LEADING ARTICLE

Drugs 2001; 61 (5): 553-564
0012-6667/01/0005-0553/$27.50/0

Emerging Strategies in Infectious Diseases

New Carbapenem and Trinem Antibacterial Agents

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Abstract

β-Lactam antibiotics represent the most commonly prescribed antibacterial agents. New β-lactams have been introduced continuously as many bacteria have developed resistance to older agents. In the late 1970s, a new class of exceptionally broad spectrum β-lactams, the carbapenems, was identified. Despite being a very potent compound, the antibacterial activity of the first carbapenem, imipenem, was compromised because of hydrolysis by the renal dehydropeptidase enzyme (DHP-1), and it is now coadministered with a potent competitive inhibitor of the DHP-1 enzyme, cilastin. Molecular modifications in the carbapenem nucleus were able to increase stability to DHP-1 and retain the antibacterial activity. However, some important pathogenic bacteria were found to be resistant to this new class of agents. In addition, other clinically important Gram-negative species, such as *Pseudomonas aeruginosa*, developed resistance mainly by the production of potent β-lactamases and reduced permeability of the outer membrane. Since the discovery of imipenem/cilastatin, a great number of carbapenems have been developed, and a few of them have been marketed. Stability to hydrolysis by DHP-1 and decrease in toxicity were achieved by meropenem and biapenem. However, only a slight increase in the antibacterial potency and spectrum has been accomplished with either the new marketed or experimental parenteral compounds. In addition, compounds that can be administered orally, such as the carbapenens faropenem, CS-834 and MK-826, and the trinem sanfetrinem, have been developed. However, when compared with the parenterally administered compounds, the oral agents seem to lose some *in vitro* antibacterial activity, especially against *P. aeruginosa*.

The dramatic global increase in resistance to antimicrobial agents among clinically significant pathogens is of great concern. The β-lactams are the most prescribed group of antibacterial agents throughout the world. Consequently, among the most prevalent mechanisms of resistance are those that reduce the activity of this class of antimicrobials. Basically, three mechanisms are responsible for decreasing the activity of β-lactams: (i) structurally altered penicillin-binding protein (PBP) target sites; (ii) β-lactamase production; and (iii) reduced outer membrane permeability.[1,2] Among Gram-negative bacteria, β-lactamase production is the most common mechanism of resistance.[1-3] The synthesis of ex-

tended-spectrum cephalosporins seemed to overcome this mechanism through their stability to hydrolysis by most commonly observed β-lactamases. However, one significant therapeutic obstacle facing these newer cephalosporins has been the production of stably derepressed chromosomally encoded cephalosporinases and, more recently, plasmid-mediated β-lactamase that are able to destroy these agents.[4,5]

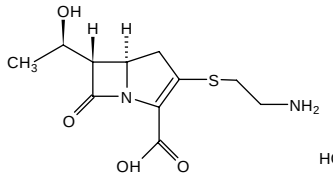
In the late 1970s, searching for compounds resistant to the action of β-lactamases, two research groups discovered compounds that would belong to a new class of β-lactams, the carbapenems. Carbapenems most resemble penicillins, except that the 5-membered ring contains a double bond between carbons 2 and 3 and the sulphur atom is replaced by a carbon (fig. 1).[1] Imipenem (*N*-formimidoylthienamycin) was the first thienamycin derivative to be selected for clinical evaluation because of its improved chemical stability, excellent antibacterial activity, and accessibility in large quantities by total synthesis.[6] Despite being a very potent compound, its antibacterial activity was compromised because of its hydrolysis by renal dehydropeptidase enzymes (DHP-1) located in the brush border of the kidneys.[6,7] To retain its *in vivo* activity, imipenem was coadministered with cilastatin, a potent competitive inhibitor of the DHP-1 enzyme.[6] This combination parenteral product has been utilised for more than 15 years in the treatment of serious infections.[8,9]

After the discovery of imipenem, research in the carbapenem field has concentrated on the development of a single compound that could combine the antibacterial spectrum and potency of imipenem with significantly enhanced chemical and metabolic stability. As a result, non-natural carbapenems were synthesised based on systematic variations of the thienamycin nucleus. Modifications at C-3, C-5 and C-6 failed to improve the natural properties of carbapenems.[10] On the other hand, modifications introducing a 1β-methyl group at C-1 into the carbapenem nucleus increased stability to DHP-1, and retained the antibacterial activity.[10,11] Numerous compounds including this modification were synthesised, and named 1β-methylcarbapenems.

