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Ertapenem for Prophylaxis and Treatment of Infections in Children

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Ertapenem, the newest of the carbapenem antibiotics, was approved by the Food and Drug Administration on November 29, 2001.¹ Initially approved for use in adults, it received an indication for use in children on February 11, 2005 and was relabeled with pediatric dosing guidelines on May 18, 2005.² Merck, the manufacturer of ertapenem, received a patent extension under the Pediatric Exclusivity Program which encourages the pharmaceutical industry to study their products in children who might benefit from their use. This issue of *Pediatric Pharmacotherapy* will review the antimicrobial spectrum and pharmacology of ertapenem and describe the pediatric studies conducted by the manufacturer.

Mechanism of Action

As with other carbapenems, the bactericidal activity of ertapenem is the result of inhibition of cell wall synthesis, produced through binding to penicillin binding proteins. Ertapenem is stable against hydrolysis by many beta-lactamases, with the exception of metallo-beta-lactamases.^{1,3-5}

Antimicrobial Spectrum

Ertapenem has demonstrated both in vivo and in vitro activity against a wide variety of gram-positive, gram-negative, and anaerobic microorganisms. It is active against *Staph. aureus* (methicillin-susceptible strains), *Strep. agalactiae*, *Strep. pneumoniae* (penicillin-susceptible strains), and *Strep. pyogenes*. It is also effective against many gram-negative microorganisms, including *E. coli*, *H. influenzae* (non-beta-lactamase strains), *Klebsiella pneumoniae*, and *Moraxella catarrhalis*. Ertapenem is also active against Bacteroides species, *Clostridium clostridioforme*, *Eubacterium lentum*, Peptostreptococcus species, *Porphyromonas asaccharolytica*, and *Prevotella bivia*.^{1,3-5}

In vitro testing with ertapenem has demonstrated activity (a minimum inhibitory concentration less than or equal to the susceptible breakpoint for ertapenem) against *Strep. pneumoniae*

(penicillin-intermediate strains only), *Citrobacter freundii*, *Citrobacter koseri*, *Enterobacter aerogenes*, *Enterobacter cloacae*, Haemophilus species, *Klebsiella oxytoca* (not all strains), *Morganella morganii*, *Proteus vulgaris*, *Providencia rettgeri*, *Providencia stuartii*, *Serratia marcescens*, *Bacteriodes vulgatus*, *Clostridium perfringens*, and Fusobacterium species. Unlike other carbapenems, ertapenem has poor Pseudomonas coverage.^{1,3-5}

Indications

Ertapenem is indicated for the treatment of patients 3 months of age and older with complicated intra-abdominal infections, complicated skin and skin structure infections, community acquired pneumonia (CAP), complicated urinary tract infections (UTI), and acute pelvic infections. Ertapenem is not recommended for the treatment of meningitis due to the inability to achieve sufficient drug concentrations in the cerebrospinal fluid.³

Clinical Experience in Children

The manufacturer has conducted two pediatric clinical trials with ertapenem. Neither of the trials has been published in the medical literature, but details may be obtained from the prescribing information or the FDA website.^{3,4,6}

The first study (Protocol 036) was a double-blind, randomized, multicenter comparative study of ertapenem and ceftriaxone in 404 children with complicated UTI, skin and soft tissue infection, or CAP. Patients were randomized to receive either ertapenem (15 mg/kg every 12 hours in patients 3 months to 12 years and 1 gram once daily in patients 13 to 17 years of age) or ceftriaxone (50 mg/kg/day given in two divided doses to patients 3 months to 12 years and 50 mg/kg given once daily in children 13 to 17 years of age). Both groups were treated for up to 14 days. The clinical response rates in the evaluable patients with skin and soft tissue infections were 95.5% (64/67) for ertapenem and 100% (26/26) for ceftriaxone. In CAP patients, response rates were 96.1% (74/77) for ertapenem

and 96.4% (27/28) for ceftriaxone. In the children with UTI, the microbiologic response rates were 87% (40/46) for ertapenem and 90% (18/20) with ceftriaxone.^{3,6}

