REVIEW ARTICLE

A BRIEF REVIEW OF ERTAPENEM AND ITS UTILITY IN PEDIATRIC PATIENTS

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Introduction

Organisms producing extended spectrum beta-lactamase enzymes (ESBLs) and AmpC chromosomal beta-lactamase enzymes are resistant to third generation cephalosporins and pose a formidable challenge in the management of seriously ill patients. Of the innumerable beta lactams, carbapenems are the novel class of antibiotics that possess an exceptional spectrum of activity and great potency against gram positive and gram negative bacteria as well as anaerobes like Bacteroides fragilis and Clostridium difficile. Carbapenems demonstrate stability against ESBL and AmpC chromosomal beta lactamases; inhibit penicillinase producing staphylococci and some methicillin-resistant staphylococcus aureus (MRSA). (1) In addition, they have a favorable safety profile. These properties have taken carbapenems to the top of the antibiotic list and they are thus reserved for serious life- threatening infections like ventilator-associated pneumonia (VAP), sepsis and polymicrobial infections including mixed aerobic and anaerobic etiology. However, recently significant alarm has been raised due to the production of carbapenemases, thus ensuing the possibility of resistance to carbapenems. (2) The older carbapenems, imipenem and meropenem, have marked their place in the management of serious bacterial infections. Ertapenem is one of the newer carbapenems with a few unique characteristics that has been approved for use in adults, children and infants over 3 months of age in the United States and Europe. (3,4) However, little is known about its utility in pediatric patients. This article discusses the pharmacokinetic profile of ertapenem and its use in pediatrics.

Chemistry

Ertapenem structurally differs from imipenem in that it has an additional methyl group in the 1-beta position of the core B-lactam structure. This ensures stability against mammalian hydrolase, dehydropeptidase-1 (DHP-1), found in the renal brush border and thus, can be administered without a dehydropeptidase-1 inhibitor. (1) It differs from both imipenem and meropenem by the presence of a meta-substituted benzoic acid on the functional group at position two. (1) This provides extensive protein binding and longer half-life than either imipenem or meropenem, thus allowing once daily-dosing. (4)

Antibacterial spectrum

Ertapenem is a group 1 carbapenem with broad-spectrum antimicrobial activity against several gram-positive and negative aerobes and anaerobes. (5) This includes methicillin-sensitive Staphylococcus aureus (MSSA), Streptococcus pneumonia, S. pyogenes and S. agalactiae among the gram positive aerobes and Hemophilus influenza, Moraxella catarrhalis and clinically relevant Enterobacteriaceae (Escherichia coli, Klebsiella spp., Citrobacter spp., Enterobacter spp., Morganella morganii, Proteus spp. and Serratia marcescens) among the gram negative aerobes. It has also demonstrated good in vitro activity against a wide range of anaerobes, including the Bacteroides fragilis group of pathogens, Clostridium clostridioforme, C. perfringens, Eubacterium lentum, Fusobacterium spp., Peptostreptococcus spp., Porphyromonas spp. and Prevotella spp. It is resistant to nearly all beta-lactamases, including extended-spectrum beta-lactamases and AmpC chromosomal beta-lactamase enzymes. (7) Similar to the other carbapenems, it lacks activity against ampicillin-resistant Enterococcus faecium, methicillin-resistant staphylococci, Stenotrophomonas maltophilia and some isolates of Clostridium difficile. However, in contrast to imipenem and meropenem, it has limited activity against non-fermentative gram negative bacilli, Pseudomonas aeruginosa and Acinetobacter species. (2) This narrower spectrum makes ertapenem suitable for serious community acquired infections.

