β-Lactam antimicrobials have been widely prescribed to treat serious infections for nearly 60 years owing to their excellent efficacy, safety and tolerability profiles. Among the many different structurally distinct classes of β-lactams, the carbapenem class, while sharing these general β-lactam features, is regarded as the class that is most potent and that has the widest spectrum of antimicrobial activity. At the time that the carbapenems were last reviewed in this journal,1 imipenem and meropenem were the only carbapenems that were available in the majority of the world. Since then ertapenem (formerly MK-0826), a new long-acting, parenteral carbapenem (Figure 1), has received regulatory approval in the United States (November 2001) and the European Union (April 2002).

The introduction of ertapenem should make us reconsider how we think of the carbapenems. Ertapenem is sufficiently different in some key attributes from imipenem and meropenem that we can no longer consider all available carbapenems as if they were a homogeneous class. In order to consider the appropriate role of ertapenem in the current antimicrobial armamentarium, this article reviews the key attributes of ertapenem and the other carbapenems and proposes a classification scheme for the carbapenem class; imipenem and meropenem will be discussed first.1,2

Imipenem and meropenem

Pharmacology

Imipenem, the first marketed carbapenem, is co-administered with cilastatin, a dehydropeptidase-I (DHP-I) inhibitor. Meropenem, a 1-β-methyl carbapenem, does not require cilastatin co-administration as the 1-β-methyl group renders it more resistant to DHP-I hydrolysis. Imipenem and meropenem have an elimination half-life of approximately 1 h, are administered several times a day, and are primarily renally eliminated. Both require dose-adjustment in patients with significant renal impairment.

Microbiology

These carbapenems are rapidly bactericidal and demonstrate time-dependent killing.3 They have a similar very broad spectrum of antimicrobial activity. Both are active against non-fermentative Gram-negative bacilli, such as *Pseudomonas aeruginosa* and *Acinetobacter* species, which generally are associated with nosocomially acquired severe infections. In general, based on MIC90 values, imipenem is slightly more potent than meropenem against Gram-positive pathogens whereas meropenem is slightly more potent against Gram-negative pathogens. Pathogenic bacteria that are usually resistant to carbapenems include *Stenotrophomonas maltophilia* and *Burkholderia cepacia*. The general resistance profile of these agents has remained remarkably stable despite >15 years of clinical experience, with increasing resistance generally only observed against the non-fermentative Gram-negative bacilli.4,5

The stability of carbapenems against a wide variety of β-lactamases, including the extended-spectrum β-lactamases (ESBLs) and AmpC-type β-lactamases,6 is potentially of increasing importance as the incidence of clinical strains expressing ESBLs appears to be increasing. Carbapenem resistance mediated by acquired metallo-β-lactamases has been reported, generally in the setting of small local outbreaks of resistant Gram-negative infections;7 in some Asian countries (e.g. Taiwan, Korea), acquired metallo-β-lactamase-mediated resistance in non-fermentative Gram-negative bacilli, although still uncommon, appears to be of a more endemic nature.

Clinical use

Widespread clinical experience over many years has confirmed the excellent clinical efficacy of imipenem and meropenem and has led many physicians to regard imipenem and meropenem as among the most reliable agents available for the treatment of severely ill patients with nosocomial infections.

Adverse reactions

Imipenem and meropenem, when the dose is appropriate for the degree of renal impairment, are generally well tolerated.9 Seizures have been observed in carbapenem-treated patients, for example in patients who have received a dose of imipenem which is too high relative to the degree of renal impairment.

Ertapenem

Pharmacology

Ertapenem is a 1-β-methyl carbapenem and is administered as a single agent (i.e. co-administration with cilastatin is not required) either via the intravenous10 or intramuscular route.11 At plasma...
concentrations achieved with the usual clinical dose, ertapenem is approximately 94% protein bound. Its long elimination half-life of approximately 4 h, attributable to the level of reversible protein binding, allows for once-daily dosing. The adult dose is 1 g parenterally once a day. Ertapenem is not hepatically metabolized and is primarily eliminated by the renal route; dose reduction to 0.5 g once a day is required in patients with severe renal insufficiency (i.e. creatinine clearance <30 mL/min/1.73 m²). Drug–drug interactions are unlikely since ertapenem does not inhibit P-glycoprotein-mediated or cytochrome P450-mediated drug clearance.

