REVIEW ARTICLE

Drugs 2007; 67 (7): 1027-1052
0012-6667/07/0007-1027/$49.95/0

Comparative Review of the Carbapenems

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Abstract

The carbapenems are β-lactam antimicrobial agents with an exceptionally broad spectrum of activity. Older carbapenems, such as imipenem, were often susceptible to degradation by the enzyme dehydropeptidase-1 (DHP-1) located in renal tubules and required co-administration with a DHP-1 inhibitor such as cilastatin. Later additions to the class such as meropenem, ertapenem and doripenem demonstrated increased stability to DHP-1 and are administered with-

out a DHP-1 inhibitor. Like all β-lactam antimicrobial agents, carbapenems act by inhibiting bacterial cell wall synthesis by binding to and inactivating penicillin-binding proteins (PBPs). Carbapenems are stable to most β-lactamases including AmpC β-lactamases and extended-spectrum β-lactamases. Resistance to carbapenems develops when bacteria acquire or develop structural changes within their PBPs, when they acquire metallo-β-lactamases that are capable of rapidly degrading carbapenems, or when changes in membrane permeability arise as a result of loss of specific outer membrane porins.

Carbapenems (imipenem, meropenem, doripenem) possess broad-spectrum *in vitro* activity, which includes activity against many Gram-positive, Gram-negative and anaerobic bacteria; carbapenems lack activity against *Enterococcus faecium*, methicillin-resistant *Staphylococcus aureus* and *Stenotrophomonas maltophilia*. Compared with imipenem, meropenem and doripenem, the spectrum of activity of ertapenem is more limited primarily because it lacks activity against *Pseudomonas aeruginosa* and *Enterococcus* spp. Imipenem, meropenem and doripenem have *in vivo* half lives of approximately 1 hour, while ertapenem has a half-life of approximately 4 hours making it suitable for once-daily administration. As with other β-lactam antimicrobial agents, the most important pharmacodynamic parameter predicting *in vivo* efficacy is the time that the plasma drug concentration is maintained above the minimum inhibitory concentration (T>MIC).

Imipenem/cilastatin and meropenem have been studied in comparative clinical trials establishing their efficacy in the treatment of a variety of infections including complicated intra-abdominal infections, skin and skin structure infections, community-acquired pneumonia, nosocomial pneumonia, complicated urinary tract infections, meningitis (meropenem only) and febrile neutropenia. The current role for imipenem/cilastatin and meropenem in therapy remains for use in moderate to severe nosocomial and polymicrobial infections. The unique antimicrobial spectrum and pharmacokinetic properties of ertapenem make it more suited to treatment of community-acquired infections and outpatient intravenous antimicrobial therapy than for the treatment of nosocomial infections. Doripenem is a promising new carbapenem with similar properties to those of meropenem, although it appears to have more potent *in vitro* activity against *P. aeruginosa* than meropenem. Clinical trials are required to establish the efficacy and safety of doripenem in moderate to severe infections, including nosocomial infections.

β-Lactam antimicrobial agents have been used in clinical practice since the introduction of penicillin in the 1940s. Carbapenems have the broadest spectrum of activity within the β-lactam class and exhibit *in vitro* bactericidal activity against numerous pathogens, including Gram-positive and Gram-negative aerobes and anaerobes; in addition, carbapenems are stable to almost all β-lactamases.[1-3] The first carbapenem to be discovered was thienamycin in the mid 1970s, a compound produced by the soil organism *Streptomyces cattleya*.[2] The unstable nature of this molecule led to the development of an *N*-formimidoyl derivative called imipenem.[2] However, imipenem is subject to rapid *in vivo* degradation by the enzyme dehydropeptidase (DHP-1) located in the proximal renal tubules of mammals.[2,4] To be used clinically, imipenem must be co-administered with cilastatin, a molecule that inhibits DHP-1.[3] The addition of a DHP-1 inhibitor also prevents the nephrotoxicity observed when imipenem is adminis-

tered alone.[2,4] Meropenem was the second carbapenem to be released for clinical use in North America.[2] This compound differed in that it was intrinsically stable to DHP-1 degradation and could be administered alone.[3]

Microbiological studies have documented that imipenem has slightly more potent *in vitro* activity against Gram-positive pathogens and slightly less activity against Gram-negative pathogens compared with meropenem.[4] Both of these agents have been used for the treatment of a variety of complicated as well as hospital-acquired (nosocomial) infections. Both imipenem and meropenem possess short serum half-lives necessitating multiple daily administration. Ertapenem was developed as a long half-life analogue suitable for once-daily administration for the treatment of complicated infections not involving hospital pathogens such as *Enterococcus* spp., *Pseudomonas aeruginosa* and other non-fermentative Gram-negative bacteria.[5] Doripenem is one of the newest members of this class to be investigated for clinical use and phase III clinical trials are currently ongoing. The antimicrobial spectrum of doripenem is similar to both imipenem and meropenem, but with increased *in vitro* activity against *P. aeruginosa*.[6]

Carbapenems have been used clinically to treat a variety of infections. With the addition of new compounds to the class there is a need to examine the differences between these new agents and imipenem and meropenem. The purpose of this review is to examine each of the carbapenems and compare their chemistry, *in vitro* activity, pharmacokinetic and pharmacodynamic properties, and efficacy and safety in clinical trials. The search for imipenem, meropenem and ertapenem focused on published data obtained in the last 10 years. Regarding doripenem, all published data on PubMed was reviewed as were recent international scientific meetings. Two carbapenems, panipenem and biapenem, have been marketed in Asia and are included for comparative purposes in section 1 and the table in section 5. The clinical trials with these agents are not discussed, as they are not being developed for the non-Asian market. Tebipenem, a novel oral carbapenem, is currently undergoing phase II clinical trials in Japan. The limited published data on tebipenem limits its inclusion to the chemistry and role in therapy sections (table I).[7]

Faropenem, a member of the unique penem class of β-lactams, is only be briefly discussed here as it is not a carbapenem, and thus has different chemical and microbiological properties compared with carbapenems.[8,9] Faropenem medoxomil is a new orally administered penem antibacterial with a chiral tetrahydrofuran substituent at position C2 responsible for its improved chemical stability and reduced CNS effects compared with imipenem. Faropenem demonstrates broad-spectrum *in vitro* antimicrobial activity against many Gram-positive and Gram-negative aerobes and anaerobes, and is resistant to hydrolysis by nearly all β-lactamases, including extended-spectrum β-lactamases and AmpC β-lactamases. Faropenem is not active against methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecium*, *P. aeruginosa* or *Stenotrophomonas maltophilia*. Prospective, multicentre, randomised, double-blind, comparative (not vs placebo) clinical trials in patients with acute bacterial sinusitis (ABS), acute exacerbations of chronic bronchitis (AECB), community-acquired pneumonia (CAP), and uncomplicated skin and skin structure infections (SSSI) demonstrated that faropenem medoxomil has equivalent efficacy and safety to cefuroxime, clarithromycin, azithromycin, amoxicillin, cefpodoxime and amoxicillin/clavulanic acid. The evidence supports faropenem medoxomil as a promising new oral β-lactam with proven efficacy and safety for the treatment of a variety of community-acquired infections. However, the US FDA recently

Table I. Current status of carbapenems

Compound name	US approval date or current status
Imipenem	1987
Meropenem	1996
Ertapenem	2001
Doripenem	Phase III clinical trials
Tebipenem	Phase II clinical trials (Japan)
Panipenem	Marketed in Japan, China and Korea
Biapenem	Marketed in Japan

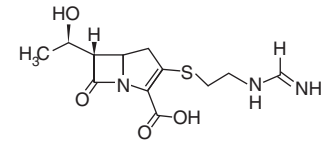
rejected faropenem for all four indications stating the clinical trials in ABS and AECB should have been performed versus placebo. In the CAP studies, the FDA stated that they could not be certain of the validity of the study population actually having the disease and for uncomplicated SSSI, the FDA stated that only a single trial was not adequate evidence for efficacy for this indication.[8]

1. Chemistry

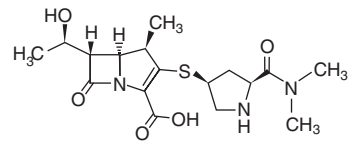
The carbapenems are β-lactam antimicrobial agents that differ from penicillins (penams) in having a carbon atom replacing the sulphur at position 1 and an unsaturated bond between C2 and C3 in the five-membered ring structure[3,10] (figure 1). The broad spectrum of activity of carbapenems is associated with their intrinsic resistance to nearly all β-lactamases. This β-lactamase stability is due to the trans-α-1-hydroxyethyl substituent at the 6 position of carbapenems; this is unique when compared with the side chains of penicillins and cephalosporins, which have *cis* configurations.[2,10]

The older carbapenems, imipenem and panipenem, are subject to DHP-1 degradation in the brush border of renal tubules and require co-administration of a DHP-1 inhibitor such as cilastatin or in the case of panipenem an organic anion tubular transport inhibitor called betamiprion to prevent uptake into renal tubules.[2,11] Later carbapenems, including meropenem, ertapenem, biapenem and doripenem are stable to DHP-1 degradation because of the presence of a 1-β methyl constituent on the carbapenem nucleus.[2,12,13]

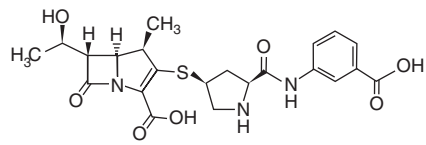
Meropenem differs from imipenem by having a pyrrolidinyl substituent at the 2 position (figure 1). This is believed to be the reason for its superior activity against Gram-negative organisms including *P. aeruginosa* when compared with imipenem.[2] Ertapenem is structurally similar to meropenem but with a meta-substituted benzoic acid group at the 2 position.[5] The meta-substitution increases the molecular weight and lipophilicity of the molecule, and creates an overall negative charge on the benzene ring at physiological pH.[2] The ionisation of the benzene ring is responsible for the extensive protein binding and longer half-life of ertapenem relative to other carbapenems.[2] The larger and more negatively charged ertapenem molecule is likely to permeate Gram-negative cell walls more slowly than meropenem and this probably contributes to its unique antimicrobial spectrum.[5] Doripenem was selected



