BIOCHEMICAL PHARMACOLOGY 71 (2006) 1085–1095

available at www.sciencedirect.com

SCIENCE DIRECT®

journal homepage: www.elsevier.com/locate/biochempharm

Redefining penems

Axel Dalhoff[a,*], *Nebojsa Janjic*[b], *Roger Echols*[c]

[a] *University Hospital Schleswig-Holstein, Campus Kiel, Institute for Infection Medicine, Brunswiker Str 4, D-24105 Kiel, Germany*
[b] *Replidyne, Inc., 1450 Infinite Drive, Louisville, CO 80027, USA*
[c] *Replidyne, Inc., 472 Wheelers Farms Road, Milford, CT 06460, USA*

ARTICLE INFO

Article history:
Received 2 September 2005
Accepted 6 December 2005

Keyword:
Penems

ABSTRACT

The antimicrobial class of penems has the potential to address most of the relevant resistance issues associated with β-lactam antibiotics because of their exceptionally broad spectrum of antibacterial activity and their intrinsic stability against hydrolytic attack by many β-lactamases including ESBL and AmpC enzymes. The subclass of carbapenems covers the spectrum of hospital pathogens whereas the subclass of penems covers community pathogens. The only currently available penem, faropenem, has a low propensity for resistance development, β-lactamase induction and selection of carbapenem-resistant *Pseudomonas aeruginosa*. This makes it attractive for the treatment of community-acquired infections and for step-down or sequential therapy following carbapenem treatment without jeopardizing the activity of carbapenems or the entire β-lactam class in the hospital environment.

1. Introduction

The discovery of penicillin in 1929 [1] and its isolation in 1940 [2], the isolation of 6-aminopenicillanic acid in 1959 [3] and the synthesis of 7-aminocephalosporanic acid in 1962 [4] provided the basis for the initial development of β-lactams antibiotics. By the middle of the 1970s, virtually all the significant developments had been achieved by adding different side chains to the classical penicillin (i.e., penam) and cephalosporin (i.e., cephem) nuclei [5]. Since that time, further attempts to manipulate the penicillin or cephalosporin nucleus failed to deliver substantially novel agents [6].

Nevertheless, the large variety of commercially available β-lactams antibiotics covered a broad range of Gram-positive and Gram-negative bacterial species, including penicillinase-producing staphylococci. Because of their widely recognized in vitro activity, clinical efficacy and low toxicity, β-lactams have become the cornerstones of antibacterial treatment. However, their extensive use and sometimes inappropriate overuse has contributed to the development of microbial resistance to these agents. Resistance has occurred because of the expression of bacterial β-lactamases, lower target affinity to the modified penicillin-binding proteins, impaired entry or increased efflux. Consequently, there remains a high medical need for the development of new agents that overcome the structurally inherent weaknesses of the existing penams and cephems.

Since the late 1970s, considerable progress in useful alterations of the basic penam or cephem ring structures has been made. Naturally occurring oxapenams (e.g., clavulanic acid), monocyclic β-lactams (e.g., monobactams) and carbapenems (e.g., olivanic acid) were discovered [7–10] and the penems were synthesized [11]; these compounds were found to be inhibitors of some β-lactamases. Drugs that belong to some of these structural classes are still used widely in clinical practice.

Thienamycin, which is produced by *Streptomyces cattleya* and identified because of its exceptionally broad spectrum and high β-lactamase stability, was the first representative of a

* *Corresponding author.*
E-mail addresses: Adalhoff@t-online.de (A. Dalhoff), Njanjic@replidyne.com (N. Janjic), rechols@replidyne.com (R. Echols).
0006-2952/$ – see front matter
doi:10.1016/j.bcp.2005.12.003

diverse family of naturally occurring and synthetic antibiotics that all have the carbapenem nucleus in common [12]. The term ''carbapenem'' was introduced into the nomenclature by the researchers as it ''denotes similarity with the 4:5 fused ring lactam of penicillins, the substitution of carbon for sulfur and the presence of unsaturation in the five-membered ring'' [13]. Since the discovery of thienamycin, many other related compounds have been extensively studied [14–16], but most have been either abandoned as development candidates or have not yet been fully exploited. The compounds that are in clinical use in North America and in Europe are imipenem, meropenem, and ertapenem; doripenem is under development. In Japan, two other carbapenems are used clinically, panipenem and biapenem. Like thienamycin, all of these compounds have a carbon atom at position 1 of the penem core structure and are thus classified as carbapenems. Faropenem, which is orally bioavailable, is in clinical use in Japan (as the sodium salt) and is in the pre-registration phase in the U.S. as the medoxomil (or daloxate) ester. Faropenem has obvious structural similarities to carbapenems but also an important difference with a sulfur atom at position 1 (Fig. 1). Therefore, the taxonomic assignment of faropenem should be distinct from but related to carbapenems. Consequently, the Clinical Laboratory Standards Institute (CLSI) recently renamed the carbapenem class of drugs as simply ''penems'' with two subclasses, i.e., ''carbapenems'' and ''penems.'' The appearance in the CLSI M100 Glossary is as follows: (1) antimicrobial class = penem; (2) antimicrobial subclass = penem with the only agent faropenem included and the second subclass = carbapenems, which currently includes doripenem, ertapenem, imipenem, and meropenem. This assignment follows exactly the precedent of the 5:6 fused ring system of cephems.

This article provides a brief synopsis of the chemical and functional identities, similarities, and differences between the two subclasses, i.e., the penems and the carbapenems. It is not the aim of this article to summarize in depth the antibacterial spectra and potency of penems, their pharmacology or their clinical utility and safety.

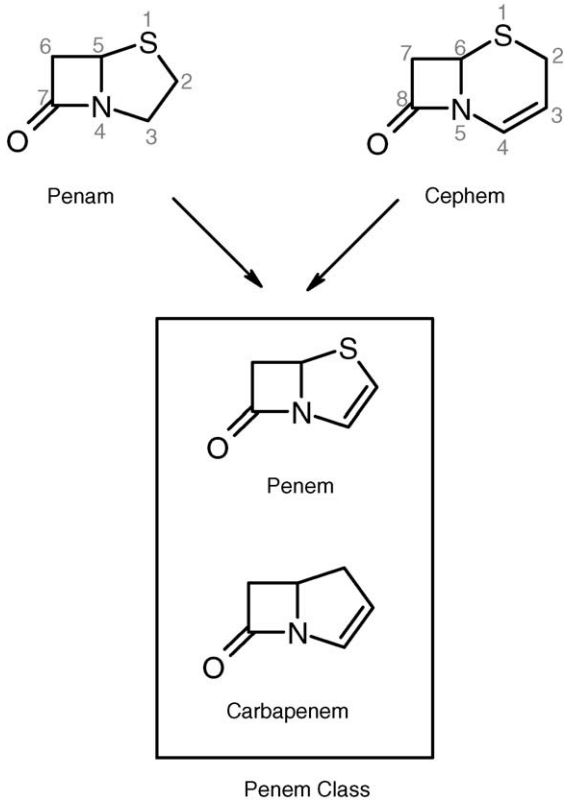


Fig. 1 – General structures of penems and carbapenems as they relate to penams (penicillins) and cephems (cephalosporins).

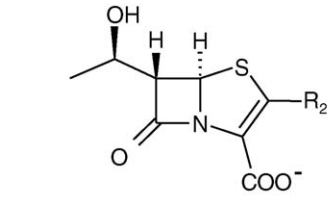
2. Chemistry

In general, β-lactam antibiotics consist of the 4-membered β-lactam ring fused either to a five-membered (as in penams and penems) or six-membered (as in cephams or cephems) heterocyclic ring which is either saturated or unsaturated with a double bond positioned either between C-2 and C-3 of the five-membered heterocycle or C-3 and C-4 of the six-membered heterocycle (Fig. 1). The chemical reactivity of the β-lactam ring, which is important for antibacterial activity, is influenced to a large degree by the nature of the five- or six-membered rings to which it is fused.

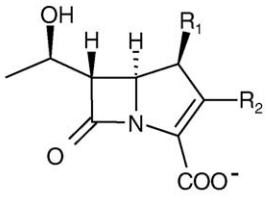
2.1. *Antimicrobial class of penems*

Penems (as a class) differ from the conventional penicillins and cephalosporins by two features: first, the C-6 hydroxyethyl side chain of thienamycin and most other carbapenems as well as faropenem is radically different from the acylamino side chain of the penicillins and the cephalosporins. Second, the hydrogen atoms at C-5 and C-6 of the penems are in the *trans*-orientation, i.e., each hydrogen is on the opposite side of the β-lactam ring, with *S* stereochemistry at the C-6 position (Fig. 2). In penicillins and cephalosporins, both hydrogens are in the *cis* configuration, with *R* stereochemistry at the corresponding C-6 or C-7 position. These differences result in the entire C-6 side chain of penems being oriented on the opposite side of the β-lactam ring compared to the analogous position of penicillins and cephalosporins. This unusual stereochemical configuration is responsible for making the penems in general remarkably stable to degradation by β-lactamases.

A shared feature of penems as a class is the double bond between positions C-2 and C-3. Like with cephalosporins, the presence of a double bond conjugated to the β-lactam nitrogen increases the reactivity of the β-lactam ring in two ways. First, the double bond conjugated to the amide nitrogen competes for the unshared nitrogen electrons thus reducing the extent to which they are delocalized into the adjacent carbonyl group and raising the ground state energy of the β-lactam ring [11]. Second, the conjugated double bond reduces the basicity of the departing amine nitrogen thus making it a better leaving group and lowering the transition state energy of the β-lactam ring cleavage [17,18]. The net effect is increased reactivity of the β-lactam ring to various nucleophiles including water (i.e., hydrolysis), amines, as well as the active site serine residues of penicillin-binding proteins.



Penem



Carbapenem

	R_2
Faropenem	

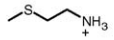
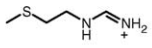
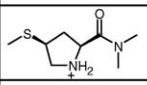
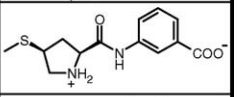
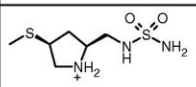
	R_1	R_2
Thienamycin	H	
Imipenem	H	
Meropenem	Me	
Ertapenem	Me	
Doripenem	Me	

Fig. 2 – Structural comparison of penem and carbapenem subclasses.

2.2. *Antimicrobial subclass of carbapenems*

Carbapenems are considered to be intrinsically less stable than penams. The clinical development of thienamycin was prevented by its instability in both concentrated solutions and the solid state; the primary amine in the C-2 side chain of one thienamycin molecule is both a base and a strong nucleophile that can interact with the β-lactam ring of a second molecule to assist in hydrolysis or to form an inactive dimer. Furthermore, thienamycin is quickly hydrolyzed by the renal enzyme dehydropeptidase-I (DHP-I) and its degradation products are nephrotoxic [19,20]. Imipenem, bearing a more basic amidine function which is essentially fully protonated at physiological pH, is chemically more stable than thienamycin but has to be co-administered with cilastatin to prevent hydrolysis by DHP-I [20]. Cilastatin also reduces the nephrotoxicity seen with imipenem alone. Meropenem is relatively stable to DHP-I because of its 1-β-methyl side chain and can be administered as a single agent [21]. In addition, the secondary amine of the C-2 side chain of meropenem is sterically more hindered compared to thienamycin (Fig. 2). Nevertheless, both imipenem and meropenem are rather unstable at 25–37 °C. Aside from hydrolysis, the instability of imipenem results from a complex, pH-dependent process that can be accounted for by the intermolecular attack on the β-lactam ring by the carboxyl group or the formylimidoyl group [17,23]. In meropenem, the 1-β-methyl group provides some degree of protection against attack on the β-lactam ring [24], however, its stability in concentrated solution remains limited [17]. Both imipenem and meropenem are degraded by 70 and 60%, respectively, at 37 °C within 24 h [17,22]. Published data on the stabilities of ertapenem and doripenem, respectively, are not yet available; however, it is reasonable to expect that both carbapenems are relatively unstable because of their structural similarity to meropenem. According to the product information, the lyophilized powder of ertapenem has to be stored below 25 °C and the dissolved drug has to be used within 6 h.

Another shared feature of carbapenems is a positively charged C-2 side chain due to the basic amine or amidine moieties that are extensively protonated at physiological pH.

2.3. *Antimicrobial subclass of penems*

The first penem was synthesized by Woodward as a fusion of the penam and cephem nuclei (Fig. 1). The importance of Woodward's synthetic achievement is best illustrated by the question he posed: ''Suppose we put the double bond (of cephalosporins) in the 5-membered ring (of the penam system): will we have here the best of both worlds?'' [11]. Unlike the carbapenems, this hybrid β-lactam structure does not occur naturally, and the penems are produced entirely synthetically. With smaller C–S–C bond angle and longer C–S bond length, the presence of a thiazoline ring with sulfur at position 1 instead of carbon in a pyrroline ring results in altered conformation of the five-membered ring and reduced intra-ring stress [17,18,25]. At present, faropenem is the only representative of this subclass that is either in its pre-registration phase (U.S., faropenem medoxomil) or is commercially available (Japan, faropenem sodium).

Although faropenem shares with the carbapenems the same unsaturation in its five-membered ring as well as the stereochemistry and substituents in the β-lactam ring, it differs from the carbapenems in that it lacks a protonatable C-2 side chain which in faropenem is a chiral, abasic tetrahydrofuran ring. Crystal structures of faropenem and related

Table 1 – In vitro activities of carbapenems and the penem faropenem against selected key pathogens[a]

	Dori	Erta	Imi	Mero	Faro
E. coli, ESBL−	≤0.015/≤0.015	≤0.015/≤0.015	0.12/0.25	≤0.06/≤0.06	0.25/1
E. coli, ESBL+	0.03/0.06	0.03/0.05	0.25/0.5	≤0.015/0.06	1/1
K. pneumoniae ESBL−	0.03/0.03	≤0.015/0.03	≤0.06/≤0.06	≤0.12/≤0.12	0.5/1
K. pneumoniae ESBL+	0.06/0.12	0.06/0.25	0.5/1	0.03/0.06	0.5/1
P. aeruginosa	0.25/0.5	4/16	1/2	0.25/1	>128/>128
H. influenzae	0.12/1	0.06/0.25	0.5/1	–	0.25/0.5
M. catarrhalis	≤0.015/0.03	≤0.015/≤0.015	0.06/0.12	≤0.015/≤0.015	0.25/0.5
S. pneumoniae (penS)	≤0.015/≤0.015	≤0.015/0.03	≤0.06/≤0.06	≤0.015/≤0.015	≤0.015/0.03
S. pyogenes (penS)	≤0.015/≤0.015	≤0.015/≤0.015	≤0.015/≤0.015	≤0.015/≤0.015	0.03/0.03
S. aureus (MSSA)	0.06/0.06	0.25/0.25	≤0.06/≤0.06	0.06/0.25	0.12/0.12
S. aureus (MRSA)	1/4	2/16	0.12/2	1/8	2/2
E. faecalis	2/>32	8/>32	1/>8	8/16	1/8
B. fragillis	0.25/0.5	0.5/1	0.25/1	0.12/1	0.25/2
Prevotella spp.	0.12/0.25	0.25/1	0.25/1	0.12/0.25	0.25/0.5

