Ertapenem: a Group 1 carbapenem with distinct antibacterial and pharmacological properties

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Ertapenem, a Group 1 carbapenem, is the most recent β-lactam antibiotic to enter clinical practice in the USA and Europe. While structurally a carbapenem, the overall molecular structure of ertapenem has been modified to focus its antibacterial spectrum on important community-acquired aerobic and anaerobic pathogens, and to increase its plasma half-life, permitting once-a-day dosing for this parenteral antibiotic. A number of chemical features are responsible for the unique properties of ertapenem. The inclusion of a trans-1-hydroxyethyl group in the structure of ertapenem enables the drug to maintain antibacterial efficacy against the vast majority of β-lactamase-producing organisms. A critical 1β-methyl substituent shields the β-lactam carbonyl group and serves to reduce dehydropeptidase (DHP)-1 catalysed hydrolysis of the β-lactam, enabling ertapenem to be administered without a DHP-1 inhibitor. A meta-substituted benzoic acid substituent increases the molecular weight and lipophilicity of the molecule, and the carboxylic acid moiety, ionized at physiological pH, results in ertapenem having a net negative charge. As a result, ertapenem is highly protein bound and has an extended half-life, permitting a once-a-day treatment regimen.

Keywords: pharmacology, β-lactams, antimicrobial agents, molecular structure, once-daily dosing

Introduction

The initial clinical use of penicillin in 1942 constituted a volley in a continuing battle between man and microbes. For the ensuing 60 years chemists have tailored the properties of β-lactam antibiotics to battle the inevitable rise of antibacterial resistance and to optimize the pharmacological properties and antibacterial spectrum of new agents. Ertapenem (formerly MK-0826; Merck & Co. Inc.) is the most recent β-lactam antibiotic to enter clinical practice in the USA and Europe. While structurally a carbapenem, ertapenem represents a departure from earlier members of this class in that the overall molecular structure has been modified to focus its antibacterial spectrum on important community-acquired aerobic and anaerobic pathogens, and to increase its plasma half-life, permitting a once-a-day dosing regimen for this parenteral antibiotic (Figure 1). This article will discuss some of the chemical features of ertapenem that are responsible for its unique properties.

The mechanism of action of ertapenem

At their most simple level all β-lactam antibiotics exert their antibacterial action by chemically acylating an active-site serine residue on a target bacterial penicillin-binding protein (PBP). The resulting covalently modified enzyme is stable and therefore unable to complete its biological function, in this case the transpeptidation of peptidoglycan to form a structurally stable bacterial cell wall. Ertapenem, for example, has excellent affinity for a number of the essential PBPs in Escherichia coli, in particular PBP2 (IC₅₀ 0.01 mg/L) and PBP3 (IC₅₀ 0.04 mg/L), consistent with its excellent in vitro activity against this organism (IC₅₀ is the concentration of test drug necessary to inhibit by 50% the labelling of [³H]penicillin to requisite PBP in an E. coli membrane preparation). With regard to PBP2, ertapenem has similar potency to imipenem and is 60-fold more potent than ceftriaxone; with regard to PBP3, ertapenem is similar in potency to ceftriaxone and is 60-fold more potent than imipenem. It should be noted that ertapenem, like all marketed β-lactams, has little affinity for Staphylococcus aureus PBP2a, the expression of which mediates methicillin resistance in staphylococci.

The trans-1-hydroxyethyl substituent

β-Lactamases, which contain an active-site serine residue, use the intrinsic chemical reactivity of β-lactams to inactivate the antibiotic. As with PBPs, the active-site serine of the β-lactamase is acylated, but the resulting covalently modified protein is not stable, and is instead hydrolysed to regenerate the unmodified β-lactamase and the hydrolysed, inactivated, β-lactam. Ertapenem, like other clinically useful carbapenems, has the ability to maintain antibacterial efficacy against the vast majority of β-lactamase-producing organisms. The stability of carbapenems toward β-lactamases is due primarily to the trans-1-hydroxyethyl substituent and its unique juxtaposition to the β-lactam carbonyl group (Figure 1). Unlike the penicillins and cephalosporins, which have cis substituents at the corresponding position, the trans-1-hydroxyethyl substituent in carbapenems extends below the
The 1β-methyl substituent

