Pharmacokinetics and pharmacodynamics of ertapenem: an overview for clinicians

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Ertapenem, a Group 1 carbapenem, is a once-a-day parenteral β-lactam antibiotic recently licensed in the USA and Europe. Monotherapy with ertapenem dosed as 1 g once a day has been shown to be highly effective in clinical trials for the treatment of complicated infections of skin and skin structures, complicated intra-abdominal infections, community-acquired pneumonia, acute pelvic infections and complicated urinary tract infections. Dosing modifications have not been recommended for adults on the basis of gender, age, weight or liver disease. Presently there are no data regarding the use of ertapenem in children. Dose reductions are indicated for patients with advanced renal insufficiency. Ertapenem is neither a substrate nor an inhibitor of P-glycoprotein or cytochrome P450 enzymes; significant drug interactions between ertapenem and drugs handled by these systems are not expected.

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Introduction

Ertapenem (formerly MK-0826; Merck & Co., Inc) is a once-a-day parenteral β-lactam antibiotic recently licensed in the USA in November 2001 and in Europe in April 2002.¹⁻² This Group 1 carbapenem¹ is active at readily achievable concentrations against most Gram-positive and Gram-negative aerobic and anaerobic bacteria commonly recovered from community-acquired infections.³⁻¹² Ertapenem is not indicated for patients infected with Pseudomonas aeruginosa, Acinetobacter species, methicillin-resistant staphylococci or enterococci. Susceptible organisms are inhibited in vitro by concentrations of ≤4 mg/L. The standard dose of 1 g of ertapenem once a day has been highly effective monotherapy for acute pelvic infections, complicated intra-abdominal, skin and urinary tract infections, and typical community-acquired pneumonia requiring hospitalization in clinical trials.⁷,¹³,¹⁴

This brief review describes the disposition of ertapenem in healthy volunteers and certain special populations.¹⁵⁻¹⁷ In total, nine clinical pharmacokinetic studies of parenteral ertapenem are summarized here. Since ertapenem is a highly protein-bound drug, both total and unbound drug levels were measured in four of these studies. The relative value of total versus unbound drug concentrations in predicting efficacy and toxicity is still debated.¹⁵,¹⁶,¹⁸⁻²⁰ Fortunately, adequate clinical data are available to establish the clinical utility of ertapenem at 1 g once a day as therapy for a wide range of community-acquired bacterial pathogens.¹³,¹⁴ Plasma concentrations of total drug were principally used to assess differences across populations as well as to judge the need for and magnitude of any dosage adjustment in the presence of organ insufficiency. Pharmacodynamic properties of ertapenem are also discussed briefly.

Plasma concentrations

The pharmacokinetics of single doses of intravenous ertapenem were investigated in two studies over a wide range of doses. All stock solutions for ertapenem were prepared in 0.1 M 2-(4-morpholino)ethyl sulphonate (MES) buffer, pH 6.5, in which the drug is >95% stable at room temperature or 5°C for at least 23 h. The initial protocol [n = 66 subjects; 88% male; median (range) age, 30 (18–45) years] examined the AUC for escalating single doses ranging from 0.04 to 3 g. In a follow-up study [n = 16 subjects; 50% male; median (range) age, 32 (25–45) years], the dose proportionality of ertapenem was systematically assessed between 0.5 and 3 g using a randomized crossover design. Maximum plasma concentrations of total ertapenem immediately after a 1 g dose infused intravenously over 30 min averaged ~150 mg/L. Both studies demonstrated that the plasma concentrations of total and unbound ertapenem were nearly proportional to the administered dose. Because of saturable plasma protein binding (see section ‘Protein binding’), the unbound fraction increased disproportionately with doses of >2 g; this non-linearity was noted when total drug concentrations were >150 mg/L (315 μM). The pharmacokinetics of multiple intravenous doses of ertapenem were then extensively studied. With once-daily administration, no drug accumulation was observed. Following 8 days of dosing at 0.25–3 g daily, the AUC on day 8 was comparable to the AUC on the first day of therapy.