[a] Data represent MIC_{50}/MIC_{90} values in μg/mL [28–35].

molecules have revealed that the already constrained cyclic tetrahydrofuran ring at the C-2 position is further conformationally restrained by the van der Waals contact between the S1 and the O2′ atoms [26]. It is probably because of these unique structural differences that faropenem shows remarkable chemical stability. Faropenem is inactivated by only 6% in aqueous solution at 37 °C and neutral pH after 24 h and its stability is superior to that of cephalosporins that contain basic substituents (like carbapenems) at the C-3 position [17]. Faropenem is also relatively stable to hydrolysis by DHP-I [27]. Thus, faropenem as a representative of the penem subclass is chemically distinct from the carbapenems.

These differences may have pleiotropic implications. The stability and neutral C-2 side chain of faropenem versus the instability of carbapenems and positively charged side chain at physiological pH have clinical relevance in that, first, carbapenems as injectable drugs have a limited dosing flexibility. Second, excitability of the central nervous system (CNS) is closely correlated to the positive charge of the molecule. Third, the protonation state (and thus charge) of the C-2 side chain has an impact on the antibacterial spectrum of the carbapenems and penems, respectively. These aspects will be discussed below.

3. Antibacterial spectrum

In general, the antibacterial spectrum, activity and clinical use of an antibiotic are dependent on many physicochemical factors such as lipophilicity/hydrophilicity and the charge at physiological pH. In general, activity against Gram-positive bacteria is favored by lipophilicity, whereas hydrophilicity allows penetration through the water-filled porins of Gram-negative organisms. Antipseudomonal activity in particular and in a broad sense activity against Gram-negative bacteria is dependent on the charge of the drug.

Table 1 provides an overview of the antibacterial activities of carbapenems and the penem faropenem against bacterial species selected according to the key pathogens causing bacterial infections in the Food and Drug Administration (FDA) approved or clinically studied indications (Table 2). This synopsis of the in vitro activities of carbapenems and the

Table 2 – FDA-approved indications for the carbapenems, imipenem, meropenem, and ertapenem

Imipenem/cilastatin (Primaxin)	Meropenem (Merrem)	Ertapenem (Invanz)	Doripenem[a]	Faropenem[a]
Lower respiratory tract infection	Skin and skin structure infection	Complicated intra-abdominal infection	Nosocomial pneumonia (fast track)	Acute bacterial sinusitis
Urinary tract infection	Intra-abdominal infection	Complicated skin and skin structure infection	Complicated skin and skin structure infection	Acute exacerbations of chronic bronchitis
Intra-abdominal infection	Bacterial meningitis (pediatric)	Community-acquired pneumonia	Complicated urinary tract infections including pyelonephritis	Community-acquired pneumonia
Gynecological infection		Complicated urinary tract infection		Uncomplicated skin and skin-structure infections
Bacterial septicaemia		Acute pelvic infection		
Bone and joint infection				
Skin and skin structure infection				
Endocarditis				
Polymicrobial infection				

[a] For doripenem and faropenem, indications under clinical development are listed.

penem [28–35] clearly indicates that zwitterionic carbapenems (e.g., doripenem, imipenem, meropenem) have favorable activity against *Pseudomonas aeruginosa* and Enterobacteriaceae. Ertapenem, which has a net negative charge at physiological pH with a second carboxylate group at the C-2 side chain, also exhibits activity against a broad spectrum of Enterobacteriaceae and is less active than imipenem against *P. aeruginosa* and the enterococci. Molecules with uncharged substituents at the C-2 position (e.g., faropenem), however, are less active against Enterobacteriaceae or inactive against *P. aeruginosa* as compared to imipenem (Table 1). In general, β-lactamase (ESBL) production status of the Enterobacteriaceae does not affect the activity the penems in Table 1.

Furthermore, both penem subclasses exhibit good activity against methicillin-susceptible staphylococci, penicillin-susceptible and penicillin-resistant streptococci and other pathogens causing community-acquired respiratory tract infections as well as certain anaerobes. None of these drugs have clinically relevant activity against methicillin-resistant isolates of *S. aureus*.

In summary, the differences in the chemistry of the two penem subclasses are mirrored by the differences in their antibacterial spectra. The subclass of carbapenems covers hospital pathogens, whereas the penem subclass representative faropenem is active against pathogens causing community-acquired infections. In this context it is worth noting that all the carbapenems have to be administered parenterally; however, faropenem medoxomil (previously called faropenem daloxate) has very good oral bioavailability of 70–80%. The high oral bioavailability of faropenem medoxomil is in large part due to the ester pro-drug form of the antibiotic. While faropenem sodium is poorly absorbed (20–30%), faropenem medoxomil is rapidly absorbed upon oral administration and subsequently hydrolyzed in serum to the active moiety faropenem. Therefore, faropenem medoxomil may be a suitable candidate for sequential therapy (i.e., switch from intravenous to oral administration) and a step-down therapy (i.e., more focused spectrum) following previous intravenous treatment of infections like community-acquired pneumonia with e.g., ertapenem. Its primary use, however, is likely to be in ambulatory patients with community-acquired infections.

4. Mechanisms of and propensity for resistance selection in difficult to treat organisms

In general, the activity of β-lactams is either affected by target modifications, efflux, or by the production of β-lactamases. To date, the latter mechanism has proved to be the most important clinically. Although more than 400 β-lactamases have been described, they can be classified on the basis of their primary structure into four molecular classes (class A through D, Ambler-classification), or phenotypically on the basis of their substrate spectrum (Bush-classification) and responses to β-lactamase inhibitors. Class A, C, and D are active site serine-β-lactamases and class B enzymes are metallo β-lactamases. Class A and D enzymes are frequently encoded by genes carried on plasmids, thus contributing to their intraspecies spread and interspecies exchange; class B and C enzymes are frequently encoded by chromosomal genes and are therefore confined to particular species. The substrate preferences of the various β-lactamases are summarised in Table 3. In contrast to penicillins (exemplified by penicillin G) and cephalosporins (exemplified by cephaloridine), carbapenems and the penem faropenem are stable against hydrolysis by most of the β-lactamases, except class B enzymes [88].

With a *trans*-configured C-6 side chain, penems are intrinsically stable against hydrolysis by almost all class A, C, or D-β-lactamase producing organisms, including those producing ESBL or AmpC β-lactamases. In all the other β-lactam antibacterials the relative configuration at the C-6 is *cis*, and thus, these agents are labile to β-lactamase promoted hydrolysis (Table 3).

More recently, so called ''carbapenemases'' were described. In assessing this threat it is important to note that ''carbapenemases'' are class B enzymes, i.e., metallo β-lactamases. Carbapenemases are a diverse group of β-lactamases, comprising the IMP-, the VIM- and KPC-families as well as SPM- and GIM-enzymes. These enzymes have a wide geographic distribution throughout the world; however, they remain rare. The carbapenemases have the ESBL (i.e., oxyimino-cephalosporins) and AmpC (i.e., cephamycins plus oxyimino-cephalosporins) substrate profile and hydrolyze the carbapenems and penems. Most recently, some OXA-type serine β-lactamases with

Table 3 – Substrate preferences of various β-lactamases[a]

Molecular classes (Ambler)	Functional group (Bush)	Activity[b]				Inhibition by clavulanate
		Penicillin	Cephaloridine	Imipenem	Faropenem	
Serine β-lactamases						
A	2a	+++	±	–	–	++
	2b	+++	++	–	–	++
	2c	++	+	–	?	+
	2e	++	++	–	–	++
	2f	++	+	++	?	+
C	1	++	+++	–	–	–
D	2d	++	+	–	Inhibitor	±
Metallo β-lactamases						
B	3	++	++	++	++	–

[a] Modified according to Refs. [40,88].
[b] +++, preferred substrate (highest V_{max}); ++, good substrate; +, hydrolyzed; ±, barely hydrolyzed; –, stable;?, not known as not tested.

carbapenemases activity have been described; these enzymes hydrolyse carbapenems poorly (recent reviews by Walsh et al. [89] and Jacoby and Munoz-Price [90]).

Clearly, β-lactamase stability is of significant clinical relevance since many Enterobacteriaceae have acquired plasmid-mediated β-lactamases. ESBL- or AmpC-producing organisms are being isolated with increasing frequency and have started to spread into the community setting [36]. β-lactamase induction and selection of ESBL producers will not only put the inducing and/or selecting agent at risk but may jeopardize the entire class of β-lactam antibiotics.

To preserve the utility of penems as powerful agents for the treatment of ESBL producers, it is of utmost importance that penems do not act as β-lactamase inducers and/or that they do not select for resistance and ESBL production in Enterobacteriaceae, in particular the gut Enterobacteriaceae. Imipenem acts as a strong inducer of ESBL production, whereas meropenem acts as weak inducer; both carbapenems were not selective for derepressed mutants [37–39]. In contrast to carbapenems, faropenem was not found to act as an ESBL inducer [40]. This is likely to be due to its preferential affinity for the high molecular weight penicillin-binding proteins [41]. Published data on ertapenem and doripenem are not yet available. Thus, faropenem is at present the only agent within the entire penem class that is known not to act as an inducer of ESBL/AmpC enzymes. Therefore, it is unlikely that faropenem will select for ESBL producers; this is of clinical relevance since the gut Enterobacteriaceae are exposed to faropenem following its oral administration, although this problem is alleviated to some extent by the high oral bioavailability of the pro-drug form of faropenem (faropenem medoxomil) and the fact that the pro-drug lacks antimicrobial activity.

The pronounced antibacterial effect of the class of penems against Enterobacteriaceae but the variable degree of activity of carbapenems and the lack of activity of faropenem against *P. aeruginosa* results from an interplay of poor penetration and efflux. In contrast to penams and cephems which are effluxed by a large variety of different transporters in Gram-positive and Gram-negative bacteria, carbapenems and penems are extruded only by efflux pumps expressed in *P. aeruginosa* [91]. Multidrug efflux in *P. aeruginosa* is mediated by four pumps, with MexAB-OprM being the most important one. With respect to their anti-pseudomonal activities it is interesting to note that in contrast to any other carbapenem or penem, imipenem is a poor substrate for MexAB-OprM, probably because it lacks any lipophilic phenyl or heterocyclic side chains. Consequently, mutations in MexAB-OprM increase the MICs of all the carbapenems except imipenem.

Carbapenems but no other β-lactams are taken up through the porin OprD; the primary role of OprD is the uptake of basic amino acids. Imipenem is taken up through this porin 10 times faster than meropenem [42]. In contrast, faropenem, with a neutral C-2 side chain, does not penetrate through the OprD porin and therefore does not interfere with imipenem uptake through this channel [43]. Furthermore, faropenem is not likely to select for efflux-mediated carbapenem resistance. Although faropenem is pumped out by the MexAB-OprM efflux system, it appears to have a distinct binding site since it does not interact with other MexAB-OprM substrates (i.e., β-lactams, β-lactamase inhibitors, quinolones, chloramphenicol, sulphamethoxazole, novobiocin) [43,44] (Table 4). Furthermore, two general aspects are worth mentioning: first, all of these efflux pumps, and the MexAB-OprM in particular, are characterized by a very broad substrate specificity. Consequently, chemically unrelated drug classes select for carbapenems resistance. For example, in the era of carbenicillin and ticarcillin therapy of *P. aeruginosa* infections these penicillins selected for carbapenem resistance. Thus, resistance mediated by porins and pumps is unspecific and not a class phenomenon. Second, efflux may cooperate with other resistance mechanisms. In *P. aeruginosa*, the high-level carbapenem resistance results from the interplay between outer membrane barrier, active efflux by MexAB-OprM, and AmpC derepression. As mentioned above, faropenem does not derepress AmpC production.

As would be anticipated, assessments of resistance selection with faropenem have confirmed an almost non-existent induction of carbapenem resistance in *P. aeruginosa*. It is likely therefore that faropenem may not affect the clinical usefulness of imipenem or meropenem in the treatment of severe infections due to non-fermenters in the hospital.

The carbapenems, however, do select for cross-resistant *P. aeruginosa* mutants [47]. Imipenem largely escapes efflux-mediated resistance in *P. aeruginosa* but is affected by a mutational loss of OprD, which occurs frequently during imipenem therapy [49–51]. The OprD mutants selected with imipenem are mostly resistant to carbapenems only. Ertapenem-selected mutants develop through OprD loss and another, yet undefined mechanism, called MK-X [46]. It is likely that this mechanism is associated with additional membrane modifications. Ertapenem also selects for MexAB-OprM mutants, as well as other phenotypically diverse mutants [52]. Likewise, meropenem and doripenem select

Table 4 – Consequences of mutations affecting efflux pumps and/or outer membrane proteins[a]

Mutational event	Dori	Erta[b]	Imi	Mero	Faro[b]
Up regulation of MexAB-OprM	R	R	–	R	R
Up regulation of MexEF-OprN	nd	nd	r/R	R	(r)
Loss of OprD	r	R	R	r	–
Loss of OprD plus up regulation of MexAB-OprM	R	R	R	R	R

–: No effect on MICs, r: moderate effect on MICs, R: resistance usually conferred or substantial increase in MICs (≥8-fold) in case of intrinsic resistance. (r) MexEF-OprN over expression occurs only in MexAB-OprM deficient background; thus, this phenomenon may not be clinically relevant, nd: not done.

[a] Modified according to [51] and amended with data from [46,49,52].

[b] Ertapenem and faropenem are intrinsically inactive against *P. aeruginosa*.

for OprD and efflux mutants [45,49] (Table 4). Although the selection of efflux and porin double mutants seem less likely in vivo [48,51], efflux mutants are often combined with other drug-resistant phenotypes, including resistance to non-β-lactam antibiotics. Consequently, meropenem-, doripenem- and ertapenem-resistant *P. aeruginosa* mutants are cross-resistant to carbapenems, other β-lactams and non-β-lactam antibacterials.

5. Pharmacodynamics

The in vitro activities of antibacterial agents are most commonly described by determining the minimal inhibitory concentration (as summarized in Table 1) or by performing time-kill experiments using constant drug concentrations. Typically, the bactericidal activities of penicillins and cephalosporins show minimal enhancement with increasing drug concentrations beyond the concentration producing a maximal effect, which is generally near the MIC [48,53]. Likewise, the in vivo efficacy is dependent on the time that serum concentrations exceed the MICs [53,54], but independent of maximal serum concentrations.

However, penems are not typical of the β-lactams class. Carbapenems such as imipenem, meropenem and ertapenem show increasing bacterial killing with increasing concentrations; these observations have been made with *S. aureus*, *S. pneumoniae*, *H. influenzae*, Enterobacteriaceae, *P. aeruginosa* and *Acinetobacter* spp. [55–58]. The penem faropenem kills strains of *H. influenzae*, *M. catarrhalis*, *S. pneumoniae* including penicillin-resistant strains, *S. pyogenes*, *S. aureus*, *E. coli*, *K. pneumoniae* and *B. fragilis* in a concentration-dependent manner also [59,60] (Fig. 3).

Furthermore, carbapenems like imipenem, meropenem and LJC 11,036 as well as experimental penems like CGP17520, CGP31608 and their congeners were found to be exceptional in that they retained superior bactericidal activity against slowly growing cultures of several pathogens [61–66]. The pronounced effect of imipenem or the penems tested against slowly growing bacteria is in contrast to that of penams and cephems. As a general rule, penicillins and cephalosporins kill bacteria at a rate that is strictly proportional to the rate of bacterial growth such that a constant fraction of the population is killed per generation [67]. In contrast, the growth rate is not the rate-limiting attribute for the bactericidal activity of carbapenems and penems.

Another aspect differentiating penicillins and cephalosporins from the penem class is the impact of drug exposure on organism growth after the elimination of the drug from the focus of infection, i.e., the post-antibiotic effect (PAE). Moderate to prolonged PAEs have been found with carbapenems [56] and the penem faropenem [59] but minimal or no PAEs were seen with penams or cephems against Gram-negative bacteria and streptococci [53,54].

Studies integrating pharmacokinetics (PK) and pharmacodynamics (PD) have demonstrated that the efficacy of β-lactam antibiotics in general is dependent on the time during which free drug serum concentrations remain above the MIC ($T > \text{MIC}$). The carbapenems and the penem faropenem require distinctly less $T > \text{MIC}$ (approximately 20% of the dosing interval) than penicillins which in turn require slightly less $T > \text{MIC}$ than cephalosporins [54]. Most of the penams and cephems require $T > \text{MIC}$ of approximately 40% of the dosing interval [54] (Table 5). These differences in the magnitudes of the PK/PD indices required for efficacy mirror the differences in the PD characteristics between carbapenems or penems, on the one hand, and penams or cephems, on the other.

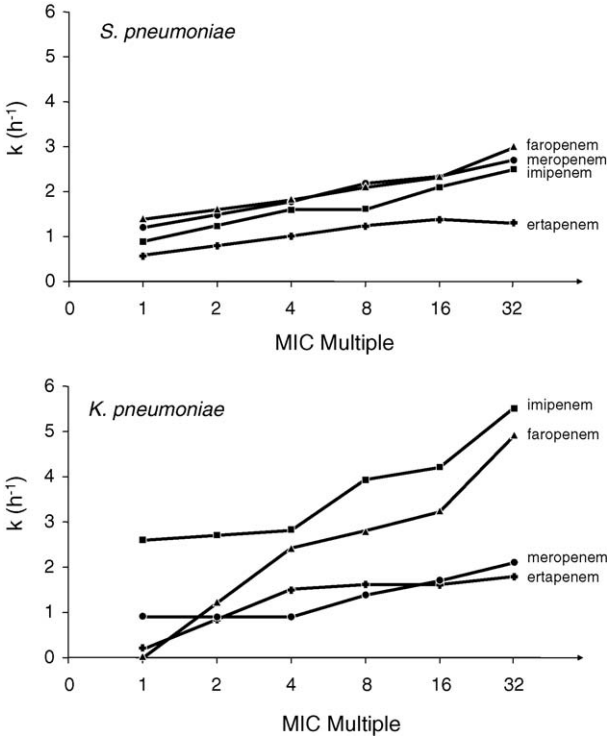


Fig. 3 – Apparent first-order kill rate constants (*k*) of carbapenems and the penem faropenem against *S. pneumoniae* and *K. pneumoniae* as a function of concentration. The kill rate constants for each point were calculated as described in Ref. [58] by analyzing the time- and concentration-dependent decrease in viable counts. The bacteria were exposed to multiples of their individual MICs.

6. CNS excitability

Although characterized by low toxicity, all β-lactam antibiotics are recognized to have excitatory potential and may cause seizures if given at high doses, particularly in patients with moderate to severe renal insufficiency.

It is suggested that the excitatory potential of β-lactams may be due to inhibition of binding of gamma-aminobutyric acid (GABA) to its receptors [73], thus causing convulsions; however, this explanation is incomplete [14,15,74].

In general, the neurotoxicity of carbapenems depends primarily on their C-2 side chain [75,76]. The convulsant activity of carbapenems in animal models and the affinity of the carbapenems to the GABA receptor A was found to correlate with the basicity of the C-2 side chain. The more basic the side chain, the higher the tendency to produce neurotoxicity [77];

Table 5 – In vivo pharmacodynamic activity of carbapenems and the penem faropenem against *S. pneumoniae* and Gram-negative bacteria

Drug	Infecting organism	$T > MIC$
Faropenem	*S. pneumoniae*	13.9
Ertapenem	*S. pneumoniae*	24.0
Ertapenem	Enterobacteriaceae + *P. aeruginosa*	32.0
Doripenem	*P. aeruginosa*	10.4
Imipenem	*P. aeruginosa*	22.1
Meropenem	*P. aeruginosa*	22.5
Ceftazidime	*P. aeruginosa*	>33.0
Amoxicillin	*S. pneumoniae*	25–30
Ceftriaxone	*S. pneumoniae*	39.0
Cefotaxime	*S. pneumoniae*	38.0

For comparison, the data for three cephems, i.e., ceftazidime, ceftriaxone and cefotaxime, and the penam amoxicillin are provided. The data were generated in the thigh muscle infection model in *neutropenic* mice. Animals were treated with a range of doses and a sigmoid dose–response model derived from the Hill equation was used to calculate the doses of drug producing a net bacteriostatic effect over 24 h. The time above MIC ($T > MIC$, % of 24 h) for each static dose using the free drug concentration were estimated from pharmacokinetics and MIC values. Important to note: The *presence of white blood cells* further enhances the activity of drugs in general approximately two-fold [54]; the activity of faropenem was enhanced about three- to four-fold [68]. Data were compiled from Refs. [30,68–72].