In the second study (Protocol 038), an open-label, randomized, multicenter comparative study, ertapenem was compared to ticarcillin/clavulanate in 112 children with complicated intra-abdominal infections or acute pelvic infections. Patients were treated with either ertapenem, using the dosing regimens described in the previous study, or ticarcillin/clavulanate at doses of 50 mg/kg in patients less than 60 kg and 3 grams in patients weighing greater than 60 kg given four to six times daily. The clinical response rates in the children with intra-abdominal infections were 83.7% (36/43) for ertapenem and 63.6% (7/11) for ticarcillin/clavulanate. In the patients with pelvic infections, the response rates were 100% (23/23) for ertapenem and 100% (4/4) for ticarcillin/clavulanate.^{3,6}

Pharmacokinetics

Ertapenem may be administered by intravenous (IV) or intramuscular (IM) routes. After a 1 gram IV dose, the mean peak plasma concentration is achieved within 2 to 3 hours. Ertapenem exhibits non-linear pharmacokinetics as a result of its concentration-dependent protein binding. The percentage of drug bound to serum albumin ranges from 95% at concentrations less than 100 mcg/mL to 85% at concentrations greater than 300 mcg/mL. In adults, the apparent volume of distribution is approximately 0.12 L/kg, compared to 0.2 L/kg in patients 3 months to 12 years of age and 0.16 L/kg in pediatric patients 13 to 17 years of age.^{1,3,6} Ertapenem is metabolized through hydrolysis of the beta-lactam ring and then renally excreted. The mean half-life is approximately 4 hours in adults and children over 12 years of age. In patients 3 months to 12 years of age, the half-life is significantly shorter, with a mean value of 2.5 hours. The half-life is prolonged in patients with renal insufficiency.^{1,3,6}

Drug Interactions

Administration of probenecid with ertapenem will prolong the half-life of ertapenem from 4 to 4.8 hours in adults. Because of this small effect, co-administration of probenecid in an effort to prolong ertapenem clearance is not recommended. No other clinically significant drug interactions have been reported.^{1,3,4}

Adverse Effects

In a study of 802 adults receiving ertapenem, adverse effects observed in > 1% of subjects

included diarrhea (in 10.3% of patients), nausea (8.5%), infusion site complications (7.1%), headache (5.6%), agitation/confusion (5.1%), fever (5%), constipation (4%), vomiting (3.7%), abdominal pain (3.6%), edema (3.4%), insomnia (3.2%), dyspepsia (2.6%), rash (2.5%), death/not drug-related (2.5%), dizziness (2.1%), hypotension (2%), pruritus (2%), extravasation/phlebitis (1.9%), hypotension, tachycardia, reflux, cough, erythema (all 1.6%), chest pain (1.5%), vaginitis (1.4%), anxiety (1.4%), fatigue (1.2%), dyspepsia, leg pain, and rales (all 1.1%). These values were similar in the comparison group of 774 adults given piperacillin/tazobactam.³

Similar results were found in the two clinical trials conducted in pediatric patients. In the 384 children receiving ertapenem, the most common reactions were diarrhea (11.7%), vomiting (10.2%), infusion site pain (7%), fever (4.9%), diaper rash, abdominal pain (both 4.7%), headache and cough (4.4%), redness at the infusion site (3.9%), rash (2.9%), constipation and upper respiratory tract infection (2.3%), loose stools (2.1%), infusion site phlebitis or swelling (1.8%), nausea, nasopharyngitis, hypothermia, dizziness (all 1.6%), infusion site warmth (1.3%), infusion site induration, upper abdominal pain, abdominal abscess, herpes simplex, viral pharyngitis, wheezing, and dermatitis (all 1.0%). The incidence of adverse effects was similar to that seen with the comparison groups receiving ceftriaxone or ticarcillin/clavulanate.³

