Kathmandu University Medical Journal (2009), Vol. 7, No. 4, Issue 28, 454-460

Review Article

Ertapenem

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Abstract

Ertapenem is a parenteral carbapenem licensed for use in adults and children more than 3 months of age. It is active against many Gram-positive and negative bacteria, including several anaerobic organisms but has a narrower spectrum of antimicrobial activity, compared with older carbapenems. It is highly stable against nearly all β-lactamases, including AmpC and extended spectrum beta lactamases. Ertapenem can be given intramuscularly or intravenously and its favourable pharmacokinetic profile allows once daily dosing. Ertapenem has been proven to be clinically and bacteriologically efficacious in randomised controlled trials for the treatment of community acquired infections including complicated intra-abdominal infections, complicated skin and skin-structure infections, acute pelvic infections, complicated urinary tract infections, community-acquired pneumonia and for the prophylaxis of surgical-site infection following elective colorectal surgery. Ertapenem is suited for mild to moderately ill patients with community-acquired infections and for outpatient intravenous antibacterial therapy.

Key words: Antibiotics, Carbapenems, Ertapenem

Carbapenems are a potent class of antibiotics with a broad anti-bacterial spectrum. Recently, carbepenems have been classified into three groups. Group 1 includes agents having limited activity against non-fermentive gram-negative bacilli and more suited for community use such as ertapenam, group 2 agents have good activity against non-fermentive gram-negative bacilli and more suited for nosocomial infections such as meropenem/imepenem and group 3 having additional activity against methicillin resistant staphylococci[1].

Ertapenam is a parenteral, 1 β-methyl carbapenem licensed for use in adults since 2001 and later for children more than 3 months of age since 2005. This review briefly highlights the clinical pharmacology, indications, therapeutic efficacy and adverse effects of ertapenam and compares it to other carbepenems.

Pharmacodynamics

Mechanism of Action

Ertapenem inhibits cell wall synthesis by binding to specific penicillin binding proteins (PBPs). It is highly stable against most β-lactamases including AmpC β-lactamases and extended-spectrum β-lactamases with the exception of metallo-β-lactamases. Resistance to carbapenems develops when bacteria acquire or develop structural changes within their PBPs, acquire metallo-β-lactamases capable of rapidly degrading carbapenems, or develop changes in membrane permeability as a result of loss of specific outer membrane porins.

Anti-bacterial spectrum

Ertapenem has a broad-spectrum of antibacterial action against many gram-positive and gram-negative bacteria, including several anaerobic organisms. Ertapenem is active against most isolates of the following microorganisms *in vitro* and in clinical infections. It is rapidly bactericidal and also shows significant post antibiotic effect against Gram-positive bacteria.

Gram-positive bacteria: *S. aureus* (methicillin susceptible isolates only), coagulase-negative staphylococci, *Streptococcus agalactiae, S. pneumoniae* (penicillin susceptible isolates only), *S. pyogenes* and *Enterococcus* spp[2].

Gram-negative bacteria: clinically relevant enterobacteriace, including *E. coli, H. influenzae* (Beta-lactamase negative isolates only), *Klebsiella* spp., *Moraxella catarrhalis, Proteus mirabilis, Citrobacter* spp., and *Serratia* spp[2].

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Anaerobic bacteria: *B. fragilis, B. distasonis, B. ovatus, B. thetaiotaomicron, B. uniformis, C. clostridioforme, E. lentum, Peptostreptococcus* species, *Porphyromonas spp. and Prevotella spp.*[2].

Ertapenem lacks sufficient activity against *Pseudomonas aeruginosa*, enterococci, Methicillin-resistant *S. aureus* (MRSA), *Acinetobacter* spp., *Stenotrophomonas maltophilia*, *Burkholderia cepacia* and *Aeromonas* spp. It is not indicated for use against atypical bacteria, such as *Legionella* spp., *Mycoplasma* spp. and *Chlamydia* spp[2,3,4,5]. Table 1 shows the comparison of available carbapenems.