Table 6 – Binding affinity of carbapenems and the penem faropenem for the GABA receptor A[a]

Drug	Concentration needed to inhibit 50% of specific muscimol binding (mM)
Imipenem	0.6
Imipenem/cilastatin	0.5
Meropenem	27.6
Panipenem	0.33
Biapenem	4.2
Doripenem	50.0
Ertapenem[b]	–
Faropenem[c]	>50.0

[a] Binding of the drugs to the GABA receptor A (and by inference their CNS toxicity) was examined by measuring their ability to compete with specific ^{3}H-muscimol binding to the GABA receptors. Data were compiled from Refs. [14,82,85–87].
[b] No data are available.
[c] No inhibition of ^{3}H-muscimol binding was observed at the highest concentration tested (50 mM).

thus, the excitatory potential of carbapenems is: panipenem > imipenem > biapenem > meropenem > doripenem [78–81] (Table 6). The low excitatory potential of faropenem correlates well with the uncharged nature of its C-2 side chain [82–84].

7. Conclusion

Based on differences in their chemical structures, carbapenems and penems represent two distinct subclasses within the antimicrobial class of penems. The structural differences between carbapenem and penem subclasses are mirrored by differences in chemical stability, antibacterial spectra, propensity for resistance selection and CNS excitatory potential. At the same time, carbapenems and penems have in common similar pharmacodynamic characteristics that are different from those of other β-lactam antibiotics.

The antimicrobial class of penems has the potential to address most of the relevant resistance issues associated with β-lactam antibiotics because of their exceptionally broad spectrum of antibacterial activity and their intrinsic stability against hydrolytic attack by many β-lactamases including ESBL and AmpC enzymes. The subclass of carbapenems covers the spectrum of hospital pathogens whereas the subclass of penems covers community pathogens. The only currently available penem, faropenem, has a low propensity for resistance development, β-lactamase induction and selection of carbapenem-resistant *P. aeruginosa*. This makes faropenem medoxomil attractive for the treatment of community-acquired infections and for step-down or sequential therapy following carbapenem treatment without jeopardizing the activity of carbapenems or the entire β-lactam class in the hospital environment. For a community β-lactam antibiotic, this may indeed represent the best of both worlds.

REFERENCES

[1] Fleming A. On the antibacterial action of cultures of a penicillium, with special reference to their use in the isolation of *B. influenzae*. Br J Exp Pathol 1929;10:226–36.
[2] Chain E, Florey HW, Gardner AD, Heatley NG, Jennings MA, Orr-Ewing J, et al. Penicillin as a chemotherapeutic agent. Lancet 1940;236:226–8.
[3] Batchelor FR, Doyle FP, Nayler JWC, Rolinson GN. Synthesis of penicillin, 6-amino-penicillanic acid in penicillin fermentations. Nature 1959;183:256–8.
[4] Morin RB, Jackson BG, Flynn EH, Roeske RW. Chemistry of cephalosporin antibiotics I. 7-Aminocephalosporanic acid from cephalosporin C. J Am Chem Soc 1962;84:3400–1.
[5] Rolinson GN. The Garrod lecture. The influence of 6-aminopenicillanic acid on antibiotic development. J Antimicrob Chemother 1988;22:5–14.
[6] Hamilton-Miller JTM. Chemical manipulations of the penicillin nucleus: a review. Chemotherapy 1967;12:73–88.
[7] Brown AG, Butterworth D, Cole M, Hnascomb G, Hood JD, Reading C. Naturally occurring β-lactamase inhibitors with antibacterial activity. J Antibiot 1976;29:668–9.
[8] Brown AG, Corbett DF, Eglington AJ, Howarth TT. Structures of olivine acid derivatives MM4550 and MM13902; two new, fused β-lactam isolated from *Streptomyces olivaceus*. J Chem Soc Chem Commun 1977;523–525..
[9] Aoki H, Sakai H, Kosaka M, Konomi T, Hosoda J, Nocardicin A. a new monocyclic β-lactam antibiotic. I. Discovery, isolation and characterisation. J Antibiot 1976;29:492–500.
[10] Asai H, Haibara K, Muroi M, Kintaka K, Kishi T. Sulfazecin, a novel β-lactam antibiotic of bacterial origin. Isolation and chemical characterisation. J Antibiot 1981;34:621–7.
[11] Woodward RB. In: Elks J, editor. Recent advances in the chemistry of beta-lactams. London, UK: Royal Society of Chemistry; 1977. p. 167–80.
[12] Kahan JS, Kahan FM, Goegelman RT, Currie MJ, Jackson M, Stapley EO, et al. Thienamycin, a new beta-lactam

antibiotic I: Discovery, taxonomy, isolation and physical properties. J Antibiot 1979;32:1–12.
[13] Birnbaum J, Kahan FJ, Kropp H, MacDonald JS. Carbapenems, a new class of beta-lactam antibiotics. Am J Med 1985;78(Suppl. 6A):3–21.
[14] Dalhoff A, Thomson CJ. The art of fusion: from penams and cephems to penems. Chemotherapy 2003;49:105–20.
[15] Hamilton-Miller JMT. Beta-lactams: variations on a chemical theme, with some surprising biological results. J Antimicrob Chemother 1999;44:729–34.
[16] Bryskier A. Penems: new oral beta-lactam drugs. Exp Opin Investig Drugs 1995;4:705–24.
[17] Viaene E, Chanteux H, Servais H, Mingeot-Leclerq MP, Tulkens PM. Comparative stability studies of antipseudomonal β-lactams for potential administration through portable electrometric pumps (home therapy for cystic fibrosis patients) and motor-operated syringes (intensive care units). Antimicrob Agents Chemother 2002;46:2327–32.
[18] Page MI. Structure–activity relationships: chemical (Chapter 2). In: Page MI, editor. The chemistry of beta-lactams. London: Blackie Academic and Professional; 1992. p. 79–100.
[19] Kropp H, Sundelof G, Hajdu R, Kahan FM. Metabolism of thienamycin and related carbapenems antibiotics by the renal dipeptidase, dehydropeptidase-I. Antimicrob Agents Chemother 1982;22:62–70.
[20] Kahan FM, Kropp H, Sundelof JG, Birnbaum J. Thienamycin: development of imipenem/cilastatin. J Antimicrob Chemother 1983;12(Suppl. D):1–35.
[21] Edwards JR, Turner PJ, Wannop C, Withnell EW, Grindey AJ, Nairn K. In vitro antibacterial activity of SM-7338, a carbapenem antibiotic with stability to dehydropeptidase 1. Antimicrob Agents Chemother 1989;33:215–22.
[22] Swanson DJ, DeAngelis C, Smith IL, Schentag JJ. Degradation kinetics of imipenem in normal saline and in human serum. Antimicrob Agents Chemother 1986;29:936–7.
[23] Smith GB, Dezeny GC, Douglas AW. Stability and kinetics of degradation of imipenem in aqueous solution. J Pharm Sci 1990;79:732–40.
[24] Takuguchi Y, Sunagawa M, Isobe Y, Hamazume Y, Noguchi T. Stability of a 1-β-methylcarbapenem antibiotic, meropenem (SM-7338) in aqueous solution. Chem Pharm Bull 1995;43:689–92.
[25] Sanders CC, Thompson KS. Other beta-lactam antibiotics. In: Gorbach SL, Bartlett JG, Blacklow NR, editors. Infectious diseases. 2nd ed, London: Saunders; 1998. p. 197–204.
[26] Tanaka R, Oyama Y, Imajo S, Matsuki S, Ishiguro M. Structure–activity relationships of penem antibiotics: crystallographic structures and implications for their antimicrobial activities. Bioorg Med Chem 1997;5:1389–99.
[27] Yokota T, Kanda K, Tateda-Suzuki E. SY5555, its in vitro antibacterial activity, affinity to penicillin binding proteins, inactivation of beta-lactamases, synergy with serum complement or cultured macrophages in bactericidal effect and stability against DHP-1. Chemotherapy (Tokyo) 1994;42(S-1):13–24.
[28] Jones RN, Huynh HK, Biedenbach DJ, Fritsche T, Sader HS. Doripenem (S-4661), a novel carbapenem: comparative activity against contemporary pathogens including bactericidal action and preliminary in vitro methods evaluation. J Antimicrob Chemother 2004;54:144–54.
[29] Jones RN, Huynh H, Biedenbach DJ. Activities of doripenem (S-4661) against drug-resistant clinical pathogens. Antimicrob Agents Chemother 2004;48:3136–40.
[30] Odenholt I. Ertapenem: a new carbapenem. Expert Opin Investig Drugs 2001;10:1157–66.
[31] Wexler HM, Molitoris D, John SS, Vu A, Read EK, Finegold SM. In vitro activities of faropenem against 579 strains of anaerobic bacteria. Antimicrob Agents Chemother 2002;46:3669–75.
[32] Schmitz FJ, Boos M, Mayer S, Verhoef J, Milatovic D, Fluit AC. In vitro activity of faropenem and 20 other compounds against β-lactamase-positive and -negative *Moraxella catarrhalis* and *Haemophilus* isolates and the effect of serum on faropenem MICs. J Antimicrob Chemother 2002;49:220–3.
[33] Schmitz FJ, Boos M, Mayer S, Verhoef J, Milatovic D, Fluit AC. In vitro activity of faropenem and 21 other compounds against 385 different genetically characterized isolates of antibiotic-resistant *Streptococcus pneumoniae*. J Antimicrob Chemother 2001;48:148–52.
[34] Critchley IA, Karlowsky JA, Draghi DC, Jones ME, Thornsberry C, Murfitt K, et al. Activities of faropenem, an oral β-lactam, against recent U.S. isolates of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Antimicrob Agents Chemother 2002;46:550–5.
[35] Black JA, Smith-Moland E, Lockhart TJ, Lister PD, Thomson KS. Faropenem: activity against ESBL, AmpC and other β-lactamase producing Enterobacteriaceae. In: Proceedings of the 41st ICAAC, Abstract no. 791; 2001.
[36] Pitout JDD, Nordmann P, Laupland KB, Poirel L. Emergence of Enterobacteriacea producing extended-spectrum β-lactamase (ESBLs) in the community. J Antimicrob Chemother 2005;56:52–9.
[37] Williams RJ, Yang Y-J, Livermore DM. Mechanism by which imipenem may overcome resistance in Gram-negative bacilli. J Antimicrob Chemother 1986;18(Suppl E):9–13.
[38] Shannon K, Phillips I. The effects on β-lactams susceptibility of phenotypic induction and genotypic derepression of β-lactamase synthesis. J Antimicrob Chemother 1986;18(Suppl E):15–22.
[39] Livermore DM, Yang Y. Comparative activity of meropenem against *Pseudomonas aeruginosa* strains with well-characterized resistance mechanisms. J Antimicrob Chemother 1989;24(Suppl A):149–59.
[40] Dalhoff A. High stability to beta-lactamase and low propensity for beta-lactamase induction by faropenem. In: Proceedings of the 45th ICAAC, Abstract no. C1-78; 2005.
[41] Dalhoff A, Nasu T, Okamoto K. Target affinities of faropenem and its impact on the morphology of Gram-positive and Gram-negative bacteria. Chemotherapy 2003;49:172–83.
[42] Köhler T, Michea-Hamzehpour M, Epp SF, Pechere JC. Carbapenem activities against *Pseudomonas aeruginosa*: respective contributions of OprD and efflux systems. Antimicrob Agents Chemother 1999;43:424–7.
[43] Köhler T, Cherbulliez C, Pechere JC. Interaction of faropenem with OprD porin and active efflux in *P. aeruginosa*. In: Proceedings of the 41st ICAAC, Abstract no. 1519; 2001.
[44] Okamoto K, Gotoh N, Nishino T. *Pseudomonas aeruginosa* reveals high intrinsic resistance to penem antibiotics: penem resistance mechanisms and their interplay. Antimicrob Agents Chemother 2001;45:1964–71.
[45] Masuda N, Sakagawa E, Oya S, Gotoh N, Tujimoto H, Nishimo T. Substrate specificities of MexAB-OprM, MexCD-OprJ and MexXY-OprM efflux pumps in *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 2000;44:3322–7.
[46] Kohler J, Painter RE, Inumerable JA, Griffin P, Gurnett A, Silver LL. Ertapenem resistance selection in *Pseudomonas aeruginosa*. In: Proceedings of the 41st ICAAC, Abstract no. 1518; 2001.
[47] Carmeli Y, Troillet N, Elioupoulos GM, Samore MH. Emergence of antibiotic resistant *Pseudomonas aeruginosa*: comparison of risks associated with different antipseudomonal agents. Antimicrob Agents Chemother 1999;43:1379–82.