Ertapenem is almost completely absorbed following intramuscular administration.²¹ The bioavailability of a 1 g intramuscular dose approximated 92% in 26 healthy subjects [77% male; median (range) age, 29 (22–41) years]. Plasma concentrations of total ertapenem were similar whether given intramuscularly or intravenously.
Metabolism and elimination

The plasma concentration profile of ertapenem after the recommended 1 g dose was further characterized in three additional studies. Almost 40% of the dose was excreted in the urine as intact drug. These data were then confirmed and extended in a mass-balance study [n = 7 subjects; 57% male; median (range) age, 28 (23–49) years] following intravenous administration of [14C]ertapenem. The terminal half-life was 4 h. Nearly 40% of the radioactive dose was excreted as intact drug in the urine, and a roughly equivalent amount of radioactivity was recovered in the urine as the β-lactam open-ring metabolite. Excretion of radioactivity in the faeces was ~10% of the administered dose.

The mean renal clearance of intact ertapenem was 12.8 mL/min compared with a total clearance of 28.4 mL/min. Since ~80% of an ertapenem dose is recovered in the urine, based on the [14C]ertapenem mass-balance study, the kidneys appear to be responsible for 80% of the total clearance of the drug (~22.7 mL/min). The lower renal clearance of intact ertapenem results from its renal metabolism to an open-ring metabolite. The proportion of metabolism occurring in the tubules versus the bladder has not been determined. The mean renal clearance of unbound ertapenem was 207 mL/min, indicating that ertapenem undergoes glomerular filtration and net tubular secretion. The reduction in renal clearance of unbound ertapenem to 98 mL/min with concomitant probenecid administration confirms the contribution of tubular secretion to the renal elimination of ertapenem.

Hepatic metabolism plays only a minor role in the elimination of ertapenem. Ertapenem was metabolically stable following in vitro incubation with human hepatic microsomal fractions. The only major metabolite identified in vivo in human plasma and urine was the β-lactam open-ring metabolite. In humans, the enzyme dihydropeptidase I (DHP-I), which catalyses the formation of this metabolite, is found predominantly in the kidneys. The large contribution of the open-ring metabolite to the total radioactivity recovered in the urine following administration of [14C]ertapenem, in contrast to the very high fraction of plasma radioactivity associated with intact drug, suggests that hydrolysis of the ertapenem β-lactam ring occurs almost exclusively within the urinary tract. Ertapenem is much more slowly hydrolysed by DHP-I than imipenem.

In order to determine whether ertapenem metabolites might have any appreciable antimicrobial activity, plasma and urine concentrations of ertapenem following administration of a 1 g dose were analysed by both high-performance liquid chromatography (HPLC) (measuring intact ertapenem) and a bioassay (measuring antibacterial activity). Figure 1 shows that the plasma concentration profiles determined by both analytical methods were essentially superimposable, consistent with the absence of microbiologically active metabolites.

Gender and age considerations

The AUC of total ertapenem was similar in healthy adult men and women [n = 16 subjects; 50% male; median (range) age, 32 (25–45) years]. In women, ertapenem exhibited a slightly smaller volume of distribution and accompanying higher end-of-infusion concentration, and a modestly shorter half-life compared with men.23,24 The half-life of ertapenem in women averaged 3.6 h compared with 4.4 h in men. These data, in the aggregate, indicate the absence of clinically meaningful differences in the pharmacokinetics of ertapenem between men and women.

Plasma concentrations were somewhat higher in older [n = 15 subjects; 53% male; median (range) age, 73 (66–82) years] than in young adults (39% higher AUC following a single 1 g dose). This difference was largely attributable to the age-related decline in renal function and was not considered to be of sufficient magnitude to warrant recommending a dose adjustment in elderly patients. As in young adults, elderly men and women exhibited similar AUC values for total drug. A slightly shorter half-life and a higher end-of-infusion plasma concentration were again seen in elderly women relative to elderly men, but these small differences are unlikely to be clinically meaningful. Accordingly, dosage adjustments in adults for either age or gender have not been recommended.

Ertapenem has not been approved for use in patients under 18 years of age. There are insufficient data in paediatric subjects to date to provide dosing recommendations for children.

Protein binding

Ertapenem exhibits concentration-dependent protein binding, ranging from 96% at total concentrations of 10 mg/L to 84% at concentrations of 300 mg/L. In healthy adult volunteers given a single 1 g dose of ertapenem intravenously over 0.5 h, the mean plasma concentration of total ertapenem peaked at ~150 mg/L at the end of the infusion and then exponentially declined to 10 mg/L at 12 h, 4 mg/L at 17 h and 1–2 mg/L at 24 h. The corresponding concentration of free ertapenem was 15 mg/L at the end of the infusion, declining to 1.7 mg/L at 6 h, 1.1 mg/L at 8 h and 0.5 mg/L at 12 h after the infusion. A slightly
The efficacy of β-lactam drugs appears to be determined primarily by the time bacteria are exposed to concentrations exceeding the MIC. 

Penetration of eratapenem into suction-induced skin blisters following multiple intravenous doses in adult subjects \(n = 13\) subjects; 77% male; median (range) age, 25 (19–45) years was studied as a model for drug penetration into interstitial fluid. 

Following a 1 g dose of eratapenem, a mean maximum concentration of 24.4 mg/L was achieved after about 8 h. The mean concentration was 7.8 mg/L 24 h after a single dose, which exceeds the MIC\(_{90}\) for susceptible bacteria.
The AUC$_{0-24}$ was 422 mg·h/L in blister fluid and 694 mg·h/L in plasma, equating to a penetration ratio of >60%.

Ertapenem can be detected in human breast milk for up to 5 days following discontinuation of treatment. There are presently insufficient data to quantify how much ertapenem crosses the placenta or enters cerebrospinal fluid or other protected sites.

### Special populations

A study involving patients with varying degrees of renal failure was performed because of the important role of the kidney in the disposition of ertapenem. Pharmacokinetic parameters derived from pooled data in healthy young adults and elderly subjects were used for comparison. The mean age of the pooled control group was similar to that of the patients with renal insufficiency [n = 26 subjects; 46% male; median (range) age, 58 (31–45) years]. Total clearance of ertapenem decreased with declining creatinine clearance in a roughly linear fashion. The corresponding increase in AUC of total drug was negligible in patients with mild renal insufficiency and modestly increased (~1.5-fold) in patients with moderate impairment (creatinine clearance 30–60 mL/min/1.73 m$^2$); consequently no dosage adjustment has been suggested for such patients. Patients with advanced (10–30 mL/min/1.73 m$^2$) and end-stage (<10 mL/min/1.73 m$^2$) renal failure had a 2-fold higher AUC than healthy controls. The effects of renal insufficiency on the AUC of unbound drug were modestly larger than the effects on total drug levels.

The recommended ertapenem dosage is 0.5 g once a day for patients with an estimated normalized creatinine clearance of <30 mL/min. Although extending the interval rather than reducing the dose has not been studied, the existing pharmacokinetic and pharmacodynamic data suggest that 1 g of ertapenem given every 48 h might be a convenient and appropriate adjustment for some patients with end-stage renal disease. A 4 h haemodialysis immediately after a 1 g intravenous dose removes almost one-third of the ertapenem administered. This observation prompted a recommendation that a supplemental dose of 150 mg be given immediately after haemodialysis when the patient has received the recommended daily dose of 0.5 g <6 h before the start of a 3–4 h haemodialysis session. An additional dose has not been recommended when haemodialysis follows the scheduled dose by more than 6 h. If the regular ertapenem dose could be timed to follow the haemodialysis procedure, the need for supplemental dosing would be eliminated. Formal dosing recommendations are not available for haemofiltration or peritoneal dialysis.

No pharmacokinetic studies have been conducted in subjects with impaired liver function, although liver impairment per se is not expected to alter the pharmacokinetics of ertapenem. Since the liver does not contribute to ertapenem clearance, only physiological changes accompanying liver disease (e.g. oedema and hypoalbuminaemia) would impact on ertapenem pharmacokinetics in patients with hepatic failure. Patients with severe liver impairment often have concomitant renal impairment, and renal function needs to be carefully monitored in this population.

Obesity is a common clinical problem for which specific dose recommendations are not available for ertapenem or any other β-lactam drug. 35,36 Without considering alterations in body composition, the volume of distribution should in theory simply be proportional to weight. However, obesity results in altered body composition with an increased proportion of adipose tissue. β-lactam drugs do not distribute extensively into fat. The volume of distribution in obese patients would be expected to follow the relationship:

\[ V = \text{constant} \times (\text{actual body weight} + F \times (\text{actual body weight} – \text{lean body weight})) \]

where \( F \) is the relative distribution into fat compared with lean tissue.

The value of \( F \) for small polar molecules such as ertapenem is typically between 0.3 and 0.4. A modest increase in glomerular filtration rate may occur in the obese patient, but ertapenem is a relatively ‘low-clearance’ drug; hence, small changes in renal perfusion should not significantly increase ertapenem clearance. The composite effects of obesity on ertapenem pharmacokinetics probably do not warrant dose modification in most cases.

### Drug interactions

**In vitro** studies of ertapenem were performed to assess the potential for drug interactions via the inhibition of cytochrome P (CYP) 450 isozymes or P-glycoprotein (P-gp). 37,38 Concentrations of ertapenem as high as 500 µM (240 mg/L) did not inhibit the microsomal metabolism of probe substrates for the major human CYP450 isozymes 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4. Additionally, 37,38[14C]ertapenem was found to be metabolically stable when incubated with human hepatic microsomes, suggesting that ertapenem was not a substrate of CYP450 isozymes. At concentrations up to 500 µM, ertapenem did not affect the vectorial transport of P-gp marker substrates in P-gp overexpressing L-MDR1 or KB-V1 cells. Moreover, in vitro studies using P-gp overexpressing cell lines (L-MDR1 and KB-V1) and plasma vesicles prepared from KB-V1 cells indicated that ertapenem was not a substrate for P-gp transport. Based on these results, the potential for drug interactions resulting from the inhibition of CYP450 metabolism or P-gp transport by ertapenem appears to be small.

The only clinical drug interaction study conducted to date was an assessment of the effect of probenecid on the renal clearance and plasma pharmacokinetics of ertapenem. The objective of this study was to estimate the contribution of tubular secretion to the renal clearance of ertapenem. Because renal clearance of unbound ertapenem exceeded the glomerular filtration rate, it was hypothesized that some of the renal clearance of ertapenem, as with many other β-lactam drugs, resulted from tubular secretion, a process that can largely be inhibited by probenecid. Administration of ertapenem with probenecid decreased the renal clearance of unbound ertapenem by ~50%, consistent with the inhibition of renal tubular secretion of ertapenem by probenecid. Probenecid also slightly increased the elimination half-life and AUC of total ertapenem. Because probenecid had an inconsequential effect on ertapenem half-life, co-administration of probenecid cannot be effectively used to extend the half-life of ertapenem.

### Pharmacodynamics

Similar to other β-lactams, the pharmacodynamic parameter best correlated with clinical efficacy for carbapenem antibiotics is the fraction of the dosing interval when the drug concentration exceeds the MIC (Figure 4). 12,15,30 The time above the MIC required for bacteriostasis in vivo appears to be somewhat shorter for carbapenems (30% of the dosing interval) than for cephalosporins (50% of the dosing interval). 30,31,39 In a murine model of soft-tissue infection, the time above the MIC required for a bacteriostatic effect with ertapenem ranged from 24% to 43% of the dosing interval for total drug concentration and from 6% to 25% of the dosing interval for unbound drug concentration.
In several clinical trials, ertapenem 1 g once a day was highly efficacious therapy as a single agent against most Enterobacteriaceae, group A and B streptococci, methicillin-susceptible Staphylococcus aureus, penicillin-susceptible Streptococcus pneumoniae, β-lactamase-negative Haemophilus influenzae, Moraxella catarrhalis, and most anaerobes, including the Bacteroides fragilis group. The MIC₉₀ of ertapenem for all the above-mentioned pathogens in these studies was ≤ 1 mg/L.⁹,¹⁰,¹³,¹⁴ Based on estimates derived from pharmacokinetic analyses, plasma concentrations of total ertapenem would have been expected to exceed the MIC₉₀ for susceptible bacteria for essentially the entire recommended 24 h dosing interval; similarly, plasma concentrations of free drug should have stayed above the MIC₉₀ for at least 25% of the dosing interval.

Summary and conclusions

Ertapenem is a once-a-day parenteral Group 1 carbapenem.³ Plasma concentrations of total drug with a daily dose of 1 g exceed the MIC₉₀ for susceptible bacteria throughout most of the dosing interval; free drug concentrations remain above the MIC₉₀ for ~6 h. More importantly, ertapenem 1 g once daily appears to be effective monotherapy for many patients with moderate-to-severe acute pelvic infections, complicated intra-abdominal infections, complicated urinary tract infections, typical community-acquired pneumonia and complicated infections of skin and skin structures caused by susceptible bacteria. Dosing adjustments are not recommended for adults on the basis of gender, age, weight or liver disease. Dose reductions are indicated for patients with advanced renal insufficiency and end-stage renal disease. Ertapenem is neither a substrate nor an inhibitor of P-gp or CYP450 enzymes in vitro; clinically significant drug interactions between ertapenem and drugs transported or metabolized by these systems are not likely.

Transparency declarations

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References