Hypersensitivity reactions, including anaphylaxis, have been reported after ertapenem administration. Patients with a history of sensitivity to other beta-lactam antibiotics may be at greater risk for severe hypersensitivity reactions to ertapenem. Seizures have been reported in patients receiving ertapenem, and may be more likely in patients with an underlying seizure disorder, brain lesions, or decreased renal function. As with other antibiotics, ertapenem use has been associated with the development of pseudomembranous colitis.^{1,3,4}

Dosing Recommendations

The recommended dose of ertapenem in patients 3 months to 12 years of age is 15 mg/kg given IV or IM twice daily, up to a maximum dose of 1 gram/day. In older children and adults, the recommended dose is 1 gram given once daily. When administered IV, the dose should be infused over 30 minutes. The recommended duration of therapy is up to 14 days for IV administration and up to 7 days for IM use.³

The dose of ertapenem should be reduced in patients with renal insufficiency. In adults with a creatinine clearance less than 30 mL/min/1.73 m², the recommended dose is 500 mg administered once daily. Patients undergoing hemodialysis who have received a 500 mg dose within 6 hours of a dialysis session should receive a supplemental dose of 150 mg after the session. If the last regular dose was more than 6 hours prior to hemodialysis, no supplemental dose is needed. There are no data in pediatric patients with renal insufficiency.³

Ertapenem may be mixed in sodium chloride or Ringer's solution, but should not be mixed or infused with dextrose-containing fluids. It is also unstable when mixed with mannitol. Ertapenem may be infused with hetastarch, heparin, and potassium chloride solutions.⁷

Availability and Cost

Ertapenem (Invanz[®]; Merck & Co., Inc.) is available in 1 gram vials. The average wholesale price for ertapenem is \$58.85 per vial.⁸

Summary

Ertapenem offers pediatric health care professionals another option for broad spectrum antimicrobial coverage. While little clinical trial information is available, this agent appears to be an effective therapy that is generally well tolerated in children. More research is needed to define the role of ertapenem in treating pediatric infections.

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Pharmacology Literature Review

Bupropion concentration-response relationship

The relationship between bupropion plasma concentrations and antidepressant response was studied in 16 adolescents (11 to 17 years of age). All patients were receiving the drug (100 to 200 mg/day) for depression. Steady-state plasma levels were obtained during a 24-hour period. Clinical Global Impression Improvement scale (CGI-I) scores were assessed by the patient's treating psychiatrist. In the nine children considered to be responders (CGI-I \leq 2), mean area under the concentration curves for bupropion and its metabolites were significantly higher than in those children considered to be nonresponders. The authors suggest that plasma levels of bupropion and its hydroxybupropion metabolite may be useful in predicting response to therapy. Daviss WB, Perel JM, Brent DA, et al. Acute antidepressant response and plasma levels of bupropion and metabolites in a pediatric-aged sample: an exploratory study. *Ther Drug Monit* 2006;28:190-8.

Buspirone pharmacokinetics in autistic children

Buspirone, a serotonin 5-HT-1A agonist, may be useful in the treatment of children with pervasive developmental disorder and autism. In this study, the pharmacokinetics of buspirone were studied in 21 children with autism. Patients 2-3 years of age were given 2.5 mg and patients 4-6 years of age were given 5 mg. The authors found a mean peak serum concentration of 1,141 \pm 748 pg/mL, with a time to maximum concentration of 0.8 hours. Elimination half-life was 1.6 \pm 0.3 hours. Peak concentrations of the primary metabolite (1-pyrimidinylpiperazine) were 4.5-fold higher than the corresponding buspirone concentration. Girls had significantly higher peak buspirone concentrations and a lower metabolite/parent drug ratio. The authors concluded from these data that buspirone is rapidly absorbed and eliminated in young children, with peak plasma concentrations similar to that observed in older children receiving higher doses. Edward DJ, Chugani DC, Chugani HT, et al. Pharmacokinetics of buspirone in autistic children. *J Clin Pharmacol* 2006;46:508-14.