[48] Craig WA, Ebert SC. Killing and regrowth of bacteria in vitro: a review. Scand J Infect Dis 1991;74(Suppl):63–70.
[49] Mushtaq S, Ge Y, Livermore DM. Doripenem versus *Pseudomonas aeruginosa* in vitro: activity against characterized isolates, mutants and transconjugants and resistance selection potential. Antimicrob Agents Chemother 2004;48:3086–92.
[50] Köhler T, Michea-Hamzehpour M, Epp SF, Pechere JC. Carbapenem activities against *Pseudomonas aeruginosa*: respective contributions of OprD and efflux systems. Antimicrob Agents Chemother 1999;43:424–7.
[51] Livermore DM. Of Pseudomonas, porins, pumps, and carbapenems. J Antimicrob Chemother 2001;47:247–50.
[52] Livermore DM, Mushtaq S, Warner M. Selectivity of ertapenem for *Pseudomonas aeruginosa* mutants cross-resistant to other carbapenems. J Antimicrob Chemother 2005;55:306–11.
[53] Dalhoff A, Ullmann U. Correlation between pharmacokinetics, pharmacodynamics and efficacy of antibacterial agents in animal models. Eur J Clin Micro Infect Dis 1990;9:479–87.
[54] Andes D, Craig WA. Animal model pharmacokinetics and pharmacodynamics: a critical review. Int J Antimicrob Agents 2002;19:261–8.
[55] Ferrara A, Grassi G, Grassi FA, Piccioni PD, Gialdroni Grassi G. Bactericidal activity of meropenem and interaction with other antibiotics. J Antimicrob Chemother 1989;24(Suppl A):239–50.
[56] Nadler HL, Pitkin DH, Sheikh W. The postantibiotic effect of meropenem and imipenem on selected bacteria. J Antimicrob Chemother 1989;24(Suppl A):225–31.
[57] Neu HC. Carbapenems: special properties contributing to their activity. Am J Med 1985;78(Suppl 6a):33–40.
[58] Schaper K, Schubert S, Dalhoff A. Kinetics and quantification of antibacterial effects of beta-lactams, macrolide and fluoroquinolones against Gram-positive and Gram-negative pathogens. Infection 2006;33(Suppl2), in press.
[59] Boswell FJ, Andrews JM, Wise R. Pharmacodynamic properties of faropenem demonstrated by studies of time-kill kinetics and postantibiotic effect. J Antimicrob Chemother 1997;39:415–8.
[60] Marchese A, Debbia EA, Bryskier A, Schito GC. Antimicrobial activity of faropenem, a new oral penem, against lower respiratory tract pathogens. Clin Micro Infect 1999;5:282–7.
[61] Cozens RM, Tuomanen E, Tosch W, Zak O, Suter J, Tomasz A. Evaluation of the bactericidal activity of beta-lactam antibiotics on slowly growing bacteria cultured in the chemostat. Antimicrob Agents Chemother 1986;29:797–802.
[62] Kobayashi R, Konomi M, Hasegawa K, Morozumi M, Sunakawa K, Ubukata K. In vitro activity of tebipenem, a new oral carbapenems antibiotic, against penicillin-susceptible *Streptococcus pneumoniae*. Antimicrob Agents Chemother 2005;49:889–94.
[63] Cozens RM, Markiewicz Z, Tuomanen E. Role of autolysins in the activities of imipenem and CGP31608, a novel penem, against slowly growing bacteria. Antimicrob Agents Chemother 1989;33:1819–21.
[64] Tuomanen E. Phenotypic tolerance: the search for beta-lactam antibiotics that kill non-growing bacteria. Rev Infect Dis 1986;(Suppl 3):279–91.
[65] Hikida M, Itahashi K, Igarashi A, Shiba T, Kitamura M. In vitro antibacterial activity of LJC 11,036, an active metabolite of L-084, a new oral carbapenem antibiotic with potent antipneumococcal activity. Antimicrob Agents Chemother 1999;43:2010–6.
[66] Eng RHK, Padberg FT, Smith SM, Tan EN, Cherubin CE. Bactericidal effects of antibiotics on slowly growing and nongrowing bacteria. Antimicrob Agents Chemother 1991;35:1824–8.
[67] Tuomanen E, Cozens RM, Tosch W, Zak O, Tomasz A. The rate of killing *Escherichia coli* by beta-lactam antibiotics is strictly proportional to the rate of bacterial growth. J Gen Microbiol 1986;132:1297–304.
[68] Craig WA, Andes DR. In vivo pharmacodynamics activity of faropenem against *Streptococcus pneumoniae*. In: Proceedings of the 41st ICAAC, Abstract no. 2094; 2001.
[69] Tsuji M, Matsuda H, Miwa H, Mixazaki S. Antimicrobial-induced release of endotoxin from *Pseudomonas aeruginosa*: comparison of in vitro and animals models. J Antimicrob Chemother 2003;51:353–9.
[70] Craig WA. Interrelationship between pharmacokinetics and pharmacodynamics in determining dosage regimens for broad-spectrum cephalosporins. Diagn Microbiol Infect Dis 1995;22:89–96.
[71] Andes D, Craig WA. In vivo activities of amoxicillin and amoxicillin-clavulanate against *Streptococcus pneumoniae*: application to breakpoint determinations. Antimicrob Agents Chemother 1998;42:2375–9.
[72] Takata T, Aizawa K, Shimizu A, Sakakibara S, Watabe H, Totsuka K. Optimization of dose and dose regimen of biapenem based on pharmacokinetic and pharmacodynamic analysis. J Infect Chemother 2004;10:76–85.
[73] Hopkins MH, Silverman RB. Beta-lactams: a new class of conformationally rigid inhibitors of γ-aminobutyric acid aminotransferase. J Enzym Inhib 1992;6:125–9.
[74] Hori S, Kanemitsu K, Shimada J. Effect of cephalosporins on γ-aminobutyric acid receptor binding with or without non-steroidal anti-inflammatory drugs. J Antibiot 1993;46: 1145–8.
[75] Hikida M, Masukawa Y, Nishiki K, Inomata N. Low neurotoxicity of LJC 10,627, a novel 1-beta-methyl carbapenem antibiotic: inhibition of gamma-aminobutyric acid A, benzodiazepine, and glycine receptor binding in relation to lack of central nervous system toxicity in rats. Antimicrob Agents Chemother 1993;37:199–202.
[76] Sunagawa M, Matsumura H, Sumita Y, Nouda H. Structural features resulting in convulsive activity of carbapenem compounds: effect of C-2 side chain. J Antibiot 1995;48: 408–16.
[77] Norrby SR. Neurotoxicity of carbapenem antibiotics: consequences for their use in bacterial meningitis. Antimicrob Chemother 2000;45:5–7.
[78] Patel JB, Giles RE. Meropenem: evidence of lack of proconvulsive tendency in mice. J Antimicrob Chemother 1989;24(Suppl A):307–9.
[79] Hori S, Kanemitsu K, Shimada J. Epileptogenic activity of meropenem. A new carbapenem. A comparative study on epileptogenic activity of carbapenems and beta-lactams. In: Proceedings of the 32nd ICAAC, Abstract no. 301; 1992.
[80] Sunagawa M, Matsumura H, Fukasawa M. Structure–activity relationships of carbapenems and penem compounds for the convulsive property. J Antibiot 1992;45:1983–5.
[81] Tsuji M, Ishii Y, Ohno A, Miyazaki S, Yamaguchi K. In vitro and in vivo antibacterial activities of S-4661, a new carbapenem. Antimicrob Agents Chemother 1998;42: 94–9.
[82] Hori S, Kanemitsu K, Shimada J. A neurochemical study on convulsant activity of SY5555, a new penem antibiotic. Chemotherapy (Tokyo) 1994;42(S1):201–4.
[83] Hirotsu I, Inomata N, Hayashi Y, Ohno T, Ishihara T. General pharmacological studies on SY5555; effects on central nervous system. Chemotherapy (Tokyo) 1994;42(S1):205–13.

[84] Schmuck G, von Keutz E, Dalhoff A. Determination of the excitatory potency of faropenem in the central nervous system by an in vitro model. In: Proceedings of the 41st ICAAC, Abstract no. 2196; 2001.
[85] Hikida M, Masukawa Y, Nishiki K, Inomata N. Low neurotoxicity of LJC 10,627, a novel 1-β-methyl carbapenem antibiotic: inhibition of gamma-amino butyric acid A, benzodiazepine, and glycine receptor binding in relation to lack of central nervous system toxicity in rats. Antimicrob Agents Chemother 1993;37:199–202.
[86] Jin C, Jung I, Ku HJ, Kim DH, Cho JH, Oh CH. Low convulsive activity of a new carbapenem antibiotic, DK-35C, as compared with existing congeners. Toxicology 1999;138: 59–67.
[87] Hori S, Sato J, Kawamura M, Shimada J. S-4661, a new carbapenems, has weak convulsant activity. A comparative study on convulsant activity of carbapenem and cephalosporins. In: Proceedings of the 37th ICAAC, Abstract no. F220; 1997.
[88] Livermore DM. β-Lactamases in laboratory and clinical resistance. Clin Microbiol Rev 1995;8:557–84.
[89] Walsh TR, Toleman MA, Poirel L, Nordmann P. Metallo β-lactamases: the quiet before the storm? Clin Microbiol Rev 2005;18:306–25.
[90] Jacoby GA, Munoz-Price LS. The new β-lactamases. N Engl J Med 2005;352:380–91.
[91] vanBambeke F, Glupczynski Y, Plesiat P, Pechere JC, Tulkens PM. Antibiotic efflux pumps in prokaryotic cells: occurrence, impact on resistance and strategies for the future of antimicrobial therapy. J Antmicrob Chemother 2003;51:1055–65.