Pharmacokinetics

Similar to the older carbapenems, ertapenem does not readily cross gastrointestinal membranes and has poor oral bioavailability. It has to be given intravenously. (4) In addition, unlike other carbapenems, it can also be given intramuscularly. (4) Ertapenem has a half-life of approximately 4 hours making it suitable for once-daily administration. (5) It is largely eliminated by the kidney and dosage has to be adjusted in renal impairment. It has time dependent bactericidal activity and hence duration of optimal drug concentration in plasma is important for efficacy. 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. (6)

Adverse effects

Intravenous ertapenem has an excellent safety profile with mild to moderately severe adverse events being reported. Adverse effects like diarrhea, infused vein complications, nausea, vomiting and headache have been reported in adults. Seizures have been reported in 0.5% of patients receiving ertapenem. Increased serum levels of liver enzymes, serum alkaline phosphatase, platelets and eosinophil counts have been reported. The commonly reported local symptoms at the injection site included tenderness, pain, induration and ecchymosis following intramuscular injections of ertapenem. (3)

Use in pediatrics

Owing to the limited efficacy of ertapenem against pseudomonas and acinetobacter species, it is reserved for serious community acquired infections. Food and drug association (FDA) approved indications for ertapenem in adults are skin and soft-tissue infections, urinary tract infections (UTI), community acquired pneumonia (CAP), intra-abdominal infections and prophylaxis for colorectal surgery. (7)

A few studies have been done to examine its role in pediatric patients. A double-blind randomized clinical trial was conducted to evaluate the efficacy of ertapenem in treating children with complicated UTI, skin and soft tissue infection and CAP. Children over 3 months of age were randomized in a 3:1 ratio (ertapenem: ceftriaxone) where 303 children received ertapenem and 100 children received ceftriaxone. Overall, ertapenem was found to be comparable to ceftriaxone in terms of efficacy, bacteriological cure and tolerability. (8,9) Yellin et al conducted an open-label study to examine the role of ertapenem in the treatment of complicated intra-abdominal and acute pelvic infection. (10) Children between 2-17 years of age were randomized to receive ertapenem or ticarcillin/clavulanate. This study demonstrated that ertapenem was safe and efficacious for treating complicated intra-abdominal infection and acute pelvic infection in pediatric patients. These two studies employed twice-daily dosing of ertapenem in children under the age of 12 years, in contrast to the one-daily dosing employed in adolescents and adults. Dalgic et al reported their experience of ertapenem use in 50 pediatric patients under 16 years of age with complicated UTIs, mainly pyelonephritis, caused by ESBL-producing organisms. (11) They concluded that ertapenem is promising for the treatment of culture-guided treatment of ESBL-producing gram-negative complicated UTIs in children. Another retrospective study was conducted by Karaaslan et al which looked at clinical efficacy and safety of using ertapenem for the treatment of complicated UTIs caused by ESBL-producing organism in 77 children between 3 months and 18 years of age. (12) Their findings suggested that not only was ertapenem an excellent choice for first-line therapy for UTIs caused by ESBL-producing microorganisms in children, it also has the added advantage of shorter hospital stays and lower healthcare costs.

With regards to the dosing of ertapenem in pediatric patients, one study done evaluating the dose-exposure profile of ertapenem at varying doses in children from infancy through adolescence concluded that a single intravenous dose of ertapenem appears to be well tolerated in children between 3 months and 17 years of age but weight-based dosing cannot be administered to pediatric patients irrespective of age. While doses of 20 to 40 mg/kg administered once daily appear to be suitable for children older than 12 years, children 12 years and younger would appear to benefit from a more frequent dosing of about 15 mg/kg administered every 12 hours. (13)

The adverse effects of ertapenem in pediatric patients are similar to those seen in adults. The most commonly reported drug-related adverse effects included diarrhea, pain and erythema in the infusion site and vomiting. Commonly reported drug-related laboratory abnormalities included decreased neutrophil counts and increased alanine transaminase (AST) and aspartate transaminase (ALT) levels. (3) In a study comparing the safety profile of ertapenem with ceftriaxone in children, ertapenem was found well tolerated with the safety profile comparable to that ceftriaxone. (8)

Conclusion

Ertapenem is unique in that it has limited efficacy against P.aeruginosa and Acinetobacter species, making it more suitable for the empiric treatment of serious community acquired infections. Moreover it has overcome the pharmacokinetic shortcomings of the older carbapenems, imipenem and meropenem, and its long half-life allows for outpatient once-daily dosing. Ertapenem is also equivalent to third generation cephalosporins with regards to clinical efficacy and tolerability, both in children and adults. Pediatric studies so far have been promising. Ertapenem can be considered as an effective and safe option for treating complicated UTI, CAP, skin and soft tissue infections, intra-abdominal infections and acute pelvic infections in adolescents, children and infants over 3 months of age.

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