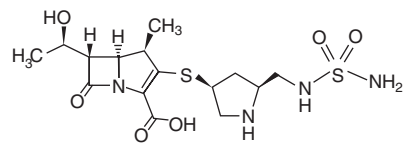
Imipenem



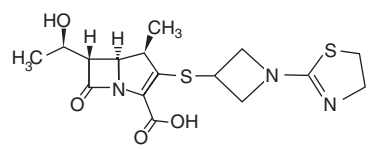
Meropenem



Ertapenem



Doripenem



Tebipenem

Fig. 1. Chemical structures of carbapenems.

for development because of the sulfamoylaminoethyl-pyrrolidinylthio group in its side chain at position 2 that enhances its activity against nonfermentative Gram-negative bacilli[13-15] (figure 1). Tebipenem pivoxil, a new oral carbapenem, has a 1-(1,3-thiazolin-2yl) azetidin-3-ylithio group at the 2 position. Tebipenem is highly stable to DHP-1 and is converted by an esterase in the intestine into its active metabolite, which is then absorbed into the bloodstream.[7]

2. Mechanism of Action

All β-lactam antimicrobial agents including the carbapenems exhibit bactericidal activity by binding to penicillin-binding proteins (PBPs).[2,3,16] The binding of the β-lactam molecule to the PBPs prevents bacteria from completing transpeptidation (cross-linking) of peptidoglycan strands, thus preventing the synthesis of an intact bacterial cell wall.[2] The more potent *in vitro* activities of meropenem and doripenem, relative to imipenem, against Gram-negative pathogens has been attributed to the varying affinities of these carbapenems for different PBPs.[2]

Imipenem binds preferentially to PBP2, followed by PBP1a and 1b, and has weak affinity for PBP3.[5] Meropenem and ertapenem bind most strongly to PBP2, followed by PBP3, but also have strong affinities for PBP1a and PBP1b.[2,5] Doripenem has been reported to have strong affinity for PBP targets that are species specific, PBP3 in *P. aeruginosa*, PBPs 1, 2 and 4 in *S. aureus*; and PBP2 in *Escherichia coli*.[14] The affinity of biapenem is strongest for PBPs 1a and 1b in *P. aeruginosa*, PBPs 1 and 3 in *S. aureus* and PBPs 1a, 2 and 4 in *E. coli*.[17] Tebipenem demonstrated strong affinity for PBPs 1a, 2b, and 3 in isolates of *Streptococcus pneumoniae*.[7]

In Gram-negative bacteria, the carbapenems achieve a rapid bactericidal action by binding with greatest affinity to PBPs 1a, 1b and 2 rather than PBP3, the primary target of aminopenicillins and cephalosporins.[3] Carbapenems achieve cell lysis without prior filamentation as observed with agents that act primarily on PBP3 such as third-generation cephalosporins, this allows for a smaller increase in bacterial cell mass before lysis and less endotoxin release.[2,3,5,18]

3. Mechanisms of Resistance

Carbapenems are known for their activity against Gram-negative bacteria that are resistant to other β-lactams (e.g. third-generation cephalosporins) because of their stability to almost all β-lactamases including AmpC β-lactamases and extended-spectrum β-lactamases (ESBLs).[1,2] When *in vitro* carbapenem activities were compared in wild-type and ESBL-producing isolates of *E. coli* and *Klebsiella pneumoniae*, no increase or at most one doubling-dilution increase in MIC_{90} was observed for imipenem, meropenem and doripenem.[19,20] In comparison, the MIC_{90} for ertapenem increased by up to three doubling-dilutions for ESBL-producing isolates relative to wild-type isolates.[19,20] Despite these increases, the ESBL-producing isolates remained susceptible to ertapenem using the Clinical and Laboratory Standards Institute (CLSI) [2005] breakpoints.[21] Similar observations were made when AmpC β-lactamase-producing isolates of *Enterobacter* spp. and *Serratia marcescens* were compared with wild-type.[22] Imipenem, meropenem and doripenem showed no increase or at most a two doubling-dilution increase in MIC_{90}, whereas the MIC_{90} of ertapenem increased by up to four doubling-dilutions with the AmpC β-lactamase-producing isolates.[19] The combination of an ESBL along with membrane permeability defects can confer ertapenem resistance in *K. pneumoniae*.[23] While these data suggest that ertapenem is less stable than other carbapenems to β-lactamases, the MICs of ertapenem still remain within the susceptible range for the majority of pathogens with ESBL or AmpC β-lactamase resistance mechanisms.[5]

The spectrum of activity of carbapenems is extremely broad; however, some organisms do demonstrate intrinsic resistance. The poor binding affinity of all β-lactams including carbapenems to PBP 2a in methicillin-resistant staphylococci (e.g. MRSA) and *E. faecium* (PBP 5) are responsible for the resistance observed in these bacteria.[2,5] The presence of spe-

cific acquired β-lactamases can result in the rapid hydrolysis of carbapenems. These include Class B metallo-β-lactamases belonging to the IMP, VIM and SPM groups, Class A enzymes belonging to the SME, NMC/IMI and KPC groups and several Class D (OXA) enzymes.[5,20] Although usually referred to as carbapenemases these enzymes can hydrolyse all penicillins and cephalosporins. The most potent Class B metallo-β-lactamases produced by species such as *S. maltophilia* and *Aeromonas* spp. are usually chromosomally encoded and contain a zinc atom at their active site.[2]

Resistance to carbapenems in *P. aeruginosa* is of particular interest because, while *P. aeruginosa* is intrinsically resistant to a variety of β-lactams, it is still generally susceptible to carbapenems.[24] Ertapenem lacks sufficient anti-pseudomonal activity to be considered clinically useful because of resistance by a combination of reduced membrane permeability and possibly an increased affinity for efflux pumps. Imipenem resistance in *P. aeruginosa* is associated with the loss of the porin OprD combined activity of chromosomal AmpC β-lactamase.[24] While loss of OprD did increase the MICs for imipenem, doripenem, and to a lesser extent meropenem, these mutants required a functioning AmpC β-lactamase to produce resistance.[24,25] For meropenem and doripenem, overexpression of multidrug efflux pumps may also be required to confer resistance; imipenem is not subject to efflux.[25] Doripenem and meropenem are hypothesised to possess slightly more potent anti-pseudomonal activity compared with imipenem because they require the presence of multiple resistance mechanisms including efflux and loss of membrane permeability, the combination of which is less likely to occur *in vivo* than the mechanisms required to confer imipenem resistance (AmpC β-lactamase expression plus loss of OprD).[25] *P. aeruginosa* isolates that have acquired carbapenemases will be resistant to all carbapenems.[20,24,25]

4. Microbiology

The carbapenems possess broad spectrum *in vitro* activity against Gram-positive and Gram-negative aerobic and anaerobic bacteria (table II, table III and table IV).[13,14,20,22,26-55] No data are reported for atypical bacteria because β-lactams do not inhibit the growth of these bacteria.

It should be noted that the data presented in tables II–IV were pooled from all the imipenem, meropenem, ertapenem and doripenem studies reviewed. Susceptibility data from hundreds to thousands of isolates were pooled to obtain the most common MIC_{50} and MIC_{90} values for each carbapenem. All carbapenems produce *in vitro* MIC_{90} values of ≤1 mg/L against the most commonly isolated species of Gram-positive aerobic bacteria

Table II. *In vitro* activity of carbapenems against Gram-positive aerobic bacteria[13,14,20,22,26,29-40,56]

Bacteria	Imipenem		Meropenem		Ertapenem		Doripenem	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Staphylococcus aureus (MS)	≤0.5	≤0.5	0.12	0.12	0.12	0.25	0.06	0.06
S. aureus (MR)	32	32	16	32	8	>32	16	16
S. epidermidis	0.016	0.016	0.12	0.12	0.25	0.25	0.03	0.06
Streptococcus pyogenes	≤0.008	≤0.008	≤0.008	≤0.008	≤0.008	≤0.008	≤0.008	≤0.008
S. agalactiae	0.016	0.016	0.03	0.06	0.03	0.06	0.016	0.016
S. pneumoniae (PS)	≤0.008	≤0.008	≤0.008	≤0.008	0.015	0.015	≤0.008	≤0.008
S. pneumoniae (PI)	0.06	0.12	0.12	0.5	0.25	1	0.12	0.25
S. pneumoniae (PR)	0.5	1	0.5	1	1	2	0.5	1
Enterococcus faecalis	1	4	8	16	8	16	4	8
E. faecium	>8	>8	>16	>16	>16	>16	>16	>16
Listeria monocytogenes	0.03	0.12	0.12	0.12	0.25	0.5	NA	NA

MIC_{50} = minimum inhibitory concentration (mg/L) of 50% of isolates; **MIC_{90}** = minimum inhibitory concentration of 90% of isolates; **MR** = methicillin-resistant; **MS** = methicillin-sensitive; **NA** = information not available; **PI** = penicillin-intermediate (penicillin MIC 0.12–1 mg/L); **PR** = penicillin-resistant (penicillin MIC ≥2.0 mg/L); **PS** = penicillin-susceptible (penicillin MIC ≤0.06 mg/L).

Table III. *In vitro* activity of carbapenems against Gram-negative aerobic bacteria[13,20,22,32,34,37,39,41-46]

Bacteria	Imipenem		Meropenem		Ertapenem		Doripenem	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Acinetobacter spp.	0.25	0.25	0.25	1	4	>8	0.25	1
Citrobacter freundii	1	1	≤0.015	0.03	≤0.015	≤0.015	0.03	0.03
Enterobacter aerogenes	2	2	0.03	0.06	≤0.015	0.06	0.06	0.12
E. cloacae	0.5	2	0.03	0.06	≤0.015	0.06	0.03	0.06
Escherichia coli	≤0.5	≤0.5	0.016	0.03	≤0.06	≤0.06	0.03	0.03
E. coli (ESBL)	≤0.5	≤0.5	0.03	0.06	≤0.06	0.25	0.03	0.06
Haemophilus influenzae	1	4	0.063	0.25	0.06	0.12	0.12	0.5
Klebsiella pneumoniae	0.25	1	0.03	0.03	≤0.06	≤0.06	0.03	0.06
K. pneumoniae (ESBL)	0.5	1	0.03	0.12	≤0.06	0.5	0.06	0.12
K. oxytoca	0.25	0.5	0.03	0.03	≤0.015	≤0.015	0.03	0.06
Moraxella catarrhalis	0.06	0.12	≤0.008	≤0.008	0.008	0.008	0.016	0.03
Morganella morganii	4	4	0.06	0.12	≤0.015	0.03	0.25	0.5
Neisseria gonorrhoeae	NA	0.016	NA	NA	0.008	0.03	NA	NA
Proteus mirabilis	1	2	0.06	0.06	≤0.06	≤0.06	0.12	0.25
P. vulgaris	2	4	0.125	0.12	0.16	0.25	0.25	0.5
Pseudomonas aeruginosa	1	>8	0.5	16	>8	>8	0.5	8
Salmonella spp.	≤0.5	≤0.5	0.03	0.03	≤0.06	≤0.06	0.06	0.06
Serratia marcescens	1	2	0.06	0.06	0.03	0.12	0.12	0.25
Shigella spp.	≤0.5	≤0.5	0.03	0.03	≤0.06	≤0.06	0.03	0.06
Stenotrophomonas maltophilia	>8	>8	>16	>16	>8	>8	>16	>16

ESBL = extended-spectrum β-lactamase; **MIC_{50}** = minimum inhibitory concentration (mg/L) of 50% of isolates; **MIC_{90}** = minimum inhibitory concentration of 90% of isolates; **NA** = information not available.

including methicillin-susceptible *S. aureus* as well as penicillin intermediate and resistant (penicillin MIC ≥2 mg/L) isolates of *S. pneumoniae* (table II),[5,13,22] but excluding *Enterococcus* spp. and MRSA.[2,5,20] In general, imipenem and doripenem are slightly more potent against Gram-positive aerobic bacteria compared with ertapenem and meropenem.[5,13,20,22,57] Although imipenem displays slightly lower MICs than other carbapenems against *E. faecalis,* none of the carbapenems demonstrate clinically useful activity against *E. faecium* (table II).[13,20,22]

There are some differences in the activities of individual carbapenems against Gram-negative bacilli (table III). Ertapenem has MIC_{90} values >8-fold higher than other carbapenems against isolates of *P. aeruginosa* and *Acinetobacter* spp.[2] Doripenem has

Table IV. *In vitro* activity of carbapenems against anaerobic bacteria[26-28,33,39,40,43,47-54]

Bacteria	Imipenem		Meropenem		Ertapenem		Doripenem	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Bacteroides fragilis	0.25	0.5	0.12	0.5	0.25	0.5	0.5	1
B. fragilis group	0.25	0. 5	0.12	0.5	0.25	1	0.5	1
Clostridium difficile	2	4	2	4	4	4	1	2
C. perfringens	0.016	0.12	≤0.06	≤0.06	0.06	0.06	NA	NA
Fusobacterium spp.	0.12	1	0.03	0.12	0.03	1	0.03	1
Lactobacillus spp.	0.12	8	0.25	>16	2	>16	NA	NA
Peptostreptococcus spp.	0.03	0.06	0.03	0.12	0.06	0.12	NA	NA
Prevotella spp.	0.03	0.5	0.12	0.25	0.25	4	0.12	0.25

MIC_{50} = minimum inhibitory concentration (mg/L) of 50% of isolates; **MIC_{90}** = minimum inhibitory concentration of 90% of isolates; **NA** = information not available.

been reported to exhibit anti-pseudomonal activity that is greater than imipenem and equal to or slightly greater than that of meropenem (table III).[13,14,20,25,26] None of the carbapenems possess any clinically useful activity against *S. maltophilia* as a result of its production of metallo-β-lactamases, which are capable of hydrolysing all β-lactams including carbapenems.[2,5,20,57] The MICs for imipenem are generally higher against Gram-negative bacteria than those of the other three carbapenems listed in table III.[13,20,57,58] As a result of their β-lactamase stability, all of the carbapenems retain their *in vitro* activity against isolates of *E. coli* and *K. pneumoniae* that produce ESBLs (table III).[2,14,19,59] This is an important observation because the presence of ESBLs can lead to resistance to and treatment failure with third-generation cephalosporins.[1,2,60,61] As was noted in section 3, ertapenem produces higher MICs in the presence of ESBLs or AmpC β-lactamases than do the other carbapenems, but isolates remain susceptible according to current (2005) CLSI breakpoints.[5,19-21]

All carbapenems display MIC_{90}s ≤2 mg/L against Gram-negative anaerobic bacteria; carbapenem MICs are higher for *Clostridium difficile* and *Lactobacillus* spp. than for other Gram-positive anaerobes (table IV).[27,28,62]

5. Pharmacokinetics

The pharmacokinetic parameters of the carbapenems after a single intravenous dose are summarised in table V. All of the currently available carbapenems are formulated as parenteral agents as they are not absorbed from the intestinal tract.[2,63]

Doripenem has been included in table V but not in the discussion because detailed pharmacokinetic information on it are not available at this time. As noted in the introduction, panipenem and biapenem are included in table V only for comparative purposes.

Imipenem/cilastatin administered by intravenous infusion to healthy volunteers at either 500mg or 1000mg doses resulted in mean maximum plasma concentrations (C_{max}) at the end of infusion of 30–35 mg/L and 60–70 mg/L, respectively.[64] These concentrations fell to 0.5 mg/L (500mg dose) and 2 mg/L (1000mg dose) between 4 and 6 hours later.[64] The area under the concentration time curve (AUC) for imipenem after 500mg and 1000mg doses administered by intravenous infusion were 42.4 mg • h/L and 186 mg • h/L, respectively.[3,63,64] Meropenem administered by intravenous infusion in 500mg and 1000mg doses produced C_{max} values of 26 mg/L and 50–60 mg/L, respectively. The corresponding AUC values were 27.2–32.4 mg • h/L for the 500mg dose and 66.9–77.5 mg • h/L for the

Table V. Pharmacokinetic parameters of carbapenems after a single intravenous (IV) dose

Drug	IV dose (g)	C_{max}[a] (mg/L)	AUC[a] (mg • h/L)	$t_{½}$ (h)	Vd[a] (L/kg)	% Protein binding	% Excreted unchanged	Dose administration interval	References
Imipenem	0.5 1	30–35 60–70	42.2 186	1	0.23–0.31	20	60–70 (with cilastatin)	tid–qid	3,63,64
Meropenem	0.5 1	26 50–60	27.2–32.4 66.9–77.5	1	0.23–0.35	2	70	tid–qid	63,65
Ertapenem	1	154.9 (22.0)[b]	572.1 (68.6)[b]	3.8	8.2 (1.5)[b]	92–95[ac]	44	od	66
Doripenem	0.5	20.2	44.1	0.93	NA	8.9	75	tid–qid	67,68
Panipenem	0.5	23.3	39.4	1.2	0.32	5	28.5	bid	11
Biapenem	0.3	17.4	29.2	1.0	0.25	NA	63.4	tid	12

a Mean or range with or without ±SD.

b Free drug in brackets for ertapenem.

c Concentration dependent.

AUC = area under the concentration-time curve; **bid** = twice daily; **C_{max}** = peak concentration reached in the plasma/serum; **IV** = intravenous; **NA** = information not available; **od** = once daily; **qid** = four times daily; **tid** = three times daily; **$t_{½}$** = half life; **Vd** = volume of distribution.

1000mg dose.[63] Ertapenem administered as a 1000mg intravenous dose produced a C_{max} of 154.9 mg/L and an AUC value of 572.1 mg • h/L.[66]

Protein binding accounts for some of the major differences in the pharmacokinetic profiles of the carbapenems. Imipenem is approximately 20% protein bound, while meropenem is only 2% bound to plasma proteins.[63] Ertapenem is extensively bound to plasma proteins; at a plasma concentration of >100 mg/L, approximately 92–95% of ertapenem is protein bound.[2] As a result of its higher protein binding, ertapenem has a longer half-life and is suitable for once-daily dose administration.[5]

5.1 Distribution

Imipenem and meropenem both penetrate well into most bodily fluids.[63,69] Studies with imipenem have demonstrated that it penetrates well into many tissue compartments.[64,70] At 1–2 hours following an intravenous infusion of imipenem, tissue concentrations were as follows after a 500mg dose: 1.6 mg/L in sputum; 2.2 mg/kg in tonsillar tissue; 5.3 mg/kg in prostatic tissue; 2.2–3.8 mg/kg in female genital organs; 16–79 mg/kg in the renal cortex and 14–102 mg/kg in the renal medulla.[64] These tissue concentrations exceed the MICs for most aerobic bacteria[64] (tables II and III). Cerebrospinal fluid concentrations of imipenem 1–8 hours following a 1000mg dose were 0.6–0.9 mg/L in healthy volunteers and 1.1–2.3 mg/L in patients with inflamed meninges.[64] Imipenem penetration into lung tissue (lung tissues not specified) 1 hour after a 1000mg intravenous infusion was 5–9 mg/L.[70] Meropenem distributes readily and rapidly into the interstitial fluid.[71] A 1000mg intravenous infusion of meropenem produced the following concentrations in various tissues after 1.5–2.5 hours: lung 1.43–8.23 mg/kg; colon 0.65–4.52 mg/kg; gall bladder 3.93 mg/kg; and skin 4.21–5.95 mg/kg.[71] One and one-half hours and 2.5 hours after a 500mg meropenem intravenous infusion concentrations in gynecological tissue were: endometrium 1.05–3.27 mg/kg; ovary 0.6–5.0 mg/kg; and uterus 1.21–1.92 mg/kg.[71] Meropenem also penetrated into the cerebrospinal fluid of patients with meningitis with concentrations reaching 0.1–2.8 mg/L after 20 mg/kg and 0.3–6.5 mg/L after 40 mg/kg.[63]

The distribution of ertapenem into interstitial fluid has been examined by measuring its penetration into suction-induced skin blisters following multiple intravenous doses in adults. In those receiving ertapenem 1g once daily by intravenous infusion for 3 days the mean maximum concentration was 24.4 mg/L after ~8 hours and at 24 hours the mean concentration was 7.8 mg/L.[72,73] The interstitial fluid concentration at 24 hours exceeds the MIC_{90} of susceptible pathogens.[73] Penetration of ertapenem into various pulmonary compartments was examined following a single 1g dose administered over a 30-minute intravenous infusion for preoperative prophylaxis.[74] Penetration into lung tissue was assessed ~3 hours post-infusion and revealed lung tissue concentrations of 7.6 mg/kg (±4.85 mg/kg).[74] Mean epithelial lining fluid concentrations at 5 hours after infusion were 2.11 mg/L (±1.80 mg/L) and alveolar cell concentrations were 0.0073 mg/L (±0.0016 mg/L).[74] Intra-abdominal tissue concentrations (resected tissue samples) of ertapenem in patients receiving a 1g intravenous dose for perioperative prophylaxis were analysed.[75] The mean tissue concentration of ertapenem was 16 mg/kg in gall bladder, 12.13 mg/kg in colon, 7.02 mg/kg in small bowel, 4.53 mg/kg in liver and 3.42 mg/kg in pancreas.[75]

5.2 Metabolism and Elimination

Imipenem is subject to rapid metabolism by DHP-1 and must be co-administered with cilastatin to achieve an appropriate *in vivo* half-life and prevent potential nephrotoxicity.[2] Both imipenem and cilastatin have similar half-lives of approximately 1 hour.[2] In the presence of cilastatin, 60–70% of imipenem is excreted unchanged in the urine.[63] Meropenem and ertapenem are intrinsically more stable to DHP-1 and are administered as single entities. Approximately 70% of meropenem is excreted renally as the parent compound.[63] Ertapenem is eliminated mainly through glomerular filtration and secretory processes.[73] Almost 80% of a 1g dose of ertapenem was recovered in the urine as

approximately equal amounts of unchanged parent compound and its major metabolite, the open β-lactam ring product of DHP-1 degradation.[2,73]

As a result of the extensive renal elimination of the carbapenems, different levels of renal impairment require dosage and/or dosage interval changes.[2,63] In patients with end-stage renal disease (creatinine clearance ≤10 mL/min), the half-life of imipenem increased to 4 hours, meropenem to 7 hours and ertapenem to 14.1 hours. In patients with end-stage renal disease, undergoing haemodialysis, imipenem, cilastatin and meropenem were effectively removed by haemodialysis, but only a small proportion of imipenem was removed by peritoneal dialysis (3–5%).[64] Approximately 30% of a 1000mg ertapenem dose was removed in a 4-hour haemodialysis session.[2] Therefore, a supplemental 150mg dose of ertapenem is recommended if the first 500mg dose is administered within 6 hours of dialysis.[2]

6. Pharmacodynamics

As with other β-lactam antibacterials the most important pharmacodynamic parameter predicting bacteriological and clinical efficacy is the time that the plasma drug concentration is maintained above the MIC (T>MIC).[2,73,76] For the majority of β-lactams the T>MIC value should remain ≥50% for the duration of the dosage interval.[2,73] For carbapenems, a T>MIC of ~20% is required for bacteriostatic effects while T>MIC of ~40% achieves bactericidal effects.[73] Unlike other β-lactams, the carbapenems have been reported to exhibit a post-antibiotic effect (PAE) against both Gram-positive and Gram-negative bacteria.[77] PAEs in the range of 2 and 4 hours for *E. coli* and *P. aeruginosa*, respectively, exposed to imipenem at a concentration of four times their MIC have been reported.[77] With meropenem, the PAE for *E. coli* and *P. aeruginosa* was reported to be 4 and 5 hours, respectively.[77] Ertapenem and imipenem were shown to exhibit a PAE with *S. aureus* of 1.5 and 1.3 hours, respectively, after a 2-hour exposure to ten times the MIC.[78]

7. Clinical Trials

As broad-spectrum antimicrobials, the carbapenems have been used for some time for a variety of infectious diseases. Included in this section are summarised accounts of various comparative clinical trials conducted using carbapenems. The focus of clinical trial data for imipenem, meropenem and ertapenem was published data available through a PubMed search obtained in the last 10 years. A PubMed search for doripenem, did not find any clinical trial data. As panipenem and biapenem have been marketed only in Asia, their clinical trial data are not discussed. Whenever possible, statistical data as originally reported by the authors of the study have been included. Statistical equivalence is defined by the two-sided 95% confidence interval (CI) for the difference in response rates.[2] Data from clinical trials are presented in table VI. The table, as well as the discussion, includes clinical trials published during the last 10 years. While earlier data may still be relevant for some indications, they were not included in the interest of conciseness. Unless stated, all agents were administered intravenously.

7.1 Complicated Intra-Abdominal Infection

A comparison of imipenem/cilastatin and cefepime in the treatment of intra-abdominal infections was conducted by Barie et al.[80] in a randomised, double-blind, clinical trial. Patients (n = 323) were randomised to receive either imipenem/cilastatin 500mg every 6 hours or cefepime 2g every 12 hours in addition to metronidazole 500mg every 6 hours. The study population consisted of adults with a preoperative diagnosis of a complicated intra-abdominal infection, or a postoperative diagnosis of an abscess or peritonitis. Among the 217 protocol-valid patients, those treated with cefepime and metronidazole were deemed clinical cures (88%) more frequently then those in the imipenem group (76%) [p = 0.2].

A prospective, multicentre, open-label, randomised study by Mehtar et al.[81] examined meropenem and cefotaxime plus metronidazole in treatment of 161 patients with serious infections, the majority of which were subsequent to intra-abdomi-

Table VI. Results of clinical trials with carbapenems[2,79]

Study	Regimen	No. of patients randomised	Mean duration of parenteral treatment[a] (range) [days]	Test of cure (no. of days post-therapy)	Percentage of patients with a favourable response (no. of evaluable patients)		
					clinical	microbiological	clinical and microbiological
Complicated intra-abdominal infections							
Barie et al.[80]	IMI 500mg q6h IV vs	323	9.4	28–42	76 (93)	76 (93)	NA
	CEP 2g q12g IV and MTR 500mg q6h IV		8.8		88 (84)	89 (85)	NA
Mehtar et al.[81][b]	MER 1g tid IV vs	161	6.6	56	93 (63)[c]	NA	NA
	CFX 1g tid IV and MTR 500mg tid IV		6.0		92 (58)[c]	NA	NA
Solomkin et al.[82]	ERT 1g od IV vs	633	7.6 (4–17)	28–42	NA	NA	87 (203)[c]
	P/T 3.375g q6h IV		7.8 (4–18)		NA	NA	81 (193)[c]
Solomkin et al.[83]	IMI 500mg q6h IV vs	330	ND	28–42	81 (113)	88 (113)	NA
	CIP 400mg q12h IV and MTR 500mg q6h IV/PO		ND		84 (111)	88 (111)	NA
Wilson[84]	MER 1g q8h IV vs	427	7.2	28–42	92 (97)[d]	96 (97)[d]	NA
	CLN 900mg q8h and TOB (5 mg/kg/d in 3 divided doses IV		7.5		86 (94)[d]	93 (94)[d]	NA
Yellin et al.[85]	ERT 1g od IV[e] vs	114	4.9	NA	NA	90 (31)	84 (31)[c]
	CTX 2g od IV + MTR 500mg q8h IV[e]		5.1	NA	NA	85 (41)	85 (41)[c]
Appendicitis (gangrenous or perforated)							
Berne et al.[86]	MER 1g q8h IV vs	228	6.1	NA	92 (63)	NA	NA
	CLN 900mg q8h IV and TOB 5mg/kg/d in 3 divided doses		7.3	NA	91 (66)	NA	NA
Acute pelvic infections							
Roy et al.[87]	ERT 1g od IV vs	412	4[f] (2–12)	14–28	94 (163)[c]	94 (128)	NA
	P/T 3.375g q6h IV		4[f] (3–12)		92 (153)[c]	94 (129)	NA
Complicated urinary tract infections							
Jimenez-Cruz et al.[88]	ERT 1g od IV or IM[g]	258	3.9	5–9	NA	86 (97)[c]	86 (97)
	CTX 1g od IV or IM[g]		4.1		NA	85 (53)[c]	85 (53)

Continued next page

Table VI. Contd

Study	Regimen	No. of patients randomised	Mean duration of parenteral treatment[a] (range) [days]	Test of cure (no. of days post-therapy)	Percentage of patients with a favourable response (no. of evaluable patients)		
					clinical	microbiological	clinical and microbiological
Complicated skin and skin structure infections							
Fabian et al.[89]	MER 500mg q8h IV vs	548	5.8 (3–14)	30	86.2 (225)[c]	NA	NA
	IMI 500mg q8h IV		6.0 (3–14)		82.9 (238)[c]	NA	NA
Graham et al.[90]	ERT 1g od IV vs	540	9.1 (3–16)	10-21	82 (185)[c]	83 (155)	82 (155)
	P/T 3.375g q6h IV		9.8 (3–18)		84 (174)[c]	83 (151)	82 (151)
Naber et al.[91]	IMI 500mg q8h IV vs	237	5–14	28–42	79.9 (112)[c]	48.6 (94)[c]	NA
	P/T 2 g/500mg q8h IV		5–14		83.0 (109)[c]	59.8 (99)[c]	NA
Tomera et al.[92]	ERT 1g od IV[g] vs	592	4.1		NA	92(159)[c]	NA
	CTX 1g od IV[g]		4.0		NA	93 (171)[c]	NA
Diabetic foot ulcer							
Lipsky et al.[93]	ERT 1g od IV[h] vs	576	11.1	10	94 (180)[c]	93 (358)	NA
	P/T 3.375g q6h IV[h]		11.3		92 (162)[c]	81 (271)	NA
Community-acquired pneumonia							
Ortiz-Ruiz et al.[94]	ERT 1g od IV or IM[i] vs	502	4[f] (2–17)	7–14	92 (182)[c]	93 (96)	NA
	CTX 1g od IV or IM[i]		4[f] (2–14)		91 (201)[c]	95 (113)	NA
Vetter et al.[95]	ERT 1g od IV[i] vs	364	5.5		94.7 (182)[c]	91 (100)	NA
	CTX 1g od IV[i]		5.6		95.8 (93)[c]	92 (49)	NA
Nosocomial pneumonia							
Jaccard et al.[96]	IMI 500mg qid IV vs	154	9.9	14–28	83 (62)[c]	NA	NA
	P/T 4.5g tid IV		9.4		71 (56)[c]	NA	NA
Zanetti et al.[97]	IMI 500mg qid IV vs	281	9.4	5	70 (76)[c]	54 (38)	NA
	CEP 2g tid IV		9.1		74 (75)[c]	61 (47)	NA
Acute pulmonary exacerbations in cystic fibrosis patients							
Blumer et al.[98]	MER 40 mg/kg IV (up to 2g q8h) and TOB[j] vs	102	13.5	14–28	62 (31)[c,k]	76 (38)	NA
	CTZ 5 mg/kg IV (up to 2g q8h) and TOB[j]		14.1		44 (23)[c,k]	76 (39)	NA
Febrile neutropenia							
Biron et al.[99]	IMI 1g tid IV (50 mg/kg/d) vs	400[l]	5.7 (1–12)	7	72 (121)[c]	NA	NA

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Table VI. Contd

Study	Regimen	No. of patients randomised	Mean duration of parenteral treatment[a] (range) [days]	Test of cure (no. of days post-therapy)	Percentage of patients with a favourable response (no. of evaluable patients)		
					clinical	microbiological	clinical and microbiological
	CEP 2g bid IV		5 (1–12)		79 (139)[c]	NA	NA
Feld et al.[100]	MER 1g q8h IV vs	411	8 (5–12)	7	54 (112)[c]	45 (14)[m]	NA
	CTZ 2g q8h IV		7 (5–11)		44 (89)[c]	51 (22)[m]	NA
Fleischhack et al.[101]	MER 60 mg/kg/d IV in 3 divided doses vs	169	6 (2–34)	7	55.8 (96)[c,n]	NA	NA
	CTZ 100 mg/kg/d IV in 3 divided doses		7 (2–32)		40.0 (68)[c,n]	NA	NA
Raad et al.[102]	IMI 500mg q6h IV vs	251	NA	NA	68 (38)[c]	NA	NA
	CEP 2g q8h IV		NA	NA	75 (41)[c]	NA	NA

bid = twice daily; **CEP** = cefepime; **CFX** = cefotaxime; **CIP** = ciprofloxacin; **CLN** = clindamycin; **CTX** = ceftriaxone; **CTZ** = ceftazidime; **ERT** = ertapenem; **FEV_1** = forced expiratory volume in 1 second; **IM** = intramuscular; **IMI** = imipenem/cilastatin; **IV** = intravenous; **MER** = meropenem; **MTR** = metronidazole; **NA** = information not available; **ND** = no data; **od** = once daily; **PO** = oral; **P/T** = piperacillin/tazobactam; **qid** = four times daily; **q*x*h** = every *x* hours; **tid** = three times daily; **TOB** = tobramycin.

a Applies to evaluable patients.

b Study of serious hospital infections with 74% of infections subsequent to intra-abdominal pathology.

c Primary efficacy variable.

d Clinical and bacteriological response results at early follow-up.

e 68% of the microbiologically evaluable patients in the ertapenem group and 61% of patients in the comparator group were switched to oral ciprofloxacin plus metronidazole after ≥3 days of parenteral therapy for a mean total duration of antimicrobial therapy of 8.8 and 8.3 days, respectively.

f Median, not mean is reported.

g Most microbiologically evaluable patients were switched to an oral antimicrobial (usually ciprofloxacin) after ≥3 days of parenteral therapy.

h IV therapy for a minimum of 5 days followed by oral amoxicillin/clavulanic acid (875/125mg) q12h for up to 23 days.

i Most clinically evaluable patients were switched to an oral antimicrobial (usually amoxicillin/clavulanic acid) after ≥3 days of parenteral therapy.

j Administered IV with target tobramycin concentrations of peak of ≥8 mg/L and trough of <2 mg/L.

k Clinical response at day 7 defined as a ≥15% relative increase in FEV_1 from baseline.

l Episodes.

m Percentage successful bacteriological response to only microbiologically defined infections.

n Percentage clinical response after 48 hours of monotherapy.

nal pathology (77% of the meropenem group and 75% of the cefotaxime plus metronidazole group). Patients were randomised to receive either meropenem 1g three times daily or a combination therapy of cefotaxime 1g and metronidazole 500mg both three times daily. Patients were examined for clinical response within 24 hours of stopping therapy and again up to 8 weeks later for signs of continued infection. The incidence of a satisfactory clinical response at the end of treatment was 93% (63/68) in the meropenem group and 92% (58/63) in the cefotaxime/metronidazole group.[81] At the follow-up assessment up to 8 weeks later, the rate of satisfactory clinical response was 96% (46/48) for meropenem patients and 93% (40/43) for cefotaxime plus metronidazole.[81] The difference between treatment groups was not statistically significant ($p = 0.493$; 95% CI −40.2, 47.5).[81] The prevalence of reported adverse events was 32% in the meropenem group and 25% in the cefotaxime plus metronidazole group, most were mild or moderate and did not require discontinuing therapy.[81]

The use of ertapenem in intra-abdominal infections has been investigated in two clinical trials comparing it with piperacillin/tazobactam and ceftriaxone plus metronidazole. The first trial conducted by Yellin et al.[85] featured two cohorts of patients. The first cohort of 114 patients were randomised to receive either ertapenem 1g once daily or ceftriaxone 2g once daily plus metronidazole 500mg every 8 hours. The second cohort of 106 patients was randomised to receive either ertapenem 1.5g once daily or ceftriaxone 2g once daily plus metronidazole 500mg every 8 hours. The mean duration of intravenous therapy was similar in all groups; 4.6 days for ertapenem patients and 5.1 days for ceftriaxone plus metronidazole patients in the ertapenem 1g cohort. In the ertapenem 1.5g cohort, the mean duration of intravenous therapy was 5.3 days for ertapenem and 6.0 days for ceftriaxone plus metronidazole.[85] At the test of cure visit for the ertapenem 1g cohort, the percentage of patients who showed both a favourable microbiological and clinical response was 84% for patients receiving ertapenem 1g and 85% for patients receiving ceftriaxone plus metronidazole therapy.[85] The success rates for the two groups were similar (95% CI for the adjusted difference −28, 19).[85] The response rates for patients in the ertapenem 1.5g cohort were 83% for the ertapenem patients and 77% for patients receiving ceftriaxone plus metronidazole.[85] The success rates in this cohort also showed no difference (95% CI for the adjusted difference −19, 33).[85] Ertapenem therapy in this trial was generally well tolerated and had an overall safety profile similar to ceftriaxone plus metronidazole.[85]

The second double-blind, randomised study of ertapenem in intra-abdominal infections conducted by Solomkin et al.[82] used a comparative therapy of piperacillin/tazobactam. The study population of 633 patients was randomised to receive either ertapenem 1g once daily or piperacillin/tazobactam 3.375g every 6 hours with a total of 396 patients meeting all the criteria for the clinically evaluable population. Clinical and microbiological evaluations were completed at the end of therapy, at 1–2 weeks after completion of therapy and a final assessment at 4–6 weeks after cessation of treatment. Of the modified intent-to-treat groups, 79.3% (245 of 311) of ertapenem patients were clinically cured as were 76.2% (232 of 304) patients treated with piperacillin/tazobactam (difference of 3.1%, adjusted for strata, 95% CI −3.6, 9.8). Of the microbiologically evaluable patients 86.7% (176 of 203) of patients treated with ertapenem and 81.2% (157 of 193) of patients treated with piperacillin/tazobactam were cured (difference of 5.5% adjusted for strata, 95% CI −2.2, 13.1) [these results are only the modified intent-to-treat patients].[82] Statistical analyses of the treatment at all three assessment points showed equivalence between the two treatment regimens.[82] The most commonly adverse events in both treatment groups were diarrhoea and phlebitis/thrombophlebitis, these were of a generally mild or moderate severity, four patients in the ertapenem group discontinued therapy as a result of drug-related adverse events compared with six in the piperacillin/tazobactam group.[82]

Solomkin et al.[83] also conducted an earlier randomised, double-blind, multicentre, clinical trial comparing ciprofloxacin (400mg every 12 hours) and metronidazole (500mg every 6 hours) to imipenem/cilastatin (500mg every 6 hours). The study population consisted of 671 patients, 330 of whom were valid for efficacy assessment. Patients received one of three treatment regimens: intravenous imipenem; intravenous ciprofloxacin and metronidazole; or intravenous ciprofloxacin and metronidazole followed by oral step-down therapy. Of the 330 clinically evaluable patients, treatment success occurred in 84% of the intravenous ciprofloxacin plus metronidazole group, 86% of the ciprofloxacin plus metronidazole step-down group, and 81% of the imipenem/cilastatin group.[83] These results demonstrated statistical equivalence between both intravenous treatment groups (95% CI −0.074, 0.067).[83]

A randomised, double-blind, multicentre clinical trial conducted by Wilson[84] compared meropenem (1g every 8 hours) to the combination of clindamycin (900mg every 8 hours) and tobramycin (5 mg/kg/day divided into three doses) in the treatment of intra-abdominal infections. A total of 427 patients were randomised into the two treatment groups with 191 of those patients meeting all criteria for the evaluation of efficacy, according to protocol criteria. Results showed that 92% of patients treated with meropenem were cured compared with 86% of patients treated with clindamycin plus tobramycin.[84] Adverse events occurred with similar frequency in both treatment groups.[84]

7.2 Advanced Appendicitis (Gangrenous or Perforated)

In a prospective, randomised, double-blind, clinical trial conducted by Berne et al.,[86] meropenem was compared with combination therapy of clindamycin and tobramycin. 228 patients with a diagnosis of advanced appendicitis were randomised to receive either meropenem 1g every 8 hours or clindamycin 900mg every 8 hours plus tobramycin 5 mg/kg/day in three divided doses. The mean number of days duration for post-operative fever was 3.1 ± 1.7 for meropenem recipients and 4.4 ± 2.2 for patients receiving clindamycin plus tobramycin ($p < 0.01$).[86] The mean duration of hospital stay was 6.1 ± 1.6 days for meropenem and 7.3 ± 2.2 days for clindamycin plus tobramycin ($p = 0.01$).[86] This demonstrated a small but significant difference favouring meropenem for the antibacterial management of surgically treated patients with gangrenous and perforated appendicitis.[86]

7.3 Acute Pelvic Infections

A multicentre, double-blind study of 412 women was conducted by Roy et al.[87] to compare ertapenem and piperacillin/tazobactam therapy for the management of acute pelvic infections. The 412 women were stratified into obstetric/postpartum infection or gynaecological/postoperative infection and then randomised to receive ertapenem 1g once daily or piperacillin/tazobactam 3.375g every 6 hours. The primary efficacy endpoint was a test of cure visit 2–4 weeks after cessation of antimicrobial therapy. Of the clinically evaluable patients, 93.9% (153 of 163) of patients treated with ertapenem and 91.5% (140 of 153) of patients treated with piperacillin/tazobactam were cured at the 2–4 week evaluation.[87] The cure rates for both of the treatment groups were equivalent (95% CI for the difference, adjusted for strata, −4, 8.8). The frequency and severity of adverse events in both groups were similar.[87]

7.4 Complicated Urinary Tract Infections

Two large studies have been conducted to compare the efficacy and safety of ertapenem 1g and ceftriaxone 1g both administered once daily in the treatment of complicated urinary tract infections (UTI).

In the first multicentre, prospective, double-blind study conducted by Jimenez-Cruz et al.,[88] a study population of 258 patients with complicated UTIs were stratified as to whether or not they had acute pyelonephritis and then randomised into either treatment group. The study allowed for administration of intramuscular doses after the initial intravenous dose of either ertapenem or ceftriaxone. A switch to

oral therapy usually with ciprofloxacin 500mg twice daily (although other agents were allowed as deemed appropriate by investigators) was allowed in patients who showed a clinical improvement after at least 3 days of parenteral therapy and had the baseline uropathogen eradicated. Almost all patients in either treatment arm were switched to oral therapy. The mean duration of parenteral therapy was similar in both groups: for patients in the ertapenem group 3.9 days compared with 4.1 days in the ceftriaxone group.[88] The mean duration of total therapy (both oral and parenteral) was also similar in both treatment groups with a mean of 11.1 days in the ertapenem group and 11.3 days in the ceftriaxone group.[88] Of the original 258 randomised patients, 97 (55.4%) of the ertapenem group and 53 (63.9%) of the ceftriaxone group were evaluated microbiologically.[88] The most common identified pathogen was *E. coli*, identified in 81.6% (80 of 98 isolates) of the ertapenem group and 70.4% (38 of 54 isolates) in the ceftriaxone group.[88] Clinical response rates were similar in both treatment groups with a difference, adjusted for strata, of only 0.6% (95% CI −12.9, 14.1) indicating equivalence.[88] The percentage of patients with a favourable microbiological response at the study's primary endpoint assessment 5–9 days after treatment was 85.6% in the ertapenem group and was 84.9% in the ceftriaxone group.[88] The frequency of treatment-related adverse events were similar in both groups as was the severity of these events.[88]

A similar multicentre, randomised, double-blind, prospective study by Tomera et al.[92] compared the same treatment regimens: ertapenem 1g and ceftriaxone 1g both once daily. Patients in both groups had the option of switching to an oral antibacterial at signs of improvement after 3 days of parenteral therapy. The duration of therapy, both parenteral and total days of antibacterial therapy, was similar between both groups. The mean duration of intravenous therapy was 4.1 days in the ceftriaxone group and 4.0 days in the ertapenem group. The mean of total days of antibacterial therapy was 10.8 in the ceftriaxone group and 10.0 in the ertapenem group.[92] The most common pathogen was *E. coli*, which was present in 69.8% (111 of 159) of patients in the ertapenem group and 68.9% (117 of 170) of patients in the ceftriaxone group.[92] The second most prevalent pathogen was *K. pneumoniae* isolated in 13.8% (22 of 158) of ertapenem patients and 12.3% (21 of 170) in the ceftriaxone group.[92] The percentage of patients who had a favourable microbiological response to treatment at the primary efficacy endpoint assessment 5–9 days after treatment was 91.8% of ertapenem patients and 93.0% of ceftriaxone patients.[92] These data indicate equivalence between the two treatment regimens (95% CI for the difference, adjusted for strata, −7.6, 5.1).[92]

Imipenem/cilastatin (500mg every 8 hours) has been compared with piperacillin/tazobactam (2g/0.5g every 8 hours) in the treatment of patients with complicated UTIs or acute pyelonephritis in a randomised, double-blind, multicentre trial conducted by Naber et al.[91] The study population consisted of 237 adult patients randomised 1 : 1 into each treatment group. The two groups did not differ significantly in baseline characteristics, medical history or pre-treatment conditions. The study's primary endpoint consisted of the bacteriological and clinical success rates at the early follow-up 5–9 days after the end of therapy. Clinical response rates at the 5–9 day follow-up were 83% (122/147) in the piperacillin/tazobactam group and 79.9% (123/154) in the imipenem/cilastatin group; the difference of 3.1% is not statistically significant (95% CI −5.7, 11.9).[91] The bacteriological response rates at early follow-up were 57.8% (78 of 135) for the piperacillin/tazobactam group and 48.6% (70 of 144) in the imipenem/cilastatin group.[91] The difference of 9.2% was not statistically significant (95% CI of −2.5, 20.9).[91] Both agents were well tolerated with the frequency of adverse events of 20.3% (28 of 138) in the piperacillin/tazobactam group and 16.4% (28 of 171) in the imipenem/cilastatin group, adverse events recorded were generally rated as mild or moderate.[91]

7.5 Complicated Skin and Skin Structure Infections

Fabian et al.[89] conducted a multicentre, randomised, double-blind, study comparing meropenem and imipenem/cilastatin in the treatment of hospitalised patients with complicated skin and soft tissue infections. In total, 1076 patients were enrolled in the study with 548 patients comprising the clinically evaluable arm of the study and 692 patients in the modified intention-to-treat population. Patients were randomised to receive either meropenem 500mg or imipenem/cilastatin 500mg both every 8 hours. The study's primary efficacy endpoint was clinical outcome at a follow-up assessment 7–14 days after the cessation of therapy. The percentage of patients assessed as cured in the clinically evaluable patient group at the follow-up assessment was 86.2% in the meropenem group and 82.9% in the imipenem/cilastatin group; cure rates were found to be equivalent (95% CI −2.8, 9.3).[89] In the modified intention-to-treat population, cure rates were 73.1% in the meropenem group and 74.9% in the imipenem/cilastatin group; these cure rates being equivalent (95% CI −8.4, 4.7).[89] The incidence of adverse events and drug-related adverse events were similar in both treatment groups.[89]

Ertapenem and piperacillin/tazobactam were compared as treatment for adults with complicated SSSI infections in a prospective, randomised, double-blind, multicentre study by Graham et al.[90] The study population of 540 adults was randomised to receive either ertapenem 1g once daily or piperacillin/tazobactam 3.375g every 6 hours. The most prevalent types of infections diagnosed in the study population were skin or soft tissue abscesses and lower-extremity infections associated with diabetes mellitus.[90] The mean duration of therapy was 9.1 days in the ertapenem group and 9.8 days in the piperacillin/tazobactam group.[90] At the study's primary efficacy endpoint assessment 10–21 days after treatment, 82.4% of ertapenem patients and 84.4% of piperacillin/tazobactam patients were assessed as cured. The difference in cure rate was not significant (2%, [95% CI −10.2, 6.2]).[90] The frequency and severity of treatment related adverse events were similar in both the ertapenem and piperacillin/tazobactam groups.[90]

7.6 Diabetic Foot Infections

One large, prospective, randomised, double-blind, multicentre trial of adults was conducted to compare parenteral therapy with ertapenem to piperacillin/tazobactam in patients with diabetic foot infections. Patients were randomised to receive either ertapenem 1g once daily or piperacillin/tazobactam 3.375g every 6 hours for 5 days after which oral therapy with amoxicillin/clavulanic acid (875/125mg) could be administered for up to 23 days. The study also allowed for the use of vancomycin for patients in either group in the event of a MRSA. The study population consisted of 576 patients with 445 available for assessment at the end of intravenous therapy. To be included in the study, patients with diabetes had to be diagnosed with a foot infection classified as moderate to severe and requiring treatment with intravenous antibacterials. Baseline characteristics were similar in both groups.[93] The primary outcome measure was the proportion of patients with a favourable clinical response (cure or improvement) on the day that the intravenous antibacterial therapy was discontinued. Because of the nature of diabetic foot infections, there were a variety of pathogens cultured from study participants. *S. aureus* was the most prevalent isolated pathogen appearing in 44% (90 of 206) of patients treated with ertapenem and 40% (79 of 196) of patients treated with piperacillin/tazobactam.[93] Other common isolates included *Peptostreptococcus* spp. (114 isolates), *Prevotella-Porphyromonas* group (75 isolates), Enterobacteriaceae (75 isolates), *Enterococcus* spp. (64 isolates), *S. agalactiae* (47 isolates), *Bacteroides fragilis* group (36 isolates) and *P. aeruginosa* (28 isolates).[93] Infections were polymicrobial in 47% (187 of 402) of patients and of mixed aerobic/anaerobic cultures in 27% (108 of 402).[93] Of the 445 patients available for assessment at the end of intravenous therapy, the favourable clinical response rate was similar for the 226 patients who received ertapenem and the 219 who

received piperacillin/tazobactam (94% vs 92%, respectively) with the difference between treatments of 1.9% (95% CI −2.9, 6.9).[93] Rates of favourable microbiological responses in terms of eradication rates and clinical outcomes by pathogen did not differ between the two study groups.[93] The incidence of adverse events also did not differ between the two groups.[93] These data suggest that both ertapenem and piperacillin/tazobactam are equivalent treatments for diabetic foot infections.[93]

7.7 Community-Acquired Pneumonia

Ertapenem has been compared with ceftriaxone as a treatment for CAP in two large clinical trials. The first trial conducted by Vetter et al.[95] compared ertapenem 1g and ceftriaxone 1g both once daily. At the discretion of the clinician, doses could be given as an intramuscular injection in lieu of intravenous infusion. The authors used a prospective, double-blind, multicentre design in adults with CAP. Patients were stratified according to the Pneumonia Severity Index and age, then subsequently randomised (2 : 1) into one of the treatment groups. Investigators could change to oral antibacterial therapy if patients showed signs of clinical improvement after at least 3 days of parenteral therapy. A total of 364 patients were randomised to treatment, 239 to ertapenem and 125 to the ceftriaxone group. Of the clinically evaluable patients, the mean ± SD durations of parenteral and total (parenteral plus oral) therapy were 5.5 ± 2.6 and 11.5 ± 2.7 days for the ertapenem group and 5.6 ± 2.8 and 11.7 ± 3.0 days for the ceftriaxone group. The most common pathogen isolated was *S. pneumoniae* in both treatment arms. Of the total patient population, 75.5% (275 of 364) were clinically evaluable, among these patients cure rates were 92.2% in the ertapenem group and 93.6% in the ceftriaxone group. These results demonstrate statistical equivalence between both groups (95% CI for the difference adjusted for the stratum, −8.6, 5.7). At the end of parenteral therapy, 94.7% of patients in the ertapenem treatment group and 95.8% of patients in the ceftriaxone treatment group were assessed as showing clinical improvement. The most common adverse events in both groups were vein complications (3.4% [8 of 236] in the ertapenem group and 7.3% [9 of 123] in the ceftriaxone group) and elevated serum transaminases (6.3% [13 of 207] in the ertapenem group and 7.1% [8 of 113] in the ceftriaxone group).

A second randomised, prospective, double-blind, multicentre clinical trial compared ertapenem with ceftriaxone,[94] and included 502 patients hospitalised for CAP who were randomised to receive ertapenem 1g or ceftriaxone 1g both once daily. There was an allowance to switch to oral therapy after a minimum of 3 days of parenteral treatment. The median duration of intravenous therapy was 4 days in both groups (range 2–17 days in the ertapenem group and 2–14 days in the ceftriaxone group).[94] The duration of total therapy (intravenous plus oral therapy) was 12 days (range 3–21 days in the ertapenem group and 3–17 days in the ceftriaxone group).[94] The response rates for clinically evaluable patients were 92.4% (95% CI 88.5, 96.2) in the ertapenem group and 91.3% (95% CI 87.3, 95.3) in the ceftriaxone group.[94] The difference in response rate once adjusted for strata was 1.0% (95% CI −4.9, 7.0); this indicates the results from both treatments are equivalent.[94] Both treatments were similarly well tolerated with the most common adverse events diarrhoea and nausea.[94]

7.8 Nosocomial Pneumonia

Two large multicentre, evaluator blind, prospective, randomised studies focused on the use of imipenem/cilastatin in the treatment of nosocomial pneumonia.[96,97]

The first study, conducted by Jaccard et al.,[96] compared imipenem/cilastatin (500mg four time daily) and piperacillin/tazobactam (4.5g three times daily). The study population consisted of 154 patients with nosocomial pneumonia; patient baseline characteristics were similar for both groups, with the exception of bacteraemia, which was more common in the imipenem/cilastatin group (10 of 79 vs 3 of 75; p = 0.08).[96] The most common identified microbiological cause of pneumonia was Gram-negative bacteria with 44% of isolates being *P. aeruginosa*.[96] The clinical failure rates were not signifi-

cantly different between treatment groups with 17% (13 of 75) in the piperacillin/tazobactam group and 29% (23 of 79) in the imipenem/cilastatin group (p = 0.09).[96] The numbers of deaths due to infection were also similar with 9% (7 of 75) in the piperacillin/tazobactam group and 8% (6 of 79) in the imipenem/cilastatin group (p = 0.78).[96] For infections due specifically to *P. aeruginosa* (n = 45) the occurrence of treatment failure due to resistance was higher in the imipenem/cilastatin group 50% (12 of 24) versus only 5% (1 of 21) in the piperacillin/tazobactam group.[96] The overall frequency of adverse events was similar in both groups.[96]

In a later study by Zanetti et al.,[97] the treatment of nosocomial pneumonia with imipenem/cilastatin (500mg four times daily) was compared with cefepime (2g three times daily). The study population consisted of 281 patients with 209 patients available for per protocol analysis for efficacy. To be eligible for the study, patients had to be 16 years or older, admitted to an intensive-care unit, with or without mechanical ventilation, and be diagnosed with nosocomial pneumonia. Favourable clinical responses were obtained in 70% (76 of 108) of the cefepime patients and 74% (75 of 101) of the imipenem/cilastatin patients,[97] with the 95% CI (−16, 8) not excluding the predefined lower limit for noninferiority of −15%.[97] However, a secondary intent-to-treat analysis showed the treatments were of similar efficacy (95% CI for difference −9, 14).[97] Of note, ESBL-producing pathogens were detected in 13 patients in the cefepime group and lead to four treatment failures, and although present in ten patients in the imipenem/cilastatin group, it was not associated with any treatment failures.[97] Primary or secondary resistance in *P. aeruginosa* was detected in 19% of cefepime recipients and 44% of imipenem/cilastatin recipients (p = 0.05).[97] Adverse events were present in 51% (71 of 138) of patients in the cefepime group and 44% (62 of 141) of patients in the imipenem/cilastatin group.[97] The presence of ESBL-producing pathogens and resistant strains of *P. aeruginosa* in this study suggests that choice of therapy for nosocomial pneumonia needs to be guided by local resistance patterns.[97]

7.9 Acute Pulmonary Exacerbations in Cystic Fibrosis Patients

One investigator-blind, randomised, clinical trial was conducted to compare the efficacy, safety and tolerability of therapy with a combination of meropenem and tobramycin versus ceftazidime and tobramycin in cystic fibrosis patients with acute pulmonary exacerbations. Study investigators randomised patients to receive either meropenem (40 mg/kg up to 2g every 8 hours) or ceftazidime (5 mg/kg up to 2g every 8 hours) both of which were co-administered with tobramycin (target serum peak ≥8 mg/L and trough of <2 mg/L). To be included in the study cystic fibrosis patients had to be aged ≥5 years experiencing a acute pulmonary exacerbation with ceftazidime susceptible *P. aeruginosa*. Patients were stratified by lung function before randomisation. Patients infected with *Burkholderia cepacia* complex or ceftazidime-resistant *P. aeruginosa* were assigned to receive an open-label meropenem plus tobramycin treatment. Of the 102 patients included in the comparative study, 50 received meropenem plus tobramycin therapy and 52 received ceftazidime plus tobramycin treatment. Forced expiratory volume after 1 second (FEV_1) improved at the end of treatment for patients in both treatment groups with a mean increase of 38.8 ± SD52.3% in the meropenem plus tobramycin group and a mean increase of 29.4 ± 35.1% in the ceftazidime plus tobramycin group; $p < 0.0001$ vs baseline values.[98] A satisfactory response defined as a ≥15% improvement in FEV_1 from baseline at day seven was seen in 62% of patients receiving meropenem plus tobramycin compared with 44% of those receiving ceftazidime plus tobramycin (p = 0.04),[98] and the median time to FEV_1 response was 4 days and 6 days, respectively.[98] The occurrence of adverse events and treatment-related adverse events was similar in both groups, and there was no major difference in the types or severity of the adverse events that occurred in each treatment group.[98]

7.10 Febrile Neutropenia

Several clinical trials have been conducted to compare carbapenems to both third and fourth gen-

eration cephalosporins for the treatment of febrile neutropenia.

In an open, comparative, randomised, multicentre study by Biron et al.[99] imipenem/cilastatin 1g three times daily was compared with cefepime 2g twice in 400 episodes of febrile neutropenia. Study participants consisted of a homogenous cohort of cancer patients with short-duration neutropenia following chemotherapy for solid tumours, lymphoma and myeloma. The study allowed for the addition of another antibacterial, usually a glycopeptide, if a patient did not respond after 3 days of therapy. Success of monotherapy was observed in 79% of episodes treated with cefepime and in 72% of episodes treated with imipenem/cilastatin ($p < 0.0001$).[99] The microbiological response rate for documented infections was 66% for cefepime and 61% with imipenem/cilastatin.[99] The overall response rate at the end of therapy with or without additional antibacterials was 95% for cefepime patients and 90% for the imipenem/cilastatin group.[99] Survival rates were similar in both groups being 95% and 98%, respectively.[99] The cefepime treatment was better tolerated with a 9% occurrence rate of adverse events compared with 19% for the imipenem group ($p = 0.003$).[99]

A later prospective, randomised clinical trial by Raad et al.[102] compared imipenem/cilastatin (500mg every 6 hours) to cefepime (2g every 8 hours). This study differed from that of Biron et al.[99] in the administration schedule of the drugs and the patient population, which allowed for the use of amikacin or vancomycin immediately in accordance with Infectious Disease Society of America (ISDA) guidelines.[102] The study population consisted of patients at moderate to high risk, with febrile neutropenia who required hospitalisation which was associated with a prolonged duration of neutropenia. Baseline characteristics of patients receiving either treatment regimen were similar ($p \geq 0.3$).[102] An intention-to-treat analysis showed a 68% response with the imipenem/cilastatin regimen and a 75% response rate with the cefepime regimen ($p = 0.2$).[102] The occurrence rate of antibacterial associated adverse events and superinfections did not differ significantly between the two groups ($p = 0.6$).[102]

In a study by Fleishhack et al.,[101] meropenem (60 mg/kg/day in three divided doses up to 3 g/day) and ceftazidime (100 mg/kg/day in three divided doses up to a maximum of 6 g/day) were compared as empirical monotherapy for the treatment of febrile neutropenia in paediatric cancer patients. Investigators randomly allocated 342 febrile neutropenic episodes to either treatment group. Treatments were then analysed for the clinical and microbiological responses dependent on the type of infection. After initial monotherapy, the success rate between the two treatment groups differed significantly with a 55.8% response rate for patients treated with meropenem and a 40.0% response rate for patients treated with ceftazidime ($p = 0.003$, 95% CI 0.053, 0.263).[101] There were also significant differences between the treatment groups with respect to duration of fever (median 5 days for ceftazidime and median 4 days meropenem, $p = 0.022$) and for duration of antibacterial therapy (median 7 days ceftazidime and 6 days meropenem, $p = 0.009$).[101] In the intention-to-treat analysis, the overall success rate of both treatments was 99.4%.[101] Response rates between treatments differed significantly only in fevers of unknown origin and not in documented infections.[101] The rate of adverse effects did not differ between the two treatment groups.[101]

Feld et al.[100] conducted a prospective, double-blind, randomised, multicentre clinical trial of 471 episodes of febrile neutropenia in 411 patients comparing meropenem 1g and ceftazidime 2g both every 8 hours. The study population consisted of adults aged ≥18 years with malignancies, fever, neutropenia, and a known or suspected infection. Once assigned to one of the treatment groups for a specific episode, the patient continued to receive that treatment regimen until the febrile episode resolved, treatment was discontinued, or the treatment was modified. At the end of therapy, the overall clinical response was significantly different between the two treatment groups (54% with meropenem and 44% with ceftazidime) [$p = 0.033$]. There were also significant findings in the subgroup analyses with mer-

openem showing higher response rates for fevers of unknown origin (62% vs 46% with ceftazidime), bone marrow transplant patients (73% vs 27% with ceftazidime), severely neutropenic (≤100 cells/μL) patients (55% vs 43% with ceftazidime), and patients given antimicrobial prophylaxis prior to entry into the study (71% vs 52% in the ceftazidime group).[100] However, no significant difference between treatment groups was found for clinically defined or microbiologically defined infections.[100]

7.11 Overall Evaluation of Clinical Trials

Imipenem/cilastatin and meropenem have been proven to be both bacteriologically and clinically efficacious in randomised, comparative studies in a variety of clinical infections including: complicated intra-abdominal infections, complicated SSSI, CAP, nosocomial pneumonia, complicated UTIs, meningitis (meropenem only)[63] and febrile neutropenia. Imipenem/cilastatin and meropenem have both also demonstrated efficacy in treating severely ill patients with nosocomial and polymicrobial infections. Ertapenem has proven to be both bacteriologically and clinically efficacious in randomised, comparative studies in the treatment of community-acquired infections including complicated intra-abdominal infections, complicated SSSI and CAP. Clinical trials are required to establish the efficacy and safety of doripenem.

8. Adverse Effects

The safety profiles of imipenem/cilastatin, meropenem and ertapenem are well established. Mild, self-limiting adverse events reported with both meropenem and imipenem/cilastatin are similar.[63] The most common adverse events reported with meropenem and imipenem/cilastatin include local irritation at the injection site, diarrhoea, rash, nausea, vomiting and pruritis.[63] These adverse events were considered to be mild to moderate and lead to discontinuation of therapy in 1.4% of patients treated with meropenem and 1.8% of patients treated with imipenem/cilastatin.[63] The incidence of adverse events seen with ertapenem is comparable with that seen with the other carbapenems (table VII). The most common adverse events reported with ertapenem were diarrhoea, infused vein complications, nausea and headache.[2,103] Gastrointestinal disturbances or rash caused discontinuation of ertapenem therapy in 1.2% of patients.[2]

Like other β-lactams, imipenem/cilastatin, meropenem and ertapenem can affect various laboratory tests, including mild to moderate, transient increases in hepatic enzymes such as alanine aminotransferase, alkaline phosphatase and lactate dehydrogenase.[2,63] In addition, imipenem/cilastatin and meropenem have been reported to cause increases in serum creatinine and serum urea (in <1% of subjects).[63] For meropenem and imipenem/cilastatin, the most frequently observed drug-induced haematological changes are thrombocytosis and eosinophilia (in <2% of subjects).[63,104] No significant difference has been observed in the frequency of these altered laboratory tests between meropenem and imipenem/cilastatin.[104,105] Drug-related neutropenia was infrequently reported with ertapenem.[2,103]

Of note for imipenem/cilastatin is the development of seizures.[63,104] Phase III trials and postmarketing surveillance have documented the incidence of imipenem-induced seizures to be 1.5–2%.[63] Risk factors for seizures include impaired renal function, pre-existing CNS disease or infection, stroke or history of seizures, as well as high-dose imipenem/

Table VII. Reported overall incidence of adverse events (reported as percentages) and drug-related adverse events (in parenthesis) of carbapenems currently used in clinical practice[2,103,104]

Adverse event	Imipenem (n = 1802)[104]	Meropenem (n = 5026)[104]	Ertapenem (n = 1152)[103]
Diarrhoea	3.1 (1.4)	5.0 (2.3)	9.2 (5.6)
Infused vein complication	NA	NA	5.4 (3.2)
Nausea/vomiting	7.4 (3.2)	4.9 (1.4)	10.4 (4.7)
Headache	2.9 (0.6)	1.9 (0.4)	6.8 (2.3)
Phlebitis/ thrombophlebitis	1.7 (1.3)	1.7 (1.1)	1.6 (1.0)
Pruritus	1.6 (0.9)	1.0 (0.4)	1.0 (0.5)
Rash	2.3 (1.3)	3.3 (1.4)	2.3 (1.1)
Abdominal pain	1.7 (0.1)	1.0 (0.1)	4.3 (1.0)
Constipation	1.4 (0.1)	1.0 (0.0)	NA

n = total number of patients in respective source study; **NA** = information not available.

cilastatin (1g every 6 hours).[63,104] Meropenem has a lower potential to cause seizures as supported by the results of animal studies and phase I–III trials.[106] The adverse event profile of ertapenem was studied with a population of >2000 patients; in that patient population the incidence of seizures was 0.5% overall, with 0.2% being associated with drug therapy.[103] Consistent with these data, meropenem is the only carbapenem indicated for the treatment of meningitis.[63,106]

9. Drug Interactions

The administration of probenecid with imipenem/cilastatin causes a 30% decrease in renal clearance of imipenem.[107] However this decrease is associated with an increase in non-renal clearance, as imipenem is shunted to non-renal mechanisms of elimination there is little apparent change in plasma clearance.[107] Cilastatin pharmacokinetics are more affected by the concomitant administration of probenecid, blockade of tubular secretion of cilastatin results in an increase in AUC and in elimination half-life from 0.8 to 1.7 hours.[107] Generalised seizures have been reported in patients receiving imipenem/cilastatin and ganciclovir therapy.[108] The concomitant administration of meropenem and probenecid causes increases in the plasma half-life of meropenem by 33%, but does not affect the urinary recovery rate.[109] Meropenem has been reported to decrease plasma concentrations of valproic acid in both animals and humans.[56,110] Probenecid was found to inhibit active renal tubular secretion of ertapenem and increase its plasma half-life from 4.0 to 4.8 hours.[73] *In vitro* studies of ertapenem have reported that it is not a substrate for cytochrome p450 enzymes or P-glycoprotein, therefore, no drug interactions are expected that are due to the involvement of these enzyme systems.[2]

10. Role in Therapy

The role of carbapenems in the therapeutic armamentarium will continue to evolve as novel compounds are added to the class. Generally, all carbapenems display broad-spectrum activity as well as stability to various β-lactamases including AmpC β-lactamases and ESBLs.[2]

Imipenem and meropenem are the most established members of this class and are used primarily to treat moderate to severely ill patients with nosocomial infections and polymicrobial infections. Clinical trials have demonstrated their effectiveness in the treatment of many moderate to severe infections including intra-abdominal infections, nosocomial pneumonia, septicaemia and febrile neutropenia.[63] While imipenem is slightly more active than meropenem against Gram-positive organisms and meropenem slightly more active than imipenem against Gram-negative organisms, direct comparisons between the two drugs report similar bacteriological and clinical cure rates.[63] In addition, meropenem is indicated for the treatment on meningitis, while imipenem is not because of the potential of imipenem to cause seizures. The current role for imipenem and meropenem in therapy remains for use in moderate to severely ill patients with nosocomial and polymicrobial infections.

Ertapenem demonstrates limited activity against *Enterococcus* spp. and *P. aeruginosa* as well as other nonfermentative Gram-negative bacteria commonly associated with nosocomial infections.[2] The extensive protein binding of ertapenem extends its half-life and allows for once-daily administration. Clinical trials have compared ertapenem to piperacillin/tazobactam as well as ceftriaxone for a variety of indications including complicated intra-abdominal infections, acute pelvic infections, complicated surgical site infections, CAP, complicated UTIs and diabetic foot infections.[2,93] These trials demonstrated that ertapenem has equivalent efficacy and safety when compared with piperacillin/tazobactam or ceftriaxone.[2] Ertapenem is not suitable for use in nosocomial infections.[2] The role of ertapenem in treating infectious diseases is for mild to moderately ill patients with community-acquired infections and for treating patients with infectious diseases using outpatient intravenous antibacterial therapy.

Doripenem is currently undergoing phase III clinical trials. Preliminary data on its *in vitro* activity

particularly against *P. aeruginosa* and pharmacokinetics are promising, but comparative clinical trials are needed to assess its role compared with imipenem and meropenem for the treatment of moderate to severely ill patients with polymicrobial and nosocomial infections. Tebipenem is still in the early stages of development and there are a lack of published data. The addition of this oral carbapenem, with its broad spectrum of activity and β-lactamase stability, may be useful, particularly in outpatient management of infections requiring a broad-spectrum agent.

Acknowledgements

Drs Zhanel and Hoban have received a study grant from Merck. The remaining authors have no conflicts of interest that are directly relevant to the content of this review. No sources of funding were used in the preparation of this review.

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