Busulfan concentrations in saliva and plasma

Measurement of busulfan concentrations in children may be used to optimize response and minimize the risk for toxicity. In this study, the pharmacokinetic parameters of busulfan were evaluated in 10 children (1.3 to 19 years of age) undergoing hematopoietic stem cell transplantation using both plasma and saliva samples. Liquid chromatography-tandem mass spectrometry was used to quantify busulfan concentrations in 69 pairs of samples. The

correlation between samples from the two sites was highly significant ($r = 0.958$). The apparent plasma clearance was higher than the apparent saliva clearance (202 ± 31 mL/hr/kg versus 189 ± 28 mL/hr/kg; $p = 0.001$), but the mean elimination half-life was not significantly different (2.31 ± 0.46 hours in the plasma samples and 2.30 ± 0.36 hours in the saliva samples). Based on their results, the authors concluded that busulfan analysis using saliva samples could be a useful alternative to plasma samples for assessing concentrations in children undergoing treatment. Rauh M, Stachel D, Kuhlen M, et al. Quantification of busulfan in saliva and plasma in haematopoietic stem cell transplantation in children: validation of liquid chromatography tandem mass spectrometry method. **Clin Pharmacokinet** 2006;45:305-16.

Cisplatin dosing adjustment

The authors of this paper introduce a new method for adjusting cisplatin dosing in children. It has previously been shown that adjustment of dose based on body surface area can lead to significant variability in area under the concentration versus time curve (AUC). Using plasma cisplatin concentrations from 19 children, the authors investigated various combinations of patient parameters in order to reduce variability in AUC. The combination of height, weight, age, maximum serum concentration, and half-life was used to create a dosing formula that gives a more constant AUC. Further studies will be needed to assess the clinical utility of this new method. Goodisman J, Souid A. Constancy in integrated cisplatin plasma concentrations among pediatric patients. **J Clin Pharmacol** 2006;46:443-8.

Extended release dexamethylphenidate

This review describes the studies conducted with extended release dexamethylphenidate (Focalin™ XR), the active d-enantiomer of methylphenidate. The authors include information on the pharmacokinetics, efficacy, and safety of this new product. The studies are presented in a concise, bullet-list format, allowing readers to quickly review the literature. Robinson DM, Keating GM. Dexamethylphenidate extended release in attention-deficit hyperactivity disorder. **Drugs** 2006;66:661-8.

Medication Errors

The objective of this study was to identify the source of 10-fold errors in pediatric medication orders in a large tertiary care hospital. In a review of medication errors reported to the hospital's Medication Incident Committee, the authors found an incidence rate of 1 error per 22,500 doses prescribed. A chart audit of 1,532 patients in the Emergency Department revealed 2

errors in 1,678 orders. In a prospective review of drugs used in 8 mock codes, there were 4 errors in 125 orders. The authors concluded that spontaneous medication error reporting systems may significantly underestimate the rate of 10-fold dosing errors in children and that the error rate during code situations may be particularly high. Kozer E, Scolnik D, Jarvis AD, et al. The effect of detection approaches on the reported incidence of tenfold errors. **Drug Safety** 2006;29:169-74.

NSAIDs during pregnancy

Nonsteroidal anti-inflammatory drugs (NSAIDs) are known to produce closure of the patent ductus arteriosus in neonates. The authors present the findings of their meta-analysis of reports of NSAID use during the third trimester and the risk of premature closure of the ductus. They compared 217 patient exposures to indomethacin and 221 controls and found that the risk of ductal closure was 15-fold higher in the women exposed to indomethacin. The authors concluded that short-term use of NSAIDs in late pregnancy is associated with an increased risk for ductal closure. Koren G, Florescu A, Costei AM, et al. Nonsteroidal anti-inflammatory drugs during third trimester and the risk of premature closure of the ductus arteriosus: a meta-analysis. **Ann Pharmacother** 2006;40:824-9.

Oxycodone pharmacