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Properties and potential of ertapenem

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Ertapenem is a carbapenem that shares the activity of imipenem and meropenem against most species, but is less active against non-fermenters. Activity is retained against most strains with AmpC and extended-spectrum β-lactamases, although resistance can arise if these enzymes are combined with extreme impermeability. Resistance can also be caused by IMP, VIM, KPC and NMC carbapenemases, but again, co-requires impermeability. Although the spread of carbapenemases in the future is a concern, they are currently very rare. Given as a 1 g intravenous (iv) infusion once daily, ertapenem has a plasma half-life of ~4 h in healthy volunteers, and a C_{max} of 155 mg/L and 13 mg/L for total and free drug, respectively. Excretion is largely renal, divided equally between native drug and an open-ring derivative. Trials show equivalence to piperacillin/tazobactam or ceftriaxone in (a) intra-abdominal infections, (b) community-acquired pneumonia, (c) acute pelvic infections, (d) skin and skin structure infections and (e) complicated urinary tract infections. The USA licence grants all these five indications; the EU licence grants the first three. Further potential uses include home iv therapy, directed therapy against Enterobacteriaceae with AmpC or extended-spectrum cephalosporinases, and tentatively, surgical prophylaxis. Widening the usage of carbapenems raises public health concerns, somewhat allayed by the continued rarity of carbapenemases after 17 years of imipenem use, and by the fact that carbapenemases occur mostly in non-fermenters outside the spectrum of ertapenem, and co-require impermeability to confer resistance in Enterobacteriaceae. Nevertheless, if ertapenem is to be used widely, its effects on the resistance ecology need to be monitored carefully.

Keywords: carbapenems, β-lactamases, MK-0826, β-lactams

Introduction

Ertapenem (INVANZ, Merck, formerly MK-0826 and L-749,345) is a carbapenem that utilizes the once-daily regimen of ceftriaxone. It shares the broad spectrum of imipenem and meropenem against Enterobacteriaceae, Gram-positive species and anaerobes, but is less active against non-fermenters. Ertapenem is licensed in the EU for the treatment of intra-abdominal and gynaecological infections, and community-acquired pneumonia. Elsewhere, including in the USA, it is also licensed for skin and skin structure infections and for complicated urinary tract infections.

Ertapenem will be promoted for wider and earlier use than imipenem and meropenem, which are mostly reserved for patients who are severely ill with multiresistant infections. If ceftriaxone is taken as a model for ertapenem's future, its potential market is vast. Whether or not ertapenem achieves this level of usage, its launch raises questions about carbapenem therapy in general, not least because it comes at a time of growing concern about the spread of metallo-β-lactamases.[1,2] The purpose of this article is to review the properties of ertapenem and to open this debate, which will doubtless expand if oral carbapenems and penems such as faropenem ultimately reach the market.

For a compound already on the market, the literature on ertapenem is still remarkably scanty: a PubMed search on 1 March 2003 (http://www.ncbi.nlm.gov/PubMed/) gave just 42 hits, plus another six under the compound's previous code numbers. This compared with 170–250 hits each for daptomycin, faropenem and gemifloxacin, none of which is yet licensed.

Chemistry and target affinity of ertapenem

Ertapenem (Figure 1) differs from meropenem solely in its 2′ substituent, where it carries a *meta*-substituted benzoic acid group. As with meropenem (and unlike imipenem), carbon 1 carries a β-methyl group, protecting against hydrolysis by renal dehydropeptidase I.[3] Otherwise, like imipenem and meropenem, ertapenem has a *trans* hydroxyethyl on the 6 position. This configuration means that the

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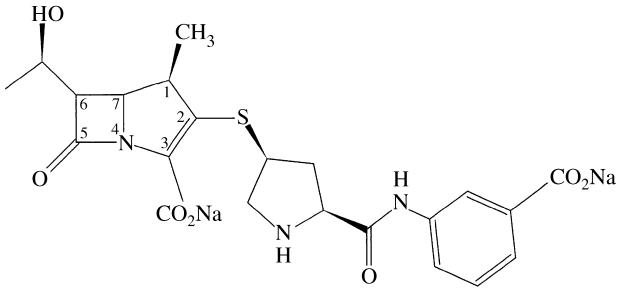

Figure 1. Structure of ertapenem (shown as free acid; the commercial formulation is disodium salt).

hydroxyethyl slopes away from the plane of the β-lactam ring, and is critical to β-lactamase stability in carbapenems.[4]

Like meropenem, ertapenem binds most strongly to penicillin-binding protein (PBP)-2 of *Escherichia coli*, then PBP-3, and has good affinity also for PBP-1a and -1b.[5] By contrast, imipenem binds primarily to PBP-2, then -1a and -1b, and has only weak affinity for PBP-3.[6] Ertapenem and meropenem saturate their primary PBP targets in *E. coli* at lower concentrations than does imipenem, probably explaining why they have lower MICs. Permeation assays have not been reported, but as a larger and more negatively charged molecule, ertapenem is likely to permeate Gram-negative bacteria more slowly than meropenem.[7] Imipenem is an exceptionally rapid permeant, being small and zwitterionic.[8]

Inactivation of PBP-1a and -1b achieves rapid bactericidal action, without the prior filamentation that occurs with agents such as third-generation cephalosporins, which bind primarily to PBP-3. This means that the carbapenems allow a smaller increase in biomass before cell lysis, minimizing endotoxin release.[9]

In vitro activity

Three large multicentre surveys have been published on the *in vitro* activity of ertapenem, examining broad ranges of species from the USA, Europe and Australia.[10–12] Collectively, these examined >10 000 recent clinical isolates. MICs have also been published for the pathogens isolated during clinical trials,[12–18] and for other specific groups, including anaerobes[19] and pneumococci.[20–22] Many studies commissioned by the manufacturer were conducted with pre-prepared microbroth panels, ensuring standardization but omitting important comparators, notably meropenem.

NCCLS susceptibility and resistance breakpoints are ≤2 and ≥8 mg/L for non-fastidious Gram-negative bacteria and staphylococci, ≤4 mg/L and ≥16 mg/L for anaerobes, and ≤1 mg/L and ≥4 mg/L for *Streptococcus pneumoniae*. The NCCLS also has susceptibility breakpoints of ≤1 mg/L for β-haemolytic streptococci, and ≤0.5 mg/L for *Haemophilus influenzae*. The British Society for Antimicrobial Chemotherapy has breakpoints of susceptible <2 mg/L and resistant >2 mg/L for all species except pneumococci, where it has values of ≤1mg/L and >1 mg/L, respectively (http://www.bsac.org.uk).

Enterobacteriaceae and other fermenters

With rare exceptions, the MICs of ertapenem for Enterobacteriaceae fall between 0.008 and 0.12 mg/L (Table 1). These values are similar to those of meropenem, and eight- to 16-fold below those of imipenem. Activity is maintained against Proteeae, which often have borderline susceptibility to imipenem.[10] Among the 1611 Enterobacteriaceae isolates from 12 centres in Europe and Australia, just three organisms, all *Enterobacter aerogenes*, required ertapenem MICs ≥ 8 mg/L, whereas MICs of 2–4 mg/L were recorded for a few isolates of *Enterobacter cloacae*, *Morganella morganii* and *Klebsiella* spp.[10] MICs ≥ 8 mg/L were also found in a few *E. cloacae* and klebsiellae among the 1563 Enterobacteriaceae collected from 11 American centres,[11] with MICs of 2–4 mg/L seen for a few *Citrobacter* spp. and Proteeae. Most ertapenem-resistant isolates were cross-resistant to imipenem, or had reduced susceptibility.

Among other fermenters, *Pasteurella* spp. are very susceptible, but data for *Aeromonas* spp. are contradictory. The European/Australian survey[10] examined 72 aeromonads and recorded an MIC_{90} of 4 mg/L, with six isolates requiring MICs ≥ 8 mg/L. The American survey examined 22 isolates, finding MICs universally ≤1 mg/L.[11] This discrepancy may reflect differences in the balance of species examined, since some aeromonads have chromosomal metallo-β-lactamases whereas others do not.[23] Whatever the explanation, the significance is limited because *Aeromonas* spp. are rare pathogens, even in neutropenic patients.

Non-fermenters

Ertapenem has only marginal activity against important non-fermenters.[10,11] MICs for *Pseudomonas aeruginosa* isolates are from 2–16 mg/L, compared with 0.25–0.5 mg/L for meropenem and 1–2 mg/L imipenem. Curiously, the MIC distribution of ertapenem for *P. aeruginosa* is notably wider than that of imipenem, but the underlying reasons are unknown.[10] Against *Acinetobacter* spp., ertapenem MICs generally exceed 4 mg/L, and imipenem remains the most active carbapenem, with MICs mostly from 0.12–0.5 mg/L, compared with 0.25–1 mg/L for meropenem. As with established carbapenems, ertapenem lacks activity against *Stenotrophomonas maltophilia*, which has a chromosomal metallo-β-lactamase. Activity against *Burkholderia cepacia* is marginal, with an MIC_{50} of 8 mg/L, compared with 16 mg/L for imipenem and 4–8 mg/L for meropenem.

Haemophilus, Moraxella and Neisseria spp.

All the *H. influenzae* isolates examined in the European/Australian and American surveys were inhibited by ertapenem at ≤0.5 mg/L.[10,11] MICs ≤0.5 mg/L were reported for isolates selected for β-lactamase-independent amoxicillin resistance,[24] but remain to be determined for those *H. influenzae* strains with high-level resistance to imipenem (MICs 32–64 mg/L). Although nowhere prevalent, such organisms have been encountered on several occasions. [25,26] They typically are resistant to biapenem (a carbapenem ultimately marketed only in Japan) as well as imipenem, but not meropenem.

Ertapenem was active against >90% of *Moraxella catarrhalis* isolates at 0.016 mg/L, and against all at 0.25 mg/L.[10,11] It was active at 0.016 mg/L against all *Neisseria meningitidis* isolates.[10,11] Activity against *Neisseria gonorrhoeae* has not been reported, but may be worth investigating in view of increasing ciprofloxacin resistance.

Staphylococci

Like imipenem and meropenem, ertapenem is active against methicillin-susceptible *Staphylococcus aureus* (MSSA) but not against methicillin-resistant *S. aureus* (MRSA). The same rule applies for coagulase-negative staphylococci. MICs for methicillin-susceptible staphylococci are 0.25 to 0.5 mg/L; the higher top values in Table 1 almost certainly reflect the mistaken inclusion of a few methicillin-resistant isolates.[10,11]

Table 1. *In vitro* activity of ertapenem (all values as mg/L)

	Europe/Australia survey			USA survey		
	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range
Citrobacter spp.	0.008	0.06	0.004–0.5	≤0.008	0.25	≤0.008–4
E. aerogenes	0.06	1	0.008–≥16	0.03[a]	0.5	<0.008–>16
E. cloacae	0.06	1	<0.008–4			
E. coli	0.008	0.03	0.06–1	≤0.008	0.016	≤0.008–16
K. pneumoniae	0.008	0.06	0.008–2	≤0.008	0.03	≤0.008–16
Klebsiella oxytoca	0.008	0.03	<0.008–0.12			
M. morganii	0.03	0.06	<0.008–1	0.016[a]	0.03	≤0.008–4
Proteus mirabilis	0.016	0.06	<0.008–1			
Proteus vulgaris	0.016	0.25	<0.008–1			
Providenica spp.	0.03	0.25	<0.008–2			
Salmonella spp.	0.008	0.016	≤0.008–0.25	≤0.008	≤0.008	<0.008–0.016
Serratia spp.	0.03	0.12	≤0.008–1	0.03	0.12	0.008–≥16
Shigella spp.	0.008	0.016	≤0.008–0.5	≤0.008	≤0.008	≤0.008
Aeromonas spp.	0.12	4	≤0.008–≥16	0.06	0.25	0.03–1
Acinetobacter spp.	4	16	0.016–≥16	4	16	0.06–>16
P. aeruginosa	4	16	<0.008–>16	8	>16	≤0.008–≥16
H. influenzae	0.03	0.12	≤0.008–0.5	0.03	0.06	≤0.008–0.5
Moraxella spp.	0.008	0.008	≤0.008–0.5	≤0.008	0.016	≤0.008–0.03
Clostridium spp.	0.12	2	0.016–4	0.06	0.06	≤0.008–0.12
Bacteroides fragilis	0.25	2	<0.008–≥16	0.25	1	0.016–4
S. aureus (methS)	0.12	0.25	0.008–>16	0.12	0.25	0.03–>16
Coagulase-negative staphylococci (methS)	0.25	16	0.03–32	0.12	0.5	0.03–4
S. pneumoniae	0.008	0.5	0.008–4	Split by penicillin phenotype; see Figure 2		
Streptococcus pyogenes	0.008	0.06	0.008–0.25	0.008	0.016	0.008–0.25
Streptococcus spp.	0.03	0.5	<0.008–>16	0.12	0.5	0.008–4
E. faecalis	16	16	1–32	8	>16	0.06–>16

[a]Species not detailed individually.
methS, methicillin susceptible.
Data from refs 10 & 11.

Pneumococci, streptococci and enterococci

Ertapenem has good anti-pneumococcal activity although, as with all β-lactams, sensitivity is reduced for penicillin-non-susceptible isolates (Figure 2).[10,11] In general, MICs are equal to or two-fold below those of benzylpenicillin, but two- to four-fold above those of meropenem and imipenem. MICs up to 4 mg/L have been recorded for exceptional pneumococci, but most penicillin-resistant isolates are susceptible at 1–2 mg/L. Similar activity is seen against other α- and non-haemolytic streptococci, but the European survey recorded one isolate with an MIC of 16 mg/L.[10]

As with meropenem, activity against *Enterococcus faecalis* is marginal (MICs of 8–16 mg/L) whereas imipenem is more active *in vitro*, with MICs of 2–4 mg/L.[10,11] *Enterococcus faecium* isolates are resistant to all β-lactams, including carbapenems, owing to expression of a low-affinity PBP.[27]

Gram-positive bacilli

Ertapenem has MIC_{90}s of 0.25 to 0.5 mg/L for *Propionibacterium acnes* and most *Corynebacterium* spp., but MICs exceeding 16 mg/L are seen for a few coryneform isolates.[11] Activity against *Bacillus* spp., including *Bacillus anthracis*, is likely to be constrained by their possession of chromosomal metallo-β-lactamases.[28]

Activity against anaerobes

The American and European/Australian surveys[10,11] showed that ertapenem has excellent anti-anaerobic activity,[11] and this was confirmed in greater detail by a study of 1001 anaerobes from 17 centres worldwide.[12] Each of these studies recorded an MIC_{90} of 1–2 mg/L for *Bacteroides fragilis* group isolates, with ertapenem about two-fold less active than imipenem. A few *B. fragilis* (<1%) isolates require ertapenem MICs >16 mg/L and it is likely (although unconfirmed) that these produce the CcrA (CfiA) metallo-β-lactamase, which has been recorded in a tiny subset of *B. fragilis* strains for over 20 years.[29,30] Its prevalence does not seem to be increasing, but surveillance is complicated because the encoding gene can remain silent unless there is appropriate mutation or migration of an insertion sequence.[31,32]

Virtually all *Prevotella*, *Fusobacterium*, *Peptostreptococcus* and *Porphyromonas* spp. are susceptible to ertapenem at ≤0.5 mg/L; most clostridia are susceptible at 1–2 mg/L, although one resistant *Clostridium difficile* isolate was recorded in the European survey.[10] Resistance was seen in 12/61 isolates of *Bilophila wadsworthia*, an anaerobe 'often present in the mixed flora of appendicitis and peritonitis'.[12] The reasons for this resistance were not investigated, and the organism is rare as a single pathogen.

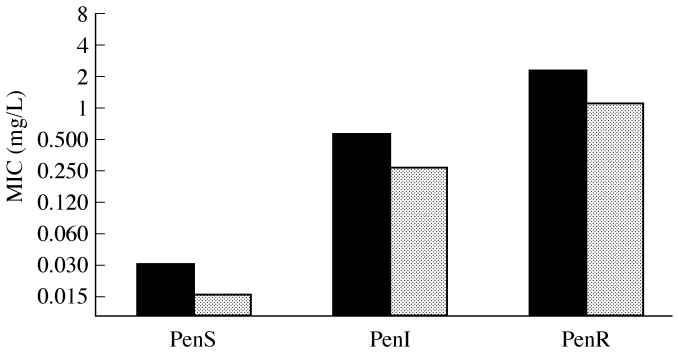

Figure 2. MIC_{90}s of ertapenem (black bars) and imipenem (grey bars) for *S. pneumoniae* isolates that are susceptible (PenS, MIC ≤ 0.06 mg/L), intermediately resistant (PenI, MIC 0.12–1 mg/L) and resistant (PenR, MIC ≥ 2 mg/L) to penicillin. Data from ref. 11.

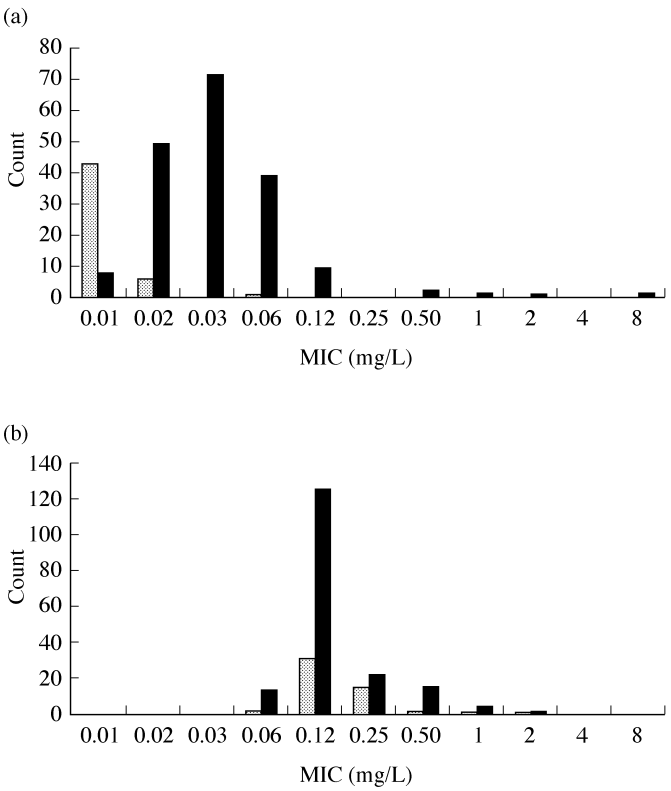

Figure 3. MIC distributions of (a) ertapenem and (b) imipenem for *Klebsiella* spp. isolates with (black bars) and without (grey bars) ESBLs. Data re-plotted from ref. 33.

Susceptibility testing methods

MIC tests in the multicentre surveys[10,11] were performed by broth microdilution but NCCLS agar dilution in Mueller–Hinton medium has also been used.[33] MICs by Etest agreed, ±1 dilution, with those by broth microdilution in 80.8% of cases and ±2 dilutions in 93% of cases, based upon tests conducted at 12 centres in Europe and Australia.[10] Similar agreement was found for imipenem in the same study (76.2% agreement ±1 dilution and 92.5% ±2 dilutions), and there was no bias for Etests to give higher or lower MICs for either carbapenem. NCCLS disc tests correlated well with broth MICs for non-fastidious bacteria;[10] thus, using 10 μg discs against 3126 isolates, the rates of 'very major' (susceptible by disc, resistant by MIC) and 'major' (resistant by disc, susceptible by MIC) errors were 0.7% and 0.45%, respectively. 'Minor' errors (intermediate by one method but resistant or susceptible by the other) arose for 3.45% of isolates.

Interactions with resistance mechanisms

It is reasonable to presume that ertapenem's lack of activity against MRSA and *E. faecium,* and its reduced activity against penicillin-resistant streptococci (Figure 2), reflect poor binding to the low-affinity PBPs of these organisms. Carbapenems active against MRSA are known, but have proved unsuitable for development.[34] Ertapenem's limited activity against non-fermenters remains to be explained, but probably reflects poor uptake or extensive efflux, perhaps contingent on its increased negative charge and greater molecular mass compared with earlier carbapenems. MICs of ertapenem are raised for *P. aeruginosa* mutants that lack the OprD (D2) porin, showing that the poor anti-pseudomonas activity does not reflect a failure to use this 'carbapenem specific'-channel.[35]

More is known about ertapenem's interactions with resistance mechanisms that compromise third-generation cephalosporins but which spare existing carbapenems. The European/Australian and American surveys[10,11] both indicated that ertapenem remained active against the great majority of cephalosporin-resistant Enterobacteriaceae isolates, and further studies therefore directly tested its activity against strains known to produce extended-spectrum β-lactamases (ESBLs) or to hyperproduce AmpC enzymes. Tests on 180 ESBL-positive klebsiellae from European ICUs indicated a modal MIC of 0.03 mg/L and an MIC_{90} of 0.12 mg/L.[33] Corresponding values for 40 ESBL-non-producing control strains were lower, at 0.008 and 0.016 mg/L, respectively. By comparison, imipenem had modal MICs of 0.12 mg/L for both the ESBL producers and the controls (Figure 3). The highest ertapenem MIC for an ESBL producer was 8 mg/L compared with only 2 mg/L for imipenem, thus reversing the general pattern whereby ertapenem was the more active carbapenem against *Klebsiella* spp. Moreover, Paterson *et al.*[36] recorded eight ESBL-positive *Klebsiella pneumoniae* from bloodstream infections in Argentina and South Africa that were resistant to ertapenem (MICs ≥ 16 mg/L) but still susceptible to imipenem and meropenem. These latter carbapenems were used successfully as therapy in seven of the cases. The isolates had various ESBL types, and except for one pair, were not clonally related. Such data all imply a slight effect by ESBLs against ertapenem. Nevertheless, the introduction of ESBL-encoding plasmids into recipient *E. coli* strains does not raise the MICs of ertapenem; nor, in contrast to cephalosporins, is there any substantial inoculum effect for ESBL-positive *Klebsiella* spp.[33] It may be that the least-susceptible ESBL producers have further mechanisms, such as reduced permeability or increased efflux. This would explain why many also have reduced susceptibility to cefoxitin, another drug that is not a substrate for ESBLs.[37]

With rare exceptions, *Enterobacter, Citrobacter freundii, Serratia marcescens* and *M. morganii* strains that hyperproduce chromosomal AmpC enzymes remained susceptible to ertapenem at ≤0.5 mg/L.[33] MICs for derepressed *Enterobacter* and *Citrobacter* spp. nevertheless were often four- to eight-fold above those for their isogenic AmpC-inducible parent strains, and those for laboratory mutants with only basal AmpC expression. Another pointer towards a slight effect by AmpC enzymes was the observation that CMY-2, a plasmid-mediated type, was associated with resistance to ertapenem (not imipenem) in one *E. coli* isolate, although not in another.[38]

Similarly, although ACT-1, another plasmidic AmpC enzyme, did not confer ertapenem resistance when transferred into a *K. pneumoniae* strain, resistant mutants could be selected from the transconjugant at a frequency of ~10^{-9}, with the ertapenem MIC raised to 8 mg/L in a first selection and 128 mg/L in a second cycle.[39] Again, it may be that those variants that expressed resistance had permeability lesions or increased efflux as well as AmpC enzymes.[38]

A few acquired β-lactamases hydrolyse carbapenems rapidly. These are loosely termed 'carbapenemases' although most are broad-spectrum enzymes that hydrolyse all cephalosporins and penicillins. Acquired carbapenemases include (a) Class B metallo-β-lactamases belonging to the IMP, VIM and SPM groups, (b) Class A enzymes belonging to the SME, NMC/IMI and KPC groups and (c) several Class D (OXA) enzymes recorded almost exclusively from *Acinetobacter* spp.[1,2] There is an imperfect correlation between carriage of carbapenemase genes and expression of carbapenem resistance, perhaps because even the most potent Class B carbapenemases can protect Gram-negative organisms against carbapenems only if they function behind an increased permeability barrier. The interplay of permeability and a potent metallo-carbapenemase is well illustrated by work showing that ertapenem and imipenem MICs of >32 mg/L for a porin-deficient *K. pneumoniae* isolate with IMP-1 β-lactamase fell to 6 mg/L and 2 mg/L, respectively, when porin expression was regained.[40] The ertapenem MIC for an *S. marcescens* isolate with SME-1 (a Class A carbapenemase) was 2 mg/L, compared with 32 mg/L for imipenem, but the imipenem and ertapenem MICs for a *K. pneumoniae* isolate with a KPC-3 β-lactamase (also Class A) were both >32 mg/L.[33]

Irrespective of susceptibility results, it seems unwise to use any carbapenem clinically against an infection suspected of harbouring a carbapenemase producer. Use against ESBL-producing and AmpC-derepressed strains seems reasonable, despite the small MIC effects seen for some producers.

Before leaving the topic of β-lactamases it should perhaps be added that, although the studies outlined here illustrate the activity of ertapenem against β-lactamase producers, kinetic studies are still awaited, and it is unclear how the *meta*-substituted benzoic acid (Figure 1) influences enzyme affinity.

Pharmacokinetics and pharmacodynamics

Ertapenem has a plasma half-life of around 4 h in healthy volunteers, allowing once-daily administration,[41] as compared with the three- and four-times daily regimens used for meropenem and imipenem, respectively. The intravenous (iv) formulation requires infusion over ~30 min, whereas an intramuscular formulation, licensed in the USA but not in Europe, can be administered with 1% lidocaine in saline, achieving a bioavailability of 90%.[42] In either case, the standard daily dosage is 1 g. Key parameters are summarized in Table 2.

The long half-life reflects binding to plasma proteins. The manufacturer believes that this binding is to the albumin and is contingent on ertapenem's negative charge.[41] However, Kiem & Craig[43] found that the addition of 95% serum raised ertapenem's MICs ~20-fold, whereas 5% albumin raised them only two-fold or less. By contrast either serum or albumin raised ceftriaxone MICs by 14- to 20-fold. Kiem & Craig interpreted these data as indicating that ertapenem bound to a component other than albumin, whereas ceftriaxone bound to albumin. Whatever the ligand, binding is concentration-dependent and is ~95% at ertapenem concentrations <100 mg/L.[41]

Table 2. Pharmacokinetics of ertapenem, based on 1 g iv in healthy young volunteers (n = 16)

Half-life in plasma (h), harmonic mean	3.8
Area under curve (mg·h/L), total drug	572.1 ± 68.6
Area under curve (mg·h/L), free drug	33.2 ± 5.5
Apparent plasma clearance (mL/min)	29.5 ± 3.4
Apparent renal clearance (mL/min)	12.9 ± 4.3
Apparent non-renal clearance (mL/min)	16.1 ± 5.4
Volume of distribution at steady state (L)	8.2 ± 1.5
C_{max} (mg/L)	154.9 ± 22.0
C_{12} (mg/L)	9.3 ± 2.8
C_{24} (mg/L)	1.2 ± 0.6
C_{max} (mg/L), free drug	12.9 ± 3.2
Area under curve, ratio day 8:day 1	1.04

Data from ref. 41.

Elimination follows non-linear kinetics, partly owing to the concentration dependence of protein binding.[41] About 80% of excretion is via the kidneys, with half as native compound and half as the open-ring derivative; a further 10% is eliminated via the faeces. As with any renally excreted drug, the AUC alters with renal insufficiency, increasing ~1.5-fold with creatinine clearance (CL_{CR}) rates 60–90 mL/min/1.73 m^2; 2.3-fold with CL_{CR} 31–59 mL/min/1.73 m^2; 4.4-fold with CL_{CR} 5–30 mL/min/1.73 m^2 and 7.6-fold with CL_{CR} <5 mL/min/1.73 m^2. A halving of the dose is suggested in the USA if the CL_{CR} is ≤30 mL/min/1.73 m^2, whereas the EU licence suggests that the drug should be avoided. Since ertapenem does not undergo hepatic metabolism or significant biliary excretion, no adjustment is needed for hepatic insufficiency.

Little has been published on tissue penetration, which is difficult to measure for protein-bound agents. Studies showed ertapenem concentrations in blister fluid rising to 24 mg/L by 4 h after a third day's 1 g iv dose, and then remaining >20 mg/L for over 12 h.[44] Concentrations in breast milk were measured in women in a pelvic infection trial (see below) and were <0.38 mg/L within 24 h of the last dose and below the detection limit of 0.13 mg/L by 120 h after the last dose.[45]

Whether one should review the MICs of protein-bound antibiotics against free or total drug levels is a long-standing debate, unlikely to be settled here. A 1 g dose of ertapenem gives a total serum level >1 mg/L (i.e. >MICs for >90% isolates, see Table 1) throughout the 24 h dosage interval. The serum level of free drug remains >1 mg/L for about 8 h, corresponding to one-third of the inter-dosage interval.[41,46] This seems acceptable based on the view that carbapenem levels must be kept above the MIC for rather less than the 40% of the inter-dose interval required for other β-lactams.[47] Nevertheless, the free drug levels do signal caution if, for example, treating infections caused by pneumococci with MICs >1 mg/L. The pneumonia trials outlined below allowed the ertapenem dosage to be increased to 2 g daily in patients with such pathogens, although this option was rarely exercised.

Clinical trials and clinical use

The spectrum of ertapenem, encompassing Enterobacteriaceae and anaerobes, lends itself to the treatment of complex mixed infections, particularly those acquired in the community, where *Acinetobacter*

Table 3. Protocol 004, ertapenem in complicated intra-abdominal sepsis (mild to moderate)

	Ertapenem	Ceftriaxone/metronidazole
Regimens	1 g iv once daily, 3–14 days	2 g iv ceftriaxone once daily; 500 mg metronidazole iv three times daily; 3–14 days
Oral switch therapy allowed	switch to oral ciprofloxacin 500/750 mg twice daily + metronidazole 500 mg three times daily after ≥3 days	
Principal exclusions	chronic immunosuppressive illness, concurrent infection impeding assessment; ischaemic bowel disease; simple cholecystitis; cases where primary cause was traumatic or unlikely to be caused by infection; APACHE II score >30	
Total patients	59 (42 male)	55 (35 male)
mean age	37.8 ± 18.1	41.1 ± 19.0
no. with appendicitis	42	42
no. with peritonitis	24	26
no. with abscess(es)	8	11
no. with visceral perforation	23	23
no. with APACHE II score >15	3	2
no. with multiple pathogens/total with pathogens isolated	28/41 (68.3%)	38/47 (80.9%)
Favourable clinical and microbiological outcome for microbiologically-assessable patients		
Test of cure, 4–6 weeks post-therapy	26/31 (83.9%)	35/41 (85.4%)
In complicated appendicitis	22/25 (88.0%)	30/33 (90.9%)

Data from ref. 48.

spp. and *P. aeruginosa* are uncommon pathogens. Its activity against respiratory pathogens suggests use in severe community-acquired pneumonia, where ceftriaxone is standard therapy in many countries.

Major clinical trials in these settings are outlined below and in Tables 3–8. As with most drug evaluations, these were powered to demonstrate equivalence, not superiority. Ceftriaxone, with or without metronidazole, or piperacillin/tazobactam served as a comparator, according to the setting. Dosages were those normally used in the USA; thus piperacillin/tazobactam was used at 3.375 g four times daily rather than at 4.5 g three times daily, as normally given in the UK. All the trials were randomized, multicentre and double-blinded and/or double dummy. General exclusions included a history of allergy to β-lactams, AIDS (though not HIV-positive status), a resistant baseline pathogen (although this did not preclude patients with mixed infections including enterococci and pseudomonads), underlying diseases expected to be rapidly progressive or fatal, and more than 24 h antibiotic therapy in the preceding 72 h. Specific exclusions are shown in Tables 3–8. Those trials with ceftriaxone as the comparator allowed a step-down to oral antibiotics after 72 h if the response was good; other trials allowed discharge on home iv therapy. Vancomycin could be added if MRSA or enterococci were confirmed to be present. Test-of-cure assessments varied among the trials according to regulatory requirements.

Intra-abdominal infections

Two trials in intra-abdominal sepsis have been published. The first and smaller (Merck Protocol 004, Phase IIA, Table 3) enrolled 114 patients and randomized them to receive ertapenem 1 g once daily or ceftriaxone 2 g once daily plus metronidazole 500 mg three times daily.[48] A further arm received ertapenem 1.5 g once daily, but these will not be discussed, since this regimen gave no advantage and was not pursued. The patients all had complicated infections that necessitated hospitalization and surgery, but which were judged not to be life-threatening. Over 70% had appendicitis, mostly with perforation. Appropriate surgery and drainage was undertaken, together with intravenous antibiotic treatment for 3–14 days, as clinically appropriate. Therapy could be stepped-down to oral ciprofloxacin (500 or 750 mg twice daily) plus metronidazole (500 mg three times daily) after 3 full days of iv treatment, if clinically warranted. Early assessment was made 7–10 days after the end of therapy, with a final test-of-cure assessment after 4–6 weeks. Favourable clinical and microbiological outcomes were obtained at early assessment in 90% of the ertapenem patients, in 88% of those receiving ceftriaxone/metronidazole and in 84% and 85%, respectively, at test-of-cure. Few microbiologically evaluable patients were, however, available for final assessment: 41 in the ceftriaxone/metronidazole arm and just 31 in the ertapenem arm. Several patients yielded a mixed infective flora including enterococci and, although none of the study agents had significant anti-enterococcal activity, these were eradicated in 6/7 ertapenem patients and 12/15 ceftriaxone/metronidazole patients. A few patients had pathogen persistence or super-infection, but there was no pattern to the organisms involved.

The second trial (Merck Protocol 017, Phase III, Table 4) was much larger, with 633 patients randomized between the two arms.[49] In general, these patients were more seriously ill than those in Proto-

Table 4. Protocol 017, ertapenem in complicated intra-abdominal sepsis (moderate to severe)

	Ertapenem	Piperacillin/tazobactam
Regimens	1 g iv once daily, 3–14 days	3.375 g four times daily; 3–14 days
Treatment modifications allowed	vancomycin could be added if enterococci or MRSA isolated	
Principal exclusions	as trial 004, Table 3, also 'simple appendicitis'	
Total patients	323 (203 clinically and microbiologically evaluable)	310 (193 clinically and microbiologically evaluable)
mean age	46.2 ± 19.0	45.4 ± 18.9
no. with appendicitis	154 (47.7%)	146 (47.1%)
Favourable clinical outcome for microbiologically-assessable patients at test of cure		
all	176/203 (86.7%)	157/193 (81.3%)
primary infection of appendix	109/123 (88.6%)	102/113 (90.3%)
primary infection of colon	26/36 (72.2%)	25/36 (69.4%)
primary infection from stomach, duodenum or small bowel	20/22 (90.9%)	15/19 (78.9%)
primary infection of biliary tract	12/13 (92.3%)	10/10 (100%)
generalized peritonitis	50/60 (83.3%)	39/53 (73.6%)
single abscess	53/59 (89.8%)	55/67 (82.1%)
multiple abscesses	8/9 (88.9%)	2/4 (50%)
patients with APACHE II ≥ 15	13/18 (72.2%)	11/13 (84.6%)

Data from ref. 49.

col 004, with moderate to severe intra-abdominal infection extending into the peritoneal cavity and requiring surgical intervention. About half had a primary diagnosis of complicated appendicitis; the remainder had infections originating from other sites along the alimentary tract, including diverticulitis, gastric, intestinal or duodenal perforation, or intra-peritoneal abscesses. The patients underwent surgery and drainage and were randomized to receive ertapenem 1 g once daily or piperacillin/tazobactam 3.375 g four times daily for 3–14 days, with follow-up as in Protocol 004. No switch to oral therapy was allowed. The results indicated equivalence; ertapenem tended to give higher response rates than in the non-appendicitis groups, but this difference was not significant once corrected for the multiple comparisons. Many patients had *P. aeruginosa* or enterococci within a mixed infective flora. Although these species are more susceptible to piperacillin/tazobactam than to ertapenem, favourable responses were obtained in 19/26 ertapenem patients who had *P. aeruginosa* among their baseline pathogens compared with 23/26 in the piperacillin/tazobactam arm. Similarly, 50/65 patients with enterococci had a favourable response to ertapenem compared with 24/37 receiving piperacillin/tazobactam.

Community-acquired pneumonia

Two trials in severe community-acquired pneumonia requiring hospitalization have been published, both comparing ertapenem 1 g once daily with ceftriaxone 1 g once daily. Each allowed step-down to oral co-amoxiclav 875 + 125 mg twice daily after 3 full days of iv therapy, if clinically appropriate. Each also allowed the ertapenem or ceftriaxone dosage of the primary treatment to be doubled if penicillin-resistant pneumococci were isolated. Although many clinicians would routinely use ceftriaxone 2 g once daily, trials suggest that this is no more effective than 1 g once daily[50] (a conclusion that might, however, vary with the local prevalence of resistant pneumococci).

The first and larger trial (Phase III, Merck Protocol 018, Table 5) enrolled 502 patients, randomizing them equally between the two arms.[51] Favourable clinical outcomes were achieved for 92.3% of the ertapenem patients and for 91% in the ceftriaxone arm. Just over 90% of patients in each arm were switched to oral therapy after a median of 4 days iv treatment. Cure rates were similarly high in both arms irrespective of the severity of the disease and the pathogen. *S. pneumoniae* accounted for >40% of all pathogens, and ertapenem cured 11/11 pneumonias caused by penicillin-non-susceptible (MIC ≥ 0.12 mg/L) *S. pneumoniae*, compared with 12/13 for ceftriaxone. However, only three patients in the ceftriaxone arm and one in the ertapenem arm had pneumococci with penicillin MICs ≥ 2 mg/L, and conclusions about efficacy against such organisms must therefore be tentative. The second trial (Phase III, Merck Protocol 020) gave similar results: 364 patients were randomized, in a 2:1 ratio, to receive ertapenem or ceftriaxone 1 g once daily.[20] Cure rates for clinically evaluable patients were 91.8% for ertapenem and 93.5% for ceftriaxone; those for microbiologically evaluable patients were 91.0% and 91.8%, respectively. Mean durations of parenteral therapy were similar (5.5 and 5.6 days) in both arms, as were the total durations of therapy (11.5 and 11.7 days). *S. pneumoniae* was again the main pathogen, and ertapenem achieved favourable clinical and microbiological outcomes in 28/33, 9/9 and 2/2 patients infected with

Table 5. Protocol 018, ertapenem in community-acquired pneumonia requiring hospitalization

	Ertapenem	Ceftriaxone
Regimens compared	1 g iv, once daily for 3–14 days	1 g iv, once daily for 3–14 days
Changes allowed	(1) switch to oral co-amoxiclav 1g twice daily after ≥3 days; (2) ertapenem and ceftriaxone could be increased to 2 g once daily if response poor and penicillin-resistant pneumococci found	
Principal exclusions (see also text)	empyema, structural lung abnormality/malignancy; nosocomial pneumonia; mechanical ventilation; tuberculosis; likelihood of atypical pneumonia especially legionellosis	
Total patients	244	258
mean age ± S.D.	55.9 ± 20.0	57.3 ± 19.7
Favourable clinical outcome: no. cured/no. evaluable		
total	168/182 (92.3%)	183/201 (91.0%)
severity index ≤3	128/138 (92.8%)	134/144 (93.1%)
severity index >3	40/44 (90.9%)	49/57 (86.0%)
Favourable microbiological outcome: no. pathogen eradicated/no. evaluable		
all pathogens	89/96 (92.7%)	107/113 (94.7%)
S. pneumoniae	44/48 (91.7%)	56/60 (93.3%)
PenI/R *S. pneumoniae*	11/11 (100%)	12/13 (92.3%)
H. influenzae	17/21 (81%)	22/23 (95.7%)
M. catarrhalis	10/10 (100%)	15/18 (83.3%)

Data from ref. 51.

penicillin-susceptible, -intermediate and -resistant strains, respectively, compared with 14/14, 5/5 and 0/0 for ceftriaxone.

So as to assess its activity in isolation, ertapenem was not combined with macrolides in these trials, and steps were taken to exclude patients likely to have atypical pneumonia. When used routinely for community-acquired pneumonia, it may be more appropriate to add a macrolide, unless atypical agents are unlikely from the presentation, as recommended in American and British guidelines for other β-lactams.[52,53]

Skin and skin structure infections

One trial of ertapenem in complicated skin and skin structure infections has been published (Phase III, Merck Protocol 016, Table 6). This recruited 540 patients and used piperacillin/tazobactam 3.375 g four times daily as the comparator.[54] Oral switch therapy was not allowed, but patients could be discharged on home iv treatment after a minimum of 2 days hospitalization (more practicable with ertapenem than for piperacillin/tazobactam). The patients were stratified depending on whether they had underlying decubitus ulcers, diabetes mellitus, or other neuropathic conditions. Based on clinical assessments 10–21 days after the end of therapy, cure was achieved in 82.4% of the ertapenem group and 84.4% of the piperacillin/tazobactam group, indicating equivalence.

Over 40% of patients with microbiological data had polymicrobial infections. Predictably, *S. aureus* was the predominant pathogen, accounting for ~40% of all isolates. More surprisingly, anaerobes were isolated from only 17%–20% of patients, as against 30%–40% in similar trials.[55,56] Outcome was equally good regardless of the pathogen, but was slightly poorer in each arm (reduced from 80.6% favourable to 76.1% favourable for ertapenem and from 80.6% to 77.5% for piperacillin/tazobactam) for mixed infections that transpired to include MRSA as well as MSSA. More generally, patients infected with MSSA alone had more favourable outcomes than those infected with MSSA together with other organisms. *P. aeruginosa* and *E. faecalis*—species susceptible to piperacillin/tazobactam but not ertapenem—were isolated from 5–10 patients in each arm and were eradicated in 50%–70% by each drug, although the numbers were too few for meaningful comparison.

Acute gynaecological infections

One trial has been published comparing ertapenem 1 g once daily with piperacillin/tazobactam 3.375 g four times daily in acute pelvic infections (Phase III, Merck Protocol 023).[45] Four hundred and twelve women, of whom 316 remained clinically evaluable (Table 7), were stratified according to whether they had obstetric/postpartum or gynaecological/post-operative infections. Over 80% were in the former category, and 75% had endometritis. Eighty percent of the patients remained microbiologically evaluable and. ~60% had polymicrobial infections, with *E. coli* and peptostreptococci as the predominant pathogens. Favourable clinical responses were recorded 2–4 weeks post-therapy in 93.9% of patients in the ertapenem arm, and in 91.5% of those in the piperacillin/tazobactam arm. Equivalence in outcome was also seen in subset analysis for those patient groups with moderate or severe infection, and for those with

Table 6. Protocol 016, ertapenem in complicated skin and skin structure infections

	Ertapenem	Piperacillin/tazobactam
Regimens	1 g iv once daily, 3–14 days	3.375 g four times daily; 3–14 days
Mean duration (days)	9.1 ± 3.1	9.8 ± 3.3
Principal exclusions (also see text)	long-term immunosuppression; infected burn wounds; necrotizing fasciitis; osteomyelitis; septic arthritis; gangrene; need for other antibiotics (e.g. versus MRSA)	
Total patients	274	266
mean age (S.D.)	48.7 ±16.5	48.0 ±17.4
Favourable outcome among clinically evaluable patients by stratum and severity		
stratum 1: underlying decubitus ulcers, diabetes mellitus, or other neuropathic condition	28/42 (66.7%)	27/36 (75.0%)
stratum II: cellulitis, abscesses, wound infections	124/143 (86.7%)	120/138 (87.0%)
moderate infection	120/145 (82.8%)	125/143 (87.4%)
severe infection	32/40 (80.0%)	22/31 (71.0%)
Favourable clinical outcomes by pathogen among microbiologically evaluable patients		
staphs, streps, enterococci	114/149 (76.5%)	116/148 (78.4%)
Gram-negative aerobic bacilli	55/70 (78.6%)	50/66 (75.8%)
Gram-positive anaerobic cocci	30/35 (85.7%)	24/27 (88.9%)
Gram-negative anaerobic bacilli	47/48 (97.9%)	43/50 (86%)

Data from ref. 54.

endometritis. In each treatment arm, the eradication rates exceeded >90% for a wide range of pathogens. Enterococci were isolated from mixed infections in 23 women in the ertapenem arm and, despite the lack of *in vitro* activity, were eradicated from all of them, as compared with 30/31 in the piperacillin/tazobactam arm. Non-fermenters were isolated from only four patients in each arm.

Complicated urinary tract infections

Two trials of ertapenem 1 g once daily in complicated urinary tract infections have been published, both with ceftriaxone 1 g once daily as the comparator. The larger trial (Merck Protocol 014, Phase III)[57] is summarized in Table 8. It randomized 592 patients equally between the study arms and allowed a switch to oral ciprofloxacin after at least 3 days if the patient became afebrile. The patients were stratified according to whether they had pyelonephritis or other complicated urinary tract infections. The predominant pathogens were *E. coli* (69%) and *Klebsiella* spp. (13%). Microbiological cure rates 5–9 days after the end of therapy were 91.8% among evaluable patients who had received ertapenem, and 93.0% among those who received ceftriaxone. Success rates were similar between the arms when compared by stratum and severity of disease. Persistence of baseline pathogens was observed in 7%–8% of patients, but was not associated with the development of resistance, except that one *E. coli* strain became ciprofloxacin resistant during the step-down regimen. Relapse rates at late follow-up, 4–6 weeks post-therapy, were 5.4% and 7.9% in the ertapenem and ceftriaxone arms, respectively. New infections, often with enterococci, occurred in 17% and 12.3% of ertapenem and ceftriaxone patients, respectively.

The second trial (Phase III, Merck Protocol 021) randomized 258 patients in a 2:1 ratio in favour of the ertapenem arm.[58] The patients received iv antibiotics for at least 3 full days, but could then be switched to oral ciprofloxacin. *E. coli* accounted for 79% of all pathogens and Enterobacteriaceae for 95%. By completion of iv therapy, a favourable clinical response was seen in 97%–98% of patients in each arm. At test-of-cure, 5–9 days after the end of all therapy, 85.6% of ertapenem patients and 84.9% of ceftriaxone patients had favourable clinical and microbiological outcomes, indicating equivalence. Reasons for the lower success rates than in Protocol 014[57] (Table 8) are unclear. Recurrence occurred by late follow-up (4–6 weeks post-treatment) in 7/63 evaluable patients from the ertapenem arm and in 2/37 from the ceftriaxone arm. Twelve ertapenem-treated patients and six ceftriaxone patients developed new infections, many of them caused by *Enterococcus* spp.

Bacteraemia

Sizeable numbers of trial patients—mostly in the pneumonia and urinary evaluation—had secondary bacteraemia.[59] The predominant pathogens were *E. coli* and *S. pneumoniae*. Primary efficacy (clin-

Table 7. Protocol 023, ertapenem in acute pelvic infections

	Ertapenem	Piperacillin/tazobactam
Regimens compared	1 g iv, once daily for 3–14 days	3.375 g iv four times daily, 3–14 days
Mean duration (days)	4 (1–13)	4 (2–12)
Changes allowed	vancomycin could be added for resistant Gram-positive bacteria	
Principal exclusions (see also text)	pelvic inflammatory disease, tubo-ovarian abscess, post operative abdominal wall infection; gynaecological malignancy; hepatic failure; hypotension; haemodialysis	
Total patients	216	196
mean age ± S.D.	25.4 ± 7.5	27.0 ± 8.9
Favourable clinical outcome: no. cured/no. evaluable at test of cure		
total	153/163 (93.9%)	140/153 (91.5%)
obstetric/post-partum infection	129/137 (94.2%)	121/132 (91.7%)
gynaecological/post-op. infection	24/26 (92.3%)	19/21 (90.5%)
endometritis	111/120 (92.5%)	104/115 (90.4%)
moderate infection	113/121 (93.4%)	110/118 (93.2%)
severe infection	40/42 (95.2%)	30/35 (85.7%)

Data from ref. 45.

ical, microbiological or both, according to the trial) was achieved in 69/86 patients treated with ertapenem, in 44/51 treated with ceftriaxone and in 28/35 treated with piperacillin/tazobactam, indicating equivalence. No patient had persistent bacteraemia.

Safety and tolerability in clinical trials

Side effects were assessed in the Phase III trials summarized above. These recorded diarrhoea in 1.7%–7% of ertapenem patients, nausea in 0.8%–7.0% and headache in 0.4%–6.5%. Between 3.2% and 15.3% of patients experienced at least one local reaction at the infusion site, although three-quarters of these amounted to no more than local erythema. Increased alanine amino-transferase levels were seen in 3.3%–9.0% of patients, increased aspartate amino-transferase in 2.1%–8.0%, and increased alkaline phosphotransferase in 1.4%–7.0%. The platelet count was increased in 1.8%–3.2% of patients. None of these rates was significantly different from those found for the comparator agents.

There is concern about the seizure risk for β-lactams in general and carbapenems in particular.[60] One 89-year-old patient receiving ertapenem 1 g once daily in the pneumonia trial 018 had a seizure, which the investigator believed to be 'probably drug related'.[51] This occurred on day 10, when treatment was already scheduled to cease. Two brief seizures also occurred on day 10 of therapy in a 76-year-old man in the other pneumonia trial (020).[20] He was a patient with a high risk of fits, with a recent change in his anti-epileptic treatment and a resected frontal meningioma; moreover, he had received ertapenem 2 g once daily from the previous day of therapy, having responded poorly to the standard 1 g regimen. Both these patients recovered without sequelae. A third patient had a seizure in the larger intra-abdominal sepsis trial, but no details are given (017).[49] There were no seizures in a Phase II intra-abdominal sepsis trial arm that routinely used ertapenem 1.5 g once daily.[48] Two patients in the ertapenem arm of the larger intra-abdominal sepsis trial (017, Table 4) developed *C. difficile*-associated diarrhoea;[49] pseudomembranous colitis was also reported in two patients in each arm of the skin and soft tissue infection trial.[54]

Further potential settings for ertapenem use

The antimicrobial spectrum and pharmacokinetics of ertapenem suggest several potential applications, not yet explored by clinical trials. Some readers may think that ertapenem is tailor-made for purposes other than those for which it is licensed.

Critical here is a potential role in outpatient/home iv therapy, where ceftriaxone has been favoured because of its long serum half-life. Ertapenem might be used on the same rationale, although the need for infusion, rather than bolus injection, would be an inconvenience in those countries where the intramuscular formulation is not licensed. Many patients can benefit from home iv therapy, often as a step-down following hospital discharge.[61] The strategy has cost advantages, and most patients would prefer to be at home. Patients with osteomyelitis involving Gram-negative pathogens are a particular group who might benefit, and who often receive ceftriaxone.[62] Ertapenem would have a potential advantage if the pathogens included those organisms, principally *Enterobacter* spp., that are prone to develop mutational cephalosporin resistance[63] and which show a rising prevalence of ciprofloxacin resistance.[64] A caution is that there are no published data on the toxicity of ertapenem over the 6 week treatment periods likely to be needed, or on its bone penetration. There is also interest in ceftriaxone for the home management of infections in neutropenic patients, and ertapenem might be investigated in this setting too, although the lack of cover against non-fermenters is a concern with either agent.[65]

Table 8. Protocol 014, ertapenem in complicated urinary tract infection

	Ertapenem	Ceftriaxone
Regimen	1 g iv once daily, 3–14 days	1 g once daily, 3–14 days
Changes allowed	switch to oral 500 mg ciprofloxacin twice daily after ≥3 days	
Principal exclusions (also see text)	uncomplicated cystitis, complete urinary obstruction, perinephric or perirenal abscess; prostatitis, renal transplant	
Total patients	298 (92 male)	294 (97 male)
Mean age (S.D.)	51.3 ± 20.8	53.0 ± 20.5
Favourable microbiological outcome among those microbiologically evaluable at test of cure		
overall	146/159 (91.8%)	159/171 (93.0%)
acute pyelonephritis	71/75 (94.7%)	74/78 (94.9%)
other complicated infection	75/84 (89.3%)	85/93 (91.4%)
mild to moderate infection	77/84 (91.7%)	85/92 (92.4%)
severe infection	69/75 (92.0%)	74/79 (93.7%)
Favourable outcomes by pathogen among microbiologically evaluable patients		
E. coli infection	104/111 (93.7%)	112/117 (95.7%)
K. pneumoniae	21/22 (95.5%)	20/21 (95.2%)
other Enterobacteriaceae	17/19 (89.5%)	27/30 (90.0%)
Pseudomonas spp.	4/6 (66.7%)	2/2 (100%)
Gram-positive cocci	6/9 (66.7%)	4/7 (57.1%)

Data from ref. 57.

Ertapenem, because of its broad spectrum and once-daily regimen, might also prove useful in the treatment of military personnel in combat zones, especially those in transit to larger bases or to specialist care in their home country.

Ertapenem's activity against AmpC-derepressed strains and ESBL producers suggests that it might be used as directed therapy once these organisms have been identified in an infection. Advantages over existing carbapenems include a more convenient regimen and, in many countries, a lower acquisition cost. Using the same logic, ertapenem might be considered as empirical therapy in a nosocomial outbreak involving ESBL producers, but any general role in nosocomial infections would be constrained by the lack of activity against non-fermenters.

A final, and controversial, use might be as single-dose prophylaxis in abdominal or gynaecological surgery. The potential lies in the spectrum and long half-life, affording cover against both anaerobes and aerobes even if surgery is delayed or protracted. Clinical trials are, however, needed with ecological follow-up to check for stool carriage of a resistant flora in recipients.

Public health and resistance risks

Ertapenem's launch comes at a time of concern about resistance, and when acquired metallo-β-lactamases are reported in increasing numbers of isolates and countries. Until 1997, IMP-1 was the sole acquired metallo-β-lactamase known, and was reported only from *P. aeruginosa*, *Serratia* and one *Klebsiella* spp. isolated in Japan. By 2000, however, there were three IMP and two VIM carbapenemase types recorded[66] and, at the time of writing, 12 VIM types, 10 VIM types and SPM-1, with these enzymes reported from continental East Asia, Japan, the Middle East, mainland Europe, the UK, and—more rarely—the Americas.[67] In addition, there has been an erosion of the anti-acinetobacter activity of imipenem in the USA, with the proportion of non-susceptible isolates at 250 hospitals rising steadily from 2.4% in 1996 to 13.5% in the first 9 months of 2002, although the extent to which this depends on carbapenemases is unclear.[68]

Carbapenem resistance is serious because imipenem and meropenem are often the last useful resort against infections caused by multi-resistant Gram-negative bacteria. Their loss would mean an increasing need to treat severe infections with long-abandoned, toxic antibiotics, such as polymyxins. Whether it is right to fear ertapenem as a major selector is less certain. Most carbapenem resistance is in non-fermenters, which lie outside ertapenem's spectrum. It might be argued, therefore, that the use of a carbapenem without anti-non-fermenter activity should mitigate selection pressure for carbapenemases in non-fermenters. Likewise, it is reasonable to suggest that ertapenem, lacking activity against *P. aeruginosa* in general, is unlikely to select specifically for strains with porin (OprD) deficiency or up-regulated efflux. However, these arguments are more relevant to the question of which carbapenem to use, rather than whether to use a carbapenem at all.

What is more relevant to ertapenem use is the sheer difficulty of obtaining carbapenem resistance in Enterobacteriaceae, as illustrated by its continued rarity 17 years after the launch of imipenem. Among

1.42 million Enterobacteriaceae from 250 hospitals reported to the TSN surveillance in the USA during 1 January 1996–30 November 2002, just 59 (0.005%) were resistant to imipenem.[67] This is despite the fact that even hyperproduced AmpC β-lactamases and ESBLs can confer carbapenem resistance if they are combined with extreme impermeability.[66,68] Since permeability mutations emerge readily *in vitro*, it follows that such mutants must be counter-selected *in vivo*, perhaps because their impermeability impedes nutrition. More surprisingly, impermeability also seems to be necessary for the IMP and VIM metallo-carbapenemases to confer carbapenem resistance in Enterobacteriaceae.[69] Since these latter enzymes confer cephalosporin resistance without permeability lesions, it is plausible (though speculative) that cephalosporins may be more selective for carbapenemases than the carbapenems themselves.

Nevertheless, one cannot wholly be sanguine about bringing carbapenems into first-line use, and the effects of ertapenem on microbial ecology need careful monitoring. In particular, studies are needed to investigate changes in the gut flora of individual patients receiving ertapenem, and studies of ertapenem's effects at the hospital level. Since carbapenemase genes can be carried without phenotypic resistance being obvious,[69] it will be essential that this surveillance incorporates gene detection methods.

Conclusion

Imipenem and meropenem have been used largely for severe nosocomial infections, often in specialist hospital units. Their value lies in their broad spectrum and in overcoming most resistance in Gram-negative bacilli. Ertapenem does not fit this mould, meaning that the carbapenems can no longer be seen as a homogeneous group. It overcomes most resistance to other β-lactams in Enterobacteriaceae but, unlike earlier carbapenems, lacks significant activity against non-fermenters, limiting its empirical role in nosocomial infection. Rather, ertapenem is proposed primarily as a first-line medication in complicated community-acquired infections, particularly where a mixed flora of aerobes and anaerobes is likely. Aside from an appropriate spectrum for these settings, ertapenem's key advantage lies in its long plasma half-life, allowing a once-daily regimen. Pharmacokinetic and pharmacodynamic data are persuasive, and clinical trials confirm equivalence to piperacillin/tazobactam in moderate to severe intra-abdominal, pelvic, skin, and skin structure tissue infections, to ceftriaxone/metronidazole in mild to moderate intra-abdominal sepsis, and to ceftriaxone in community-acquired pneumonia and complicated urinary infections. Minor side effects occurred at frequencies similar to ceftriaxone and piperacillin/tazobactam. The seizure risk is small, although definite, as with many β-lactams. The pharmacokinetics of ertapenem are convenient for home iv therapy, military medicine, and, potentially, surgical prophylaxis, although trials are needed in these settings.

There is concern as to whether it is wise to widen the use of carbapenem when carbapenemases are beginning to spread. The worst situation would be if using ertapenem, where there are alternatives, were to undermine the value of imipenem and meropenem in settings where there are no good alternatives. The arguments seem finely balanced. On the one hand, repeated experience shows that antibiotics select resistance to themselves and to their analogues; on the other, it is naive to suppose that carbapenems are the sole selectors of 'carbapenemases', most of which are much more effective at conferring resistance to cephalosporins than to carbapenems. When the debate relates to what carbapenem to use, ertapenem may have an advantage since, lacking activity against non-fermenters in general, it seems unlikely to select specifically for those variants with increased resistance.

For the time being the best advice is to carefully monitor the institutional ecology where ertapenem enters use. Trials (e.g. the Merck SMART Program) have been established for this purpose. In the future, the spread of cephalosporin resistance into community isolates may drive clinicians to use compounds such as ertapenem. TEM and SHV-type ESBLs have not yet become widely established outside hospitals, but there is some evidence from Spain that CTX-M type ESBLs are beginning to disseminate into the community.[70]

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