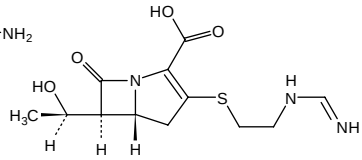
With the stability to DHP-1 achieved, research was then devoted to the search for compounds with higher antibacterial potency than imipenem. Previous studies demonstrated that a basic or positively charged group was required in the C-2–substituent to enhance the spectrum of activity and potency against Gram-negative organisms in particular.[11,12] Many thio-linked substituents at C-2 have been the major area of study in terms of C-2 modified carbapenems (panipenem, meropenem and biapenem). Interestingly, these agents contain the S-C-C-N arrangement in the C-2 group in common with the natural carbapenem thienamycin and its derivative imipenem.[13-17] Meropenem and biapenem also incorporate a 1β-methyl group modification at C-1 (fig. 1).[14]

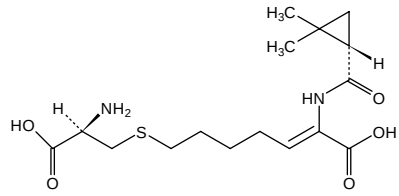
Meropenem is the only C-2–modified carbapenem available for clinical use in the US and several other countries. It is a parenteral agent utilised for treatment of severe bacterial infections, and, unlike imipenem, it is stable to hydrolysis by DHP-1 and can be used without an enzyme inhibitor.[14,16] Panipenem is a broad-spectrum, parenteral agent coadministered with *N*-benzoyl β-alanine (betamipron) because of its instability to DHP-1.[13,14]

The *in vitro* activity of biapenem has been evaluated in numerous studies.[17-23] Biapenem is more active than imipenem against most of the members of the Enterobacteriaceae family and against *Pseudomonas* species, but it is less active than imipenem against Gram-positive aerobes (table I). The activity of biapenem against *Bacteroides fragilis* is similar to that of metronidazole and of imipenem. Biapenem has been demonstrated to be more effective than imipenem/cilastatin in protecting mice against acute lethal infections caused by *Escherichia coli* and *Pseudomonas aeruginosa*; however, no difference in their efficacy was observed for treatment of intra-abdominal infections in rats.[24] Although the efficacy of imipenem and biapenem was similar, biapenem showed less neurotoxicity than imipenem in animal models. It did

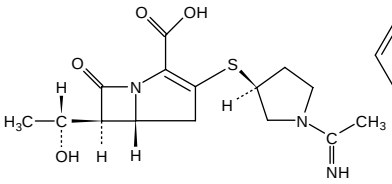


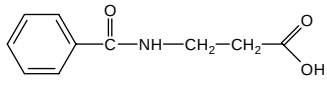
Thienamycin



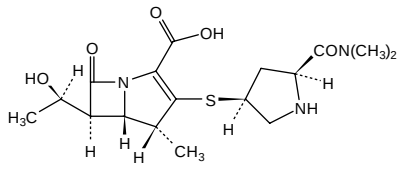


Imipenem + cilastatin

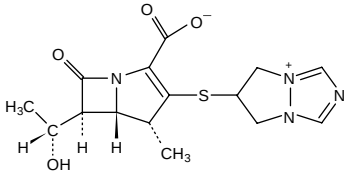




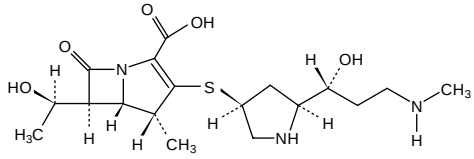
Panipenem + betamipron



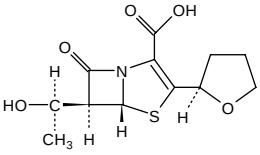
Meropenem



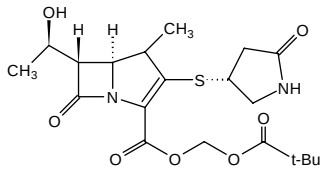
Biapenem (LJC-10627)



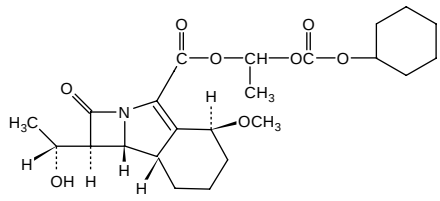
Lenapenem (BO-2727)



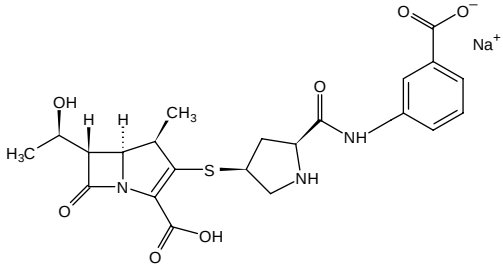
Faropenem



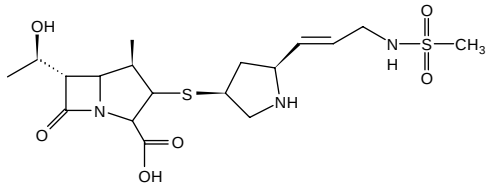
CS-834



Sanfetrinem sodium



MK-826



DA-1131

Fig. 1. Chemical structure of some of the carbapenems and the trinem, sanfetrinem.

not evoke severe convulsions or death as imipenem/cilastatin did, even when administered intraventricularly at a high dose. The low neurotoxicity of biapenem is attributable to its molecular structure.[25] In spite of several studies showing *in vitro* and *in vivo* antimicrobial activity similar or superior to that of imipenem/cilastatin and meropenem, stability to DHP-1, satisfactory pharmacokinetic/pharmacodynamic characteristics, clinical efficacy in both animal models and humans, good tolerability, and a low incidence of adverse effects in adults and children, biapenem has not become commercially available.[17-29] Other analogues, such as panipenem and faropenem, an oral agent, have recently been registered for use in Japan (fig. 1).[14,15]

Trinems, formerly tribactams, are a new class of β-lactam derivatives that contain a tricyclic nucleus as the key structural feature (fig. 1). The trinems have a carbapenem-related structure, but with a cyclohexane ring attached across carbons 1 and 2.[14] The first compound of this class to be developed was sanfetrinem (GV-104326).

The objective of this article is to review the current status of clinical development of new carbapenem compounds as well as of agents belonging to a new class of β-lactams, the trinems, which are not currently in clinical use.

1. Methylcarbapenems

1.1 Lenapenem

Lenapenem (formerly BO-2727), (*4R-5S-6S*)-6-[(R)-1-hydroxyethyl]-2{(3S-5S)-5-[(R)-1-hydroxy-3-N-methylaminopropyl]pyrrolidin-3-ylthio}-1-methyl-1-carbapen-2-em-3-carboxilic acid hydrochloride hydrate, is a new injectable carbapenem (fig. 1).[30] It is more stable to hydrolysis by DHP-1 than imipenem and meropenem, but slightly less stable than biapenem.[31] Lenapenem has high affinity for PBP-2 of *E. coli*, and PBP-2 and -3 of *P. aeruginosa* and *Staphylococcus aureus*.[32,33] The affinities for PBP-2 and -3 resemble those of imipenem and meropenem, respectively. Unlike the other carbapenems, lenapenem also demonstrated affinity for altered PBPs, such as PBP-2' of *S. aureus*, which is responsible for conferring resistance to methicillin.[32]

Table I. Comparison of the antibacterial activities of carbapenems against bacterial isolates commonly seen by clinical microbiology laboratories

