^2	6.8
V_1 (volume of distribution in the central compartment)	liters/kg	0.16
V_{area} (volume of distribution in body)	liters/kg	0.2
V_{ss} (volume of distribution at steady state)	liters/kg	0.23
Urine recovery (0 to 10 h) (with cilastatin)	%	72

[a] Values are taken from references 6 and 19.

Recent advances in synthetic chemistry have developed novel carbapenems. One interesting compound is L646,591 (Merck Sharp & Dohme), which is substituted at the 1 position with a β-methyl group (D. H. Shih, J. A. Fayter, F. Baker, L. Cama, and B. G. Christensen, 23rd ICAAC, abstr. no. 333, 1983. This compound is said to have antimicrobial activity and β-lactamase inhibitory properties similar to those of imipenem, superior chemical stability, and, possibly, superior pharmacokinetics (see below) (H. Kropp, J. G. Sundelof, J. S. Kahan, J. Huber, D. Bohn, L. Gerckens, F. M. Kahan, and J. Birnbaum, 23rd ICAAC, abstr. no. 331, 1983).

PHARMACOLOGICAL PROPERTIES

With the exception of imipenem, there is scanty information on the carbapenems. The susceptibility of this group of antibiotics to metabolic inactivation in animals has been a major problem. The enzyme responsible for this inactivation has been shown to be a renal tubular brush border dipeptidase (EC 3.4.13.11), dehydropeptidase-I. There have been two approaches to solving this problem. First, there is the structural approach. Nonbasic acylaminoalkyl-thio side chains at C-2 are less stable than other substituents; hence, appropriate alterations at this site provide relatively more stable compounds (13). Alterations at C-3 in the PS series have already been mentioned. Second, inhibitors of the dipeptidase have been sought, and two compounds, MK 0789 and MK 0791, have been studied. The latter is now known as cilastatin. The importance of having a metabolically stable compound is twofold. First, as mentioned below, the urinary recovery and, hence, the levels in urine will be greater. Second, but of greater importance, the breakdown products of imipenem administered without cilastatin were nephrotoxic in rabbits and monkeys, this adverse effect being abolished by coadministration with cilastatin. There is little suggestion that imipenem-cilastatin is nephrotoxic in humans (34).

(i) Olivanic acids. The only substance studied in animals and humans is MM 13902 (2). A crude mouse kidney preparation degrades 100 μg of this compound per ml at a rate of 1.5 μg/ml per min, the agent being one-sixteenth as stable as thienamycin. The elimination half-life in humans is 40 min, and urinary recovery is low (1.8% of the drug administered). The compound is not being further studied in humans.

(ii) Pluracidomycins. Pluracidomycin A (SF 2103A) has been studied in animals, and its protective effect in animals parallels its in vitro activity. The half-life in rats is 29.4 min, 43% of a dose was recovered in the urine, and it appeared stable to degradation by a rat kidney homogenate (Y. Kazuno, A. Tamura, T. Shomura, I. Komiya, S. Murata, and S. Inouye, 22nd ICAAC, abstr. no. 299, 1982).

(iii) PS series. It is not known whether any agents of the PS series has been given to humans. As mentioned above, it has been shown that different substituents at the C-3 position affect the stability to the dehydropeptidase of rat kidneys (Yoshioka et al., 24th ICAAC, abstr. no. 132, 1984).

(iv) Thienamycins. Due to the chemical instability of thienamycin, few in vivo studies have been performed. In protective tests in mice, the 50% effective doses of thienamycin were about two- to fourfold greater than that of imipenem. The serum half-life of thienamycin in chimpanzees was 32 min, 65% lower than that of imipenem (H. Kropp, J. G. Sundelof, J. S. Kahan, F. M. Kahan, and J. Birnbaum, 19th ICAAC, abstr. no. 231, 1979). Like other carbapenems, thienamycins were hydrolyzed (at the β-lactam bond) by the renal dehydropeptidase-I, and the recovery of the parent compound in the urine after injection in chimpanzees was low (about 10%). Further development of thienamycin has ceased.

Imipenem is also highly metabolized in chimpanzees (10% urinary recovery), and early studies in humans confirmed low and variable urine recovery (6 to 30%) with a plasma half-life of 1 h (F. Follath, A. M. Geddes, P. Spring, G. D. Ball, K. H. Jones, F. Ferber, J. S. Kahan, and F. M. Kahan, 21st ICAAC, abstr. no. 590, 1981). A number of acylamino-substituted propenoates were studied as inhibitors of renal dehydropeptidase-I and 3-pentyl-2-(dimethylcyclopropyl-carboxoxamido)-propenoate, cilastatin being chosen. In a 1:1 ratio, cilastatin increased urinary recovery to about 72% but did not significantly alter other pharmacokinetic parameters (18, 19). The pharmacokinetic parameters of imipenem are shown in Table 3. Up to 9% of radiolabeled imipenem has been found in the serum of human volunteers (20) as the open lactam metabolite, and less than 1% of the parent compound is eliminated in the feces. The fate of cilastatin in the body is similar to that of imipenem, 75% of the dose being found in the urine in 6 h. The *N*-acetyl metabolite of cilastatin was found to represent about 12% of the total radioactivity. In severely impaired renal function, the serum half-life of cilastatin increases to about 12 h, whereas that of imipenem increases to about 3 h (G. A. Verpooten, L. Verbist, and M. E. DeBroe, Proc. 13th Int. Congr. Chemother., PS 4.1/4-9, 1983). The significance of this difference is yet to be ascertained.

The 1-methyl-substituted thienamycins, as stated above, may show superior pharmacokinetics in that they are said to be stable to renal dehydropeptidases (28).

CONCLUSIONS

When reviewing the carbapenems, one cannot escape the observation that this area of antibiotic research has been a battlefield. All but one compound has fallen, the major problems being chemical and metabolic instability, together with poor semisynthetic yields. The one victor, imipenem, has been many years in development but promises well in clinical use, with its broad antimicrobial spectrum and

freedom from toxicity. The stormy history of carbapenem development cannot bode well for the future development of new compounds. The search for metabolically stable compounds will continue. It is, however, possible that many research groups will consider the possibility that other molecules, possibly the penams and monocyclic β-lactams, might prove more fruitful.

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