Microbiology
Ertapenem is rapidly bactericidal. In Escherichia coli, ertapenem binds to penicillin binding proteins (PBPs) 1a, 1b, 2, 3, 4 and 5, having highest affinity for PBPs 2 and 3. Similar to imipenem and meropenem, ertapenem has a very broad spectrum of antimicrobial activity, including Gram-positive and Gram-negative aerobic and anaerobic pathogens. In contrast to imipenem and meropenem, however, ertapenem has limited \textit{in vitro} activity against Pseudomonas species [e.g. \textit{P. aeruginosa} \text{MIC} \textsubscript{90} 16 mg/L (\textit{n} = 130)] and \textit{Acinetobacter} species [e.g. \textit{Acinetobacter} species \text{MIC} \textsubscript{90} 16 mg/L (\textit{n} = 109)]. Target pathogens for ertapenem, therefore, are Gram-positive aerobic [excluding methicillin-resistant \textit{Staphylococcus} and \textit{Enterococcus}] and anaerobic pathogens, Gram-negative anaerobic pathogens and Gram-negative aerobic pathogens including the Enterobacteriaceae and \textit{Haemophilus} species but excluding the non-fermenters. In general for these target pathogens, based on \text{MIC} \textsubscript{90} values, ertapenem has similar potency to meropenem and is slightly more potent than imipenem against Gram-negative pathogens whereas imipenem is slightly more potent against Gram-positive pathogens. Ertapenem retains activity against most Enterobacteriaceae producing either ESBLs and/or AmpC-type \textbeta-lactamases. In Gram-negative bacilli, the main forms of resistance to ertapenem appear to involve combinations of reduced accumulation and periplasmic-space hydrolysis by \textbeta-lactamases. Although the potential exists for cross-resistance between ertapenem and imipenem or meropenem, \textit{in vitro} studies and data from surveillance studies indicate that such cross-resistance is not complete. In particular, among target Gram-negative pathogens, resistance to ertapenem is extremely rare and the historical perspective provided by imipenem and meropenem suggests that resistance is unlikely to become an increasing problem.

Clinical use
The efficacy and safety of ertapenem 1 g parenterally once a day was evaluated in seven large, statistically powered, double-blind, randomized clinical studies in the following five indications: complicated intra-abdominal infection, complicated skin and skin structure infection, community-acquired pneumonia, acute pelvic infection, and complicated urinary tract infection. The comparator agents, piperacillin/tazobactam (intra-abdominal, skin, and pelvic infection) and ceftriaxone (pneumonia and urinary tract infection), are potent antimicrobials that are used routinely in the treatment of the infections studied. In each of these pivotal studies, the efficacy demonstrated by ertapenem was statistically equivalent to the comparator regimen and was consistent with the anticipated efficacy for an effective antimicrobial in each indication (Table 1). Furthermore, ertapenem was highly effective in patients with a range of disease severity within each indication, including elderly patients and patients with severe infections. Overall, the results of these studies provide substantial evidence of the efficacy of ertapenem 1 g parent-
Table 1. Efficacy of ertapenem in indications

<table>
<thead>
<tr>
<th>Infection</th>
<th>Reference</th>
<th>Primary hypothesis</th>
<th>Primary hypothesis</th>
<th>N</th>
<th>Estimated response, % (95% CI)</th>
<th>N</th>
<th>Estimated response, % (95% CI)</th>
<th>Estimated difference (A—B), % (95% CI)</th>
<th>Lower limit of confidence interval required for equivalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complicated intra-abdominal infection (comparator: piperacillin/tazobactam)</td>
<td>15</td>
<td>C + M</td>
<td>M</td>
<td>203</td>
<td>86.7 (82.3, 91.1)</td>
<td>193</td>
<td>81.2 (76.0, 86.5)</td>
<td>5.5 (−2.2, 13.1)</td>
<td>−15</td>
</tr>
<tr>
<td>Complicated skin and skin structure infection (comparator: piperacillin/tazobactam)</td>
<td>16</td>
<td>C</td>
<td>C</td>
<td>185</td>
<td>82.4 (77.0, 87.8)</td>
<td>174</td>
<td>84.4 (79.0, 89.7)</td>
<td>−2.0 (−10.2, 6.2)</td>
<td>−15</td>
</tr>
<tr>
<td>Acute pelvic infection (comparator: piperacillin/tazobactam)</td>
<td>19</td>
<td>C</td>
<td>C</td>
<td>163</td>
<td>93.9 (90.2, 97.6)</td>
<td>153</td>
<td>91.5 (87.0, 95.9)</td>
<td>2.4 (−4.0, 8.8)</td>
<td>−10</td>
</tr>
<tr>
<td>Community-acquired pneumonia (comparator: ceftriaxone)</td>
<td>17,18</td>
<td>C</td>
<td>C</td>
<td>364</td>
<td>91.9 (89.2, 94.7)</td>
<td>294</td>
<td>92.0 (88.9, 95.1)</td>
<td>0.0 (−4.5, 4.4)</td>
<td>−10</td>
</tr>
<tr>
<td>Complicated urinary tract infection (comparator: ceftriaxone)</td>
<td>20,21</td>
<td>M</td>
<td>M</td>
<td>256</td>
<td>89.4 (85.6, 93.2)</td>
<td>224</td>
<td>91.1 (87.4, 94.9)</td>
<td>−1.7 (−7.4, 4.0)</td>
<td>−10</td>
</tr>
</tbody>
</table>

Proportion of patients (estimated using a statistical model adjusting for strata) with favourable response assessments at the test-of-cure visit. For the community-acquired pneumonia and complicated urinary tract infection indications, the combined results from two studies for each indication are presented. N = number of evaluable patients in each treatment group; CI = confidence interval; M = microbiological; C = clinical.

*aComputed from a statistical model adjusting for strata.
eraly once a day in the treatment of these infections, regardless of the baseline severity of infection.

Adverse reactions

The safety profile of ertapenem was evaluated in 1954 patients who received at least one 1 g dose.\textsuperscript{22} The safety profile of ertapenem was generally similar overall to that of each of the two comparator agents, ceftriaxone and piperacillin/tazobactam. The most common adverse reactions reported with ertapenem were diarrhea, infused vein complication, nausea, headache, vaginitis in females, phebitis/thrombophlebitis, vomiting and elevated aminotransferase levels. The incidence of each of these adverse reactions was similar in the ertapenem-treated patients and those that received the comparator agents. Seizures were reported infrequently during parenteral study therapy in all treatment groups (0.2% of patients treated with ertapenem, 0.3% with piperacillin/tazobactam and 0% with ceftriaxone).

What is the role for ertapenem?

As one would anticipate with a carbapenem, ertapenem has potent \textit{in vitro} activity against a broad spectrum of bacterial pathogens including Gram-negative enterics producing ESBLs and/or AmpC-type \(\beta\)-lactamases. In rigorously designed and performed clinical studies, ertapenem has demonstrated clinical and microbiological efficacy as empiric therapy in seriously ill patients. Furthermore, ertapenem has been shown to be effective as antimicrobial monotherapy in the setting of complicated mixed aerobic/anaerobic polymicrobial infections such as intra-abdominal, skin and acute pelvic infections.

Ertapenem, however, should not just be categorized as another carbapenem. Two key attributes differentiate it from imipenem and meropenem: (1) ertapenem’s limited \textit{in vitro} activity against \textit{P. aeruginosa} and \textit{Acinetobacter} species dictate that ertapenem’s spectrum of antimicrobial activity is more suitable for the empiric treatment of serious infections acquired in the community than in those acquired nosocomially; and (2) ertapenem can be administered once a day. Based on these differentiating attributes, ertapenem is complementary to the other currently licensed carbapenems. For the management of serious infections acquired in the community, including those likely to be caused by a mix of aerobic and anaerobic pathogens and those in pretreated patients, ertapenem provides the convenience of monotherapy administered once a day. It seems intuitive that by simplifying treatment, ertapenem will help to minimize nursing/administration and pharmacy preparation costs, might diminish pharmacy- or infusion-related errors or morbidity, and might reduce overall patient care costs by enabling earlier discharge from hospital by facilitating follow-up outpatient parenteral therapy. Furthermore, if the incidence of Gram-negative enterics producing ESBLs and/or AmpC-type \(\beta\)-lactamases continues to increase in the community then ertapenem will become, by necessity, a preferred agent.

Restriction of ertapenem usage to patient groups traditionally treated with carbapenems owing to concerns about reserving the most broad spectrum agents as ‘drugs of last resort’ does not seem warranted. Limitation of ertapenem usage in this manner would preclude the use of this agent in the group of patients most likely to receive benefit. In the 21st century, the introduction of any new antimicrobial is accompanied by concerns about resistance development. Although it is not possible at present to reach a definitive conclusion about the risk that ertapenem poses in this regard, the resistance risk associated with ertapenem should be low if it is used appropriately. In particular, ertapenem should not be used empirically for nosocomially acquired infections, for ventilator-acquired infections, or for infections acquired in medical intensive care units; ertapenem should be used for relatively short durations of therapy within the hospital followed by either stopping therapy, a change to an appropriate oral therapy, or continuation of ertapenem therapy as an outpatient.

A classification scheme for carbapenems

It is clear that carbapenems should no longer be thought of as a homogeneous class. It also seems probable that additional carbapenems will be developed that will further extend the class (e.g. carbapenems with activity against MRS\textsuperscript{23}). Just as the development of numerous cephalosporins/cephamycins prompted a classification scheme (i.e. the ‘generations’ of cephalosporins\textsuperscript{25}), the introduction of ertapenem leads us to propose that the carbapenems be classified into three groups: \textbf{Group 1} includes broad-spectrum carbapenems, with limited activity against non-fermentative Gram-negative bacilli, that are particularly suitable for community-acquired infections (e.g. ertapenem); \textbf{Group 2} includes broad-spectrum carbapenems, with activity against non-fermentative Gram-negative bacilli, that are particularly suitable for nosocomial infections (e.g. imipenem and meropenem); and \textbf{Group 3} includes carbapenems with clinical activity against MRS (none currently licensed). As with the ‘generations’ of cephalosporins, the higher groups in the proposed classification scheme reflect an increasing antimicrobial spectrum against resistant organisms (i.e. non-fermentative Gram-negative bacilli and MRS). Furthermore, this simple classification scheme could be easily modified at a later date to include an oral carbapenem by subdividing each group into a parenteral and an oral subcategory (e.g. subgroups ‘a’ and ‘b’).

Conclusions

Ertapenem, the first Group 1 carbapenem, provides a new, potent, convenient choice in the treatment of mixed aerobic/anaerobic polymicrobial infections. As with the introduction of any new antimicrobial, antimicrobial susceptibility patterns should be monitored over time. Based on the recommended pattern of use, the risk of resistance development should be low and should not preclude the use of this agent in the appropriate clinical setting.

References

leading article