Naturally occurring carbapenems, such as thienamycin, and early analogues, including imipenem, are readily hydrolysed by a renal dehydropeptidase (DHP-I) resulting in inactivation of the carbapenem. For imipenem, this issue was solved by the development of a specific inhibitor, cilastatin, which results in greater urinary recovery of imipenem than would otherwise be possible. Ertapenem, like most other carbapenems developed subsequently, contains a critical 1β-methyl substituent (Figure 1), which shields the β-lactam carbonyl group and serves to reduce DHP-I-catalysed hydrolysis of the β-lactam. Thus, ertapenem does not require co-administration with a DHP-I inhibitor.

The meta-substituted benzoic acid substituent

Although ertapenem retains many of the beneficial features of previous carbapenems it differs from other members of the class by the inclusion of the meta-substituted benzoic acid substituent (Figure 1). This substituent plays a critical role in sculpting the pharmacological and antibacterial properties of ertapenem. The aromatic ring increases the overall molecular weight (the molecular weight of ertapenem is 497 daltons) and lipophilicity of the molecule, and the carboxylic acid moiety, ionized at physiological pH, results in ertapenem having a net negative charge. From a pharmacological perspective this results in a compound that is more highly plasma-protein bound than has been the case for previous carbapenems. For example, ertapenem is ~95% plasma-protein bound, whereas imipenem is ~20%. This increased protein binding relative to imipenem decreases the free or unbound fraction and leads to an extended plasma half-life, permitting a once-a-day treatment regimen similar to that used with the long-acting cephalosporins and in contrast to previous carbapenems.

Inclusion of the meta-substituted benzoic acid substituent in the structure of ertapenem also serves to focus its antibacterial spectrum. In Gram-negative bacteria, the antibacterial activity of a β-lactam is controlled by the affinity of the antibiotic for its target PBPs and the ability of the antibiotic to achieve a sufficient concentration in the periplasmic space. Drug concentration in the periplasm is, in turn, determined by the ability of the antibiotic to gain entry across the outer membrane, mediated by specific porins, and to remain active within the periplasmic space by avoiding degradation by periplasmic β-lactamases or transport by efflux pumps. In *Pseudomonas aeruginosa* it is known that both imipenem and meropenem utilize the OprD porin, a porin specific for the uptake of cationic amino acids. Although little is known about the specific porins utilized by ertapenem, a reasonable speculation is that the anionic character of ertapenem, combined with its greater molecular weight and lipophilicity, results in decreased affinity for the OprD porin, reducing its ability to reach effective levels in the periplasmic space. Alternatively, ertapenem may be a substrate for efflux pumps in *P. aeruginosa*. In any

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Figure 1. The chemical structure of ertapenem sodium.
Ertapenem: a Group 1 carbapenem

case, ertapenem is substantially less active against *P. aeruginosa* and other non-fermentative Gram-negative bacilli than are other carbapenems and is not indicated for use against these organisms. Limited coverage against nosocomial pathogens such as *P. aeruginosa* and *Acinetobacter* spp., coupled with excellent activity against community-acquired aerobes and anaerobes, makes ertapenem suitable for empirical use in community-acquired and mixed aerobic–anaerobic infections.

**Conclusion**

In conclusion, ertapenem represents an evolution in the carbapenem class. Shah & Isaacs\(^{10}\) recently proposed a new classification scheme for the carbapenem class, based on its microbiological spectrum. In this classification system, ertapenem is to be regarded as the first of the Group 1 carbapenems. Group 1 carbapenems are broad-spectrum carbapenems, with limited activity against non-fermentative Gram-negative bacilli. Group 1 carbapenems are particularly suitable for community-acquired infections and are differentiated from Group 2 carbapenems (e.g. imipenem and meropenem), which possess potent activity against Gram-negative non-fermentative bacilli and are particularly suitable for nosocomial infections. Ertapenem, as a single agent, offers excellent *in vitro* antibacterial activity against many aerobic and anaerobic pathogens generally associated with community-acquired and mixed aerobic–anaerobic infections with the convenience of a once-a-day dosing regimen.\(^{11}\)

**Transparency declaration**

M.L.H. is an employee of Merck & Co., Inc., and potentially owns stock and/or holds stock options in the Company.

**References**