Bacterial species	MIC_{50} range[a] (mg/L)						
	imipenem	meropenem	biapenem	lenapenem	CS-834 (R-95867)	MK-826	sanfetrinem
Staphylococcus aureus[b]	≤0.03-0.06	0.06-0.12	0.05-0.25	0.012	0. 125	0.12	0.03
Streptococcus pneumoniae[c]	≤0.06	≤0.06	≤0.06	≤0.06	0.008-0.025	≤0.03	0.008
Enterococcus faecalis	0.5-1.0	2.0-4.0	2-6.25	1.56	6.25-8	8	1
E. faecium	1.0->128	25	1.56->64	6.25	12.5-128	>16	8
Escherichia coli	0.03-0.25	≤0.06-0.05	0.015-0.06	0.025-0.05	0.012-0.025	≤0.03	0.125
Klebsiella pneumoniae	0.025-0.5	≤0.06	0.05-0.25	0.012	0.016-0.025	2	0.5
Enterobacter aerogenes	0.1-1	0.025-0.06	0.05-0.5	0.05	0.1-0.2	4	2
E. cloacae	0.1-1	0.025-0.06	0.05-0.25	0.05	0.1-0.78	0.12	1
Serratia marcescens	0.12-1	0.025-0.06	0.2-0.5	0.2	0.125-0.39	≤0.03	2-8
Acinetobacter spp.	0.05-0.25	0.1-0.5	0.05-0.5	0.05	0.39-0.78	4	2
Pseudomonas aeruginosa	1.56-4	0.5-1.56	0.5-1	0.78	25-32	2	64
Haemophilus influenzae	0.39-1	0.025	0.39-0.5	0.2	0.06-0.1	0.06-1	0.06
Moraxella catarrhalis	≤0.03	≤0.006	≤0.015-0.06	0.012	0.05-0.063	≤0.03	0.015-0.125
Bacteroides fragilis	0.06-0.25	0.25-2.0	0.25	0.78	0.1		0.06

a Range based on minimum inhibitory concentration (MIC_{50}) values obtained in previous studies.[17-23,33,35,40,42,43,45,63,67,78]

b Including only methicillin-susceptible *S. aureus* isolates.

c Including only *S. pneumoniae* susceptible to penicillin.

In vitro studies have shown that lenapenem exhibits excellent *in vitro* activity against *P. aeruginosa*, including imipenem-resistant isolates.[34] Lenapenem demonstrated activity inferior to that of imipenem but superior to that of other carbapenems against Gram-positive cocci (table I). However, against methicillin-resistant *S. aureus* (MRSA), lenapenem had the highest activity among tested carbapenems.[32,33,35] There are only very few studies evaluating lenapenem activity against anaerobes. The *in vitro* studies that included *B. fragilis* isolates have shown that the *in vitro* activity of lenapenem against this pathogen is similar or slightly inferior to that of imipenem and meropenem [minimum inhibitory concentration ($MIC)_{90}$ 0.5 to 1 mg/L].[35]

Lenapenem has shown therapeutic efficacy comparable to that of imipenem/cilastatin and biapenem in systemic infections caused by Gram-positive and -negative bacteria in mice.[33,35]

Although this new carbapenem seemed to be a promising compound, its further development will be difficult because of the high incidence of liver function abnormalities observed in phase II clinical trials.[33]

1.2 CS-834

CS-834 was the first oral carbapenem synthesised. CS-834 ([*1R,5S,6S*]-6-[(*R*)-1-hydroxyethyl]- 1-methyl-2-[(*R*)-5-oxopyrrolidin-3-ylthio]-1-carbapen-2-em-3-carboxylate) is an ester-type prodrug with a pivaloyloxymethyl group (fig. 1), and its active metabolite, R-95867, is released into the blood when CS-834 is absorbed from the intestinal wall.[36,37] It has been reported that some β-lactams having the pivalic acid moiety that are used for long term therapy (months) may reduce the carnitine level in skeletal muscle and increase the likelihood of carnitine deficiency.[38] Although CS-834 has the pivalic acid moiety, plasma carnitine levels reported to date were similar to those found in patients using other β-lactams, and no muscle pain or increase in lactate dehydrogenase (LDH) levels were reported.[39] However, more detailed investigations appear warranted.

R-95867 exhibited a broad-spectrum of activity covering both Gram-positive and -negative aerobes and anaerobes. The antibacterial activity of R-95867 against Gram-positive cocci was inferior to that demonstrated by imipenem, but superior to that exhibited by the oral cephalosporins such as cefpodoxime, cefuroxime, cefdinir and cefditoren. The potency of R-95867 against Gram-negative cocci was even greater than that demonstrated by the oral cephalosporins against Gram-positive cocci. Except for *Serratia marcescens* isolates, R-95867 exhibits similar activity to that of imipenem against other members of the Enterobacteriaceae family (table I). On the other hand, R-95867 is more active than imipenem against *Neisseria gonorrhoeae, Bordetella pertussis* and *Haemophilus influenzae*. R-95867 is not active against *P. aeruginosa* (MIC_{90} 50 mg/L).[40-42]

Several studies have assessed the *in vivo* efficacy of CS-834 using murine local and systemic infections caused by Gram-positive and -negative pathogens. In most cases, the efficacy of CS-834 was superior to that of cefpodoxime, cefdinir and cefditoren pivoxil.[40-43] Against respiratory tract infections induced by inoculation with penicillin-susceptible *Streptococcus pneumoniae,* amoxicillin was more effective than CS-834. However, at the same dosage (50 mg/kg three times daily), CS-834 was as effective as amoxicillin for the treatment of respiratory tract infections caused by penicillin-resistant *S. pneumoniae*.[42] Fukuoka and colleagues[41] also observed that at doses of 50 mg/kg, cefteran pivoxil and cefpodoxime proxetil had comparable efficacy to that of CS-834 against infections caused by penicillin-resistant *S. pneumoniae.*

CS-834 was well tolerated when given as a single oral dose (up to 400mg) and as multiple-dose regimens of 150mg three times daily for 7 days to healthy volunteers.[39] The pharmacokinetic parameters were very similar when single-dose regimens were compared with multiple-dose regimens. In single-dose studies, the maximum serum concentration (C_{max}) and area under the concentration-time curve (AUC) increase were almost in propor-

tion to the dose. Conversely, the half-life was independent of the dose (approximately 0.7 hours). The plasma protein binding of R-95867 ranges from 16 to 20% and is almost constant and independent of the R-95867 plasma concentration. CS-834 was well absorbed after oral administration and rapidly converted to R-95867.

Food intake did not seem to alter CS-834 pharmacokinetic parameters significantly. However, the co-administration of CS-834 with probenecid increased all the R-95867 pharmacokinetic parameters, suggesting that renal tubular secretion, as well as glomerular filtration, participated in the urinary excretion of R-95867.

In the single-dose regimen, just 1 patient presented with transient soft stool; however, in the multiple-dose regimen, all 6 healthy volunteers had mild transient soft stool. The authors did not discuss the reason for this, but the presence of soft stool may be the consequence of alteration in the faecal flora due to the anaerobic activity of CS-834. One of the volunteers in the multiple-dose regimen showed increased levels of transaminases.[39] Despite the minor adverse effects observed, CS-834 was expected to be an effective therapeutic candidate.

1.3 MK-826

MK-826 (formerly L-749345, or ZD-4433) is a new 1-β-methylcarbapenem with broad-spectrum antibacterial activity and improved stability to hydrolysis by DHP-1.[44,45] MK-826 was considerably more active than imipenem against most members of the family Enterobacteriaceae. In contrast, imipenem has higher activity against *P. aeruginosa*, *Enterobacter cloacae*, *Acinetobacter* spp., and Gram-positive cocci such as *S. aureus*. MK-826 has also shown excellent activity against respiratory pathogens such as *H. influenzae* and *M. catarrhalis*. The activity of MK-826 is similar to that of imipenem against penicillin-susceptible *S. pneumoniae;* however, imipenem has lower MICs for penicillin-resistant *S. pneumoniae*.[46-49] MK-826 was highly active against extended-spectrum β-lactamase (ESBL)-producing *Klebsiella pneumoniae* and *E. coli* isolates.[47,48]

A pronounced concentration-dependent killing has been observed against MRSA for imipenem and MK-826. In contrast, no concentration-dependent killing was detected against methicillin-susceptible *S. aureus* for imipenem and MK-826. Similar to imipenem, MK-826 has shown a post-antibiotic effect (PAE) against Gram-positive bacteria and some Gram-negative species, such as some strains of *H. influenzae* and *E. coli*.[46]

MK-826 was shown to be very effective in the treatment of both localised and systemic murine infections, but its activity was slightly inferior to that of imipenem against all Gram-positive organisms evaluated, including penicillin-resistant pneumococci.[44] Imipenem also showed greater efficacy than MK-826 against systemic infections with *E. cloacae* and *P. aeruginosa*.