Table 1: Comparison of carbapenem antibiotics

	Ertapenem	**Imipenem/Cilastatin**	**Meropenem**
Class	**I**	**II**	**II**
Differences in anti-bacterial spectrum	Ertapenem lacks activity against *Pseudomonas aeruginosa*, enterococci, *Acinetobacter* spp., *Burkholderia cepacia* and *Aeromonas* spp. Meropenem and Imepenem are sensitive. Ertapenem is less active against gram positives, particularly penicillin-resistant pneumococci. In vitro studies indicate that Ertapenem may be more active than imipenem and equal to meropenem against Enterobacteriaceae. None are effective against Methicillin-resistant *S. aureus, Enterococcus fecium* and *Stenotrophomonas maltophilia*		
Metabolism and excretion	Liver by hydrolysis and N-acetylation; half-life, 4 hours; protein binding, 85-95%	Liver by hydrolysis and N-acetylation; half-life, 1 hour; protein binding, 20 %	Liver by hydrolysis and N-acetylation; half-life, 1 hour; protein binding, ~2 %
CSF Penetration	Not recommended for meningitis because of lack of sufficient CSF penetration	Low concentration in CSF. Not recommended for meningitis.	CSF concentrations good. The only carbapenem recommended for meningitis
Adult Dose	1 gm IV or IM q 24h	250 mg- 1 g IV q 6h maximum dose of 4g/day or 50 mg/kg/day whichever is less	500 mg-1g IV q 8h for mild to moderate infections, 2g IV q 8h for meningitis or severe infections
Pediatric age recommendation	3 m to 17 y	Neonates to 16 y. Not recommended with CNS infections because of seizure risk.	3 m to 17 y
Pediatric Dose	3 m-12 y: 15 mg/kg twice daily, maximum 1 gm/day; ≥ 13 y is 1 g once a day	0-4 weeks & < 1.2 kg: 50 mg/kg/day q 12h; < 1 week & > 1.2 kg: 50 mg/kg/day q 12h; > 1 week & > 1.2 kg: 75 mg/kg/dose q 8h; 4 weeks- 3 m: 100 mg/kg/day q 6h; > 3 m: 60-100 mg/kg/day q 6h	20-30 mg/kg/dose q 8h; 40 mg/kg/dose for meningitis
Dose reduction in renal failure	If CrCl is < 30 ml/min reduce dose to 500 mg OD	If CrCl < 50 ml/min: 500 mg q 6h; CrCl 10– 50 ml/min: 250- 500 mg IV q 8h; CrCl <10 ml/min: 250 mg IV q 12h	CrCl 50 – 25 ml/min: 1g IV BD; CrCl 10– 25 ml/min: 500 mg IV BD; CrCl <10 ml/min: 500 mg IV OD
Pregnancy/ Lactation	Category B; Enters breast milk/use caution	Category C; Enters breast milk/ use caution	Category B; Excretion in breast milk unknown
Common adverse effects	Most common: N/V/D (2-5%), phlebitis, headache (5.8%), Others: platelet count increased, altered mental status, chest pain, edema, LFT elevations, seizure (0.5%)	Most common: N/V/D (2%), phlebitis (3%). Others: Confusion, drug fever, pancytopenia, psychic disturbances, acute renal failure, seizure (0.4-3%).	Most common: N/V/D (5-8%), headache, phlebitis. Others: LFT elevations, neutropenia, angioedema thrombocytopenia, seizures (0.7%),
Indications	For moderate infections: cSSSIs, cIAIs, cUTI, aPI, CAP, prophylaxis of colorectal surgery	For moderate to severe nosocomial infections: cIAI, cSSSI, septicemias, nosocomial pneumonias, cUTI, endocarditis	Similar to imepenem but can also be used for meningitis

CrCl creatinine clearance; N/V/D= Nausea/vomiting/diarrhea; cIAIs=intra-abdominal infections, cSSSIs=complicated skin and skin-structure infections, aPI=acute pelvic infections, cUTIs =complicated urinary tract infections; CAP=community-acquired pneumonia

Table 2: Clinical efficacy studies on ertapenam

Author /Year	Study Design	Study Population	Pathogens isolated	Results
Tomera et *al* 2002 (7)	P, RCT, DB, M	ERT vs. ceftriaxone in 596 adults with cUTI	*E. coli, K.pneumoniae.*	91.8% of ERT & 93.0% of ceftriaxone group had favorable response*
Jimenez-Cruz *et al* 2002 (8)	P, RCT, DB, M	ERT vs. ceftriaxone in 258 adults with cUTI	*E. coli*	85.6% of ERT & 84.9% of ceftriaxone group had favorable response*
Vetter *et al* 2002; **Ortiz-Ruiz *et al*** 2002 (9-11)	P, RCT, DB, M	ERT vs. ceftriaxone in 866 hospitalized adult patients with CAP	*S.pneumoniae*	91.9% for ERT & 92.0% of ceftriaxone group had favorable response*
Graham *et al* 2002 (12)	P, RCT, DB, M	ERT vs. PT in 540 adults with cSSSI	*S. aureus*	82.4 % of ERT & 84.4% of PT group cured*
Solomkin *et al* 2003 (13)	P, RCT, DB, M	ERT vs. PT in 633 adult patients with cIAI.	*E. coli*, *Bacteroides fragilis*, *Bacteroides* spp., *Clostridium* spp.	86.7 % of ERT % 81.2% of PT group cured.* Higher efficacy for Ertapenem in nonappendiceal infections, generalized peritonitis, postoperative infection
De La Pena *et al* *2006* (14)	P, RCT, M	ERT vs. PT in 233 adults with cIAI	*E. coli*, *B. fragilis*	90% of ERT & 94% of PT group cured*
Yellin *et al* 2002 (15)	P, RCT, M	ERT vs. ceftriaxone plus metronidazole in 165 adults in cIAI	*E. coli, B. fragilis*	84% of ERT & 85% of comparator group cured*
Roy *et al* 2003 (16)	P, RCT, DB, M	ERT vs. PT in 412 adults with aPI	*E. coli*	93.9% of ERT & 91.9% of comparator group cured*
Lipsky *et al* 2005 (17)	P, RCT, DB, M	ERT vs. PT in 586 adults with cSSSI	S.aureus, *B. fragilis*	75% of ERT & 70.8% of comparator group cured*
Itani *et al* 2008 (18)	P, RCT, DB, M	ERT vs. cefotetan in 1002 adults in Prophylaxis for Colorectal Surgery		Prophylactic success rates at 4 weeks post- treatment 70.5% for ERT & 57.2% for cefotetan.* Prophylaxis failure due to surgical-site infections occurred in 18.2% ERT & 31.0% cefotetan patients.
Yellin *et al* 2007 (22)	P, RCT, DB, M	ERT or TC in 105 children aged 2- 17 years with cIAI or API	*E.coli, B. fragilis*	Response rates were 91% for ERT& 83% for TC*
Arguedas *et al* 2005 (23)	P, RCT, DB, M	ERT or ceftriaxone in 404 children with cUTI, cSSSIs or CAP	*E.coli, S.pneumoniae, S.aureus, B. fragilis*	Clinical response rates in cSSSI were 95.5% (64 of 67) for ERT & 100% (26 of 26) for ceftriaxone.* In CAP, response rates were 96.1% (74 of 77) for ERT & 96.4% (27 of 28) for ceftriaxone.* In cUTI, microbiological response rates were 87% (40 of 46) for ERT& 90% (18 of 20) with ceftriaxone.*

P=Prospective; RCT=randomized controlled trial; DB=double-blind; M=multicenter; ERT=ertapenam; PT= piperacillin/tazobactam; TC=ticarcillin/clavulanate; cSSSI= complicated skin and skin-structure infections; cIAI= complicated intra-abdominal infections; CAP= community-acquired pneumonia; cUTI=urinary tract infections; API= acute pelvic infection * denotes equivalence of therapies

Prescribing Information

Indications and Usage

It is approved for the following infections: complicated intra-abdominal infections (cIAIs), complicated skin and skin-structure infections (cSSSIs), acute pelvic infections (aPI), complicated urinary tract infections (cUTIs) and community-acquired pneumonia (CAP) and for the prophylaxis of surgical-site infection following elective colorectal surgery in adult patients[2].

Dosage

The dose of ertapenam in patients more than_13 yrs is 1gm once a day (3 months-12 years: 15 mg/kg twice daily, maximum 1 gm/day) by intravenous (IV) or intramuscular (IM) route. The drug is available commercially as 1 g vial with dry white powder or as 1 gm single dose ADD-Vantage® vials. The lyophilized vials should be stored above 25°C (77°F). After reconstitution with normal saline or distilled water (dextrose containing diluents are not recommended), it should be infused in 50 mL of normal saline over 30 minutes within 6 hours of reconstitution (can be stored up to maximum of 24 hours under refrigeration). In paediatric patients the volume of the infusate should be reduced proportionately to a final concentration of 20 mg/mL or less. For IM administration the contents are reconstituted with 3.2 mL of 1.0% lidocaine (without epinephrine) and administered by deep IM injection into a large muscle mass (such as the gluteal muscles or lateral part of the thigh) (this reconstituted solution should not be administered IV). It can be used up to 14 days for IV infusion and up to 7 days for IM administration[2].

Contraindications

Known hypersensitivity to any component of this product or to other drugs in the same class or to beta-lactams is the only contraindication.

Drug interactions

Since it does not inhibit the liver CYP 450 isoforms, drug interactions caused by CYP 450-mediated drug clearance are unlikely.

Pharmacokinetics

The volume of distribution at steady state of ertapenam in adults is approximately 0.12 L/kg (0.2 L/kg in 3 m-12 y; 0.16 L/kg in 13-17 y). Ertapenem is almost completely absorbed following IM administration. The bioavailability is 90%. Following 1 g daily IM administration, mean peak plasma concentrations (C_{max}) are achieved in approximately 2.3 hours (T_{max}). It is extensively bound to albumin (85-95%). Tissue penetration is excellent with the exception of cerebrospinal fluid. It is primarily metabolized by the kidneys with minimal hepatic metabolism. The cytochrome P450 enzyme system is not involved. The mean plasma half-life is approximately 4 hours making it suitable for once-daily administration[6].

Clinical efficacy trials

Well-designed RCTs (7-23) including pediatric trials (22-23) have examined the efficacy and safety of Ertapenem in patients with cSSSI, cIAI, cUTIs (including pyelonephritis), CAP, aPI (including postpartum endomyometritis, septic abortion and post surgical gynecologic infection) and complicated foot infection in diabetic patients without osteomyelitis[7-21]. In addition, Ertapenem has been approved by the FDA for the prophylaxis of surgical-site infection following elective colorectal surgery in adult patients. The results of these published clinical studies are summarised in Table 2.

Efficacy of Ertapenem against special pathogens

Enterobacteriaceae

The efficacy of Ertapenem 1.0 g/day for the treatment of adults with serious infections caused by *Enterobacteriaceae* was compared with ceftriaxone 1.0 g/day (cUTI and CAP) or piperacillin/tazobactam, 3.375 g every 6 h (cIAI, cSSSI and aPI) [19]. The collective analysis included 1167 treated patients infected with Enterobacteriaceae from 7 randomized, double blind studies. *E. coli* was the most common pathogen, accounting for 65.3% of all *Enterobacteriaceae*. Among evaluable patients with deep tissue (cIAI, cSSSI and aPI) infections, the combined clinical cure rates were 84.8% (223 of 263) for Ertapenem and 82.9% (194 of 234) for Piperacillin/Tazobactam. It was concluded that Ertapenem therapy was as efficacious as either Piperacillin/Tazobactam or Ceftriaxone for serious infections caused by *Enterobacteriaceae*.

Mixed anaerobic infections

Tellado *et al.* studied Ertapenem 1.0 g/day vs. Piperacillin/Tazobactam 3.375 g every 6 h in the treatment of adults with anaerobic cIAI, cSSSI and aPI with [20]. This analysis included 623 patients, whose baseline cultures grew anaerobic pathogens, from three randomised, double blind clinical studies. The anaerobes most commonly isolated were *B. fragilis* and peptostreptococci. Cure rates for all evaluable patients with anaerobic infection were 89.3% (242 out of 271) for Ertapenem and 85.9% (220 out of 256) for Piperacillin/Tazobactam, indicating that the two treatments were equivalent.

Polymicrobial infections

The results of another subgroup analysis for comparison of Ertapenem efficacy with that of Piperacillin/Tazobactam for the treatment of polymicrobial cIAIs, cSSSIs and aPIs were published by Solomkin *et*

al.[21]. The authors concluded that in the three trials, Ertapenem 1.0 g/day was highly effective for the treatment of polymicrobial infections, and as effective as Piperacillin/Tazobactam 3.375 g every 6 hrs.

Ertapenem is now also increasing being used in pneumonia acquired in skilled-care facilities or in hospital environments outside the intensive care unit[24], and treatment of early-onset ventilator-associated pneumonia (VAP) in critically ill patients with no known risk factors for multidrug-resistant pathogens[25,26].

Use in Special Populations

Children: Safety and efficacy of ertapenam in 3 m to 17 y is based on evidence from adequate and well-controlled adult studies, pharmacokinetic data in pediatric patients, and additional data from comparator-controlled studies in pediatric patients. Indications are similar to adults. It is not recommended in less than 3 months as no data are available. Ertapenam is not recommended in the treatment intracranial infections due to lack of sufficient CSF penetration.

Renal dysfunction: No dosage adjustment is necessary in patients with CL_{CR} ≥31 mL/min/1.73 m^2. The recommended dose of ertapenam in adult patients with CL_{CR} ≤30 mL/min/1.73 m^2 is 500 mg every 24 hours. There are no data in pediatric renal insufficiency.

Post-hemodialysis: For adult patients on hemodialysis, a supplementary 150-mg post-dialysis dose is recommended if ertapenam is given within 6 hrs prior to hemodialysis.

Hepatic dysfunction: The pharmacokinetics of ertapenam in patients with hepatic insufficiency has not been established.

Geriatric age group: No dosage adjustments are necessary in elderly patients with normal renal functions.

Pregnancy: Ertapenam falls in Pregnancy Category B based on animal studies, however there are no adequate and well-controlled studies in pregnant women.

Nursing Mothers: Since ertapenam is excreted in human breast milk, caution is advised when administered to a nursing woman.

Adverse drug reactions

Its safety profile has been assessed in 240 healthy volunteers participating in 12 studies and in 2046 patients enrolled in 5 Phase IIa and 8 Phase IIb/III clinical trials (27). The most common drug-related adverse events (AEs) reported in these trials were: diarrhoea (5.0%); thrombophlebitis (4.5%), nausea (2.5%), seizures (0.2%) and elevations in alanine aminotransferase levels (8.8%) and were similar to comparator drugs. Most AEs were mild-to-moderate in severity. Ertapenem was not associated with QTc prolongation. Ertapenem was well tolerated and had overall safety and tolerability profiles similar to those of Piperacillin-Tazobactam and Ceftriaxone. Tolerability of IM Ertapenem is similar to IM Ceftriaxone (27).

Conclusions

Ertapenam appears to be a promising new carbapenem antimicrobial with excellent broad-spectrum activity against a wide variety of organisms and good stability against all β-lactamases. It has been shown to be non-inferior to comparator drugs in large multicentric randomized trials in cSSSIs, cIAIs, cUTI, aPI, CAP and prophylaxis of colorectal surgery and hence appears to be an effective empirical monotherapy for these conditions. Due to its limited efficacy against *Acinetobacter* spp., enterococci and *Pseudomonas aeruginosa*, it is less suited for late-onset nosocomial infections. The indication of Ertapenem is the treatment of mild to moderately ill patients with community-acquired infections and for treating patients with outpatient intravenous antibacterial therapy.

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