Various studies have assessed the pharmacokinetics of MK-826 in animals.[44,49] MK-826 has a long half-life and persists in the circulation longer than imipenem and almost as long as ceftriaxone. In all species tested (mouse, rhesus monkey, chimpanzee and human) the protein binding of MK-826 was very high (≥95%).[49] In healthy volunteers, the half-life of MK-826 was approximately 4.5 hours. The 48-hour urinary excretion of intact MK-826 was approximately 30 to 40% of the dose in male volunteers, and 45% of the dose in female volunteers.[50] Because of its long half-life and high antibacterial potency, MK-826 could be a suitable candidate for once-a-day therapy. It has been used as an intravenous formulation; however, there is potential for the development of an intramuscular formulation. Data obtained from one study showed rapid and complete absorption for an intramuscular dose of MK-826 in rhesus monkeys.[49]

Breakpoints for susceptibility testing have been suggested for MK-826 and its clinical efficacy evaluated in a randomised, double-blind, multicentre evaluation and safety study conducted for treatment of community-acquired pneumonia.[45,51] Outcomes and safety of the following regimens were

evaluated: MK-826 1g, MK-826 2g and ceftriaxone 2g. All regimens were administered intravenously once a day. 75 patients were randomised and received at least 3 days of intravenous therapy. The MK-826 2g regimen showed the highest percentage of clinical cure (96.0%), followed by MK-826 1g (93.0%) and ceftriaxone (85.0%) regimens. No adverse effect was observed in the groups receiving MK-826.[51]

1.4 DA-1131

DA-1131 [(1*R*, 5*S*, 6*S*) - (2S, 4S)-[(*E*)-3methansulphonylamino-1-propenyl] pyrrolidine-4-ylthiol-6-[*R*-1-hydroxiethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid], is a new carbapenem antibacterial recently developed in South Korea.[52] DA-1131 had a broad spectrum of activity against Gram-positive and -negative bacteria, and it seemed to be more active than both imipenem/cilastatin and meropenem against *S. aureus*, *K. pneumoniae*, *E. cloacae*, *Proteus mirabilis* and *P. aeruginosa*. DA-1131 was more stable to hydrolysis by DHP-1 than imipenem or meropenem, and, similar to these compounds, DA-1131 was resistant to degradation by many types of β-lactamases.[53]

Studies have demonstrated that DA-1131 was unstable when incubated in various pH solutions, especially at low and high pHs. It was also unstable after incubation in human plasma, rat liver homogenate and human gastric juice. However, it seemed to be stable in human plasma for up to 12 hours' storage at –20°C.[52] Pharmacokinetic studies in animals have shown that plasma protein binding was less than 10%. The pharmacokinetic parameters of DA-1131 were generally independent of the dose in four animal species evaluated: rats, mice, rabbits and dogs.[53] This new carbapenem was distributed mainly in the kidney and liver in comparison with other tissues in all four species. Glomerular filtration was the main route of excretion for DA-1131.[53-55] The renal clearance of DA-1131 decreased significantly in rabbits when it was administrated with probenecid, denoting the importance of renal tubular secretion. In contrast, probenecid displays no effect in rats, indicating that DA-1131 was mainly excreted by glomerular filtration in this species.[54] In addition, treatment with probenecid did not inhibit the renal tubular reabsorption of DA-1131 in dogs.[55]

Although there are no studies evaluating the pharmacokinetics of DA-1131 in healthy volunteers, a prediction of human pharmacokinetics was estimated using data obtained from 4 different animal species. Based on these models for a human weighing 70kg, the clearance of DA-1131 and its volume of distribution at steady state would be 21.2 L/h and 12.2L, respectively, after administration of 50 mg/kg. Using the same dose as a parameter, the plasma concentration of DA-1131 would be close to 1 mg/L after 60 minutes of administration.[54] In rabbits and dogs, high doses of DA-1131 resulted in severe nephrotoxicity. However, the association of DA-1131 with betamipron, a renal anionic transport inhibitor, avoided tubular necrosis, protecting the kidneys for a long period of time.[55] This new compound is currently being evaluated in preclinical trials.

1.5 Other Agents

Several other carbapenems have been developed for either parenteral or oral administration, including S-4661,[56] DZ-2640[57] and ER-35786 in Japan,[58,59] and the tetrahydrofuranyl-1β-methylcarbapenenms CL-191121, CL-188624 and CL-190294 in the US.[60,61] Preliminary studies have shown these compounds have *in vitro* antibacterial activity and potency similar to those demonstrated by imipenem and meropenem. T-5575, a carboxypenem being developed in Japan, showed higher stability to zinc-dependent β-lactamases when compared with other carbapenems.[62] However, no further studies have been carried out with this compound. Thus, the success of these new compounds will depend most on their pharmacokinetic/pharmacodynamic characteristics and safety profiles.

2. Trinems

2.1 Sanfetrinem

Sanfetrinem [(4S,8S)-4-methoxy-(9R,10S,12R)-10-(1-hydroxyethyl)-11-oxo-1azatricyclo[7.2.0.03,8] undec-2-ene-carboxylate] has shown a broad spectrum of antibacterial activity with high potency against most clinically important species. It is highly active against methicillin-susceptible staphylococci, penicillin-susceptible streptococci and ampicillin-susceptible enterococci. However, its activity is reduced in Gram-positive cocci that present high level resistance to other β-lactam agents.[63-71]

As for other β-lactams, the activity of sanfetrinem correlates with penicillin activity against pneumococci.[64,69] Doern et al.[69] evaluated 1528 *S. pneumoniae* isolates and sanfetrinem was 4- to 8-fold more active than ampicillin or ceftriaxone. MIC_{90} values of penicillin-susceptible (MIC ≤0.06 mg/L) strains were 0.015 mg/L for sanfetrinem and 0.06 mg/L for ampicillin and ceftriaxone, whereas penicillin-resistant strains (MIC ≥2 mg/L) had MIC_{90} values of 1 mg/L for sanfetrinem, 8 mg/L for ampicillin and 4 mg/L for ceftriaxone.[69] Other studies showed similar results.[64,71,72] The *in vitro* activity of sanfetrinem against pneumococci seems to be very similar to that of imipenem, independent of the strain susceptibility to penicillin.[66] The antipneumococal activity of sanfetrinem has also been confirmed in time-kill studies.[72] β-Haemolytic streptococci were usually very susceptible to sanfetrinem with highest MIC_{90} at 0.06 mg/L.[66-68] α-Haemolytic species were also very susceptible to sanfetrinem, with most MIC_{50} values at 0.06 mg/L; however, this species may present sanfetrinem MIC values as high as 2 mg/L.[67,68]

Sanfetrinem has shown excellent activity against Gram-negative bacilli responsible for respiratory tract infections such as *H. influenzae* and *M. catarrhalis*. Among 1536 *H. influenza* strains evaluated,[69] the MIC_{90} for sanfetrinem was 0.5 mg/L and the potency of sanfetrinem was not affected by the production of β-lactamases. In the same study, the MIC_{90} for sanfetrinem of β-lactamase-producing *M. catarrhalis* (688 isolates tested) was only 0.03 mg/L. The *in vitro* activity of sanfetrinem was very similar to that of imipenem against respiratory pathogens.[63]

The activity of sanfetrinem against Enterobacteriaceae seemed to be most similar to that of imipenem. In a relatively small number of isolates evaluated by Modugno et al.,[63] imipenem was 2- to 4-fold more active than sanfetrinem against most Enterobacteriaceae species, except for *Proteus* spp. Against these latter pathogens, sanfetrinem was 8-fold more potent than imipenem. Wise et al.[67] found similar MIC results for sanfetrinem against Enterobacteriaceae; however, they did not compare the compound with imipenem.

Only one publication evaluated the *in vitro* activity of sanfetrinem against non-fermentative Gram-negative bacilli.[67] The trinem had no activity against *P. aeruginosa* or *Stenotrophomonas maltophilia*, but had modest activity against *Acinetobacter* spp. (MIC_{50} 2 mg/L; MIC_{90} 6 mg/L). There was no obvious pattern of cross-resistance between the β-lactams versus *Acinetobacter* spp. isolates. For example, some strains were not susceptible to cefpirome (MIC ≥16 mg/L) and yet susceptible to sanfetrinem (MIC 1 to 4 mg/L).

Sanfetrinem has shown good activity against some anaerobic bacteria, such as *B. fragilis* (MIC_{50} 0.06 to 0.1 mg/L; MIC_{90} 0.25 to 0.5 mg/L), *Clostridium perfringens* (MIC_{90} 0.03 to 0.06 mg/L) and peptostreptococci (MIC_{90} 0.12 mg/L). However, *Clostridium difficile* strains have shown higher MICs (MIC_{90} 4 to 8 mg/L).[63,67,73]

The interactions of sanfetrinem with representative class A, B, C and D β-lactamases are similar to those of the clinically available carbapenems, except that sanfetrinem was a weaker inducer of AmpC enzyme types.[74,75]

Two studies evaluated the effect of sanfetrinem on the interaction between human polymorphonuclear granulocytes (PMNs) and antibacterial-resistant strains.[76,77] These studies suggest that sanfetrinem acts directly on the bacteria in such a way that it enhances bacterial vulnerability to phagocyte activity. The results of these studies also indicated

that sanfetrinem is able to rapidly and effectively penetrate human PMNs in its microbiologically active form by a passive process. Once it had been accumulated, sanfetrinem was capable of acting effectively on the replicating phagocytosed bacteria.

Very few studies evaluating the *in vivo* antibacterial activity of the trinems have been published. Sanfetrinem cilexitel, the prodrug of sanfetrinem, showed potent efficacy against experimental murine septicemia caused by *S. aureus*, *Streptococcus pyogenes* and *E. coli*. In murine respiratory infections caused by penicillin-susceptible and -resistant *S. pneumoniae*, sanfetrinem was more effective than amoxicillin in reducing the number of bacteria in infected lungs.[78]

There has been very limited published information on the pharmacokinetics of sanfetrinem. A preliminary study showed high plasma drug concentrations (43.2 mg/L) after an intravenous infusion of sanfetrinem 1g.[79] Following a 500mg oral dose of prodrug, the maximum plasma drug concentration varied from 2.5 to 3.5 mg/L in two studies using different formulations.[80] The half-life also varied widely (1.3 to 1.97 hours). The percentage of the drug recovered in the urine was approximately 25% after the oral dose and 60% after intravenous administration.

Sanfetrinem penetrates rapidly into inflammatory fluid; however, its penetration is relatively poor when compared with other β-lactams. Sanfetrinem penetration is approximately 50%, compared with 81% for ampicillin, 79% for cefprozil and near complete for cefpodoxime.[80] The poor penetration into inflammatory fluid cannot be explained by the serum protein binding since the rate for sanfetrinem protein binding is 20%. However, similar to the carbapenens, sanfetrinem had a modest lack of stability in body fluids, which could explain its poor penetration into the inflammatory exudate.

The results of these preliminary pharmacokinetic studies[80] suggest that the 125mg oral dose may be sufficient to treat pathogens with MICs ≤0.12 mg/L, such as highly susceptible *S. pneumoniae* and other streptococci, *Neisseria* spp., and methicillin-susceptible *S. aureus*. However, the higher oral dose (500mg) would be appropriate to treat *Enterobacteriaceae* and more resistant respiratory tract infections since these pathogens have higher MICs (≥2 mg/L). In addition, sanfetrinem has shown a PAE against pneumococci, indicating that the compound may be administered twice daily, despite the documented short half-life.[72]

3. Conclusions

The therapeutic crisis produced by emerging antimicrobial resistance has compromised the chemotherapy of hospitalised and clinic patients with serious infections. A wide variety of microbes have acquired resistance to antimicrobials over the last two decades. Initially, we noticed the rise of Gram-positive cocci as the dominant species causing various antimicrobial-resistant infections.[81,82] More recently, the appearance and dissemination of multiresistant Gram-negative bacilli, principally *Acinetobacter baumannii* and *P. aeruginosa* strains susceptible only to polymyxins, has become alarming.[83-85]

To overcome these pathogens the development of new drugs such as the carbapenems/trinems has presented a dilemma: enhanced antibacterial activity at the cost of increased toxicity. A review of the currently available medical literature shows that very few β-lactams with spectrum expansion beyond the carbapenems meropenem and imipenem will be commercially available in the near future. The appearance of new antimicrobial agents from other classes or a new class of agents with activity against the carbapenem-resistant Gram-negative bacilli in the next few years also seems unlikely.

Acknowledgements

We would like to thank Dr Ronald N. Jones for critically reviewing the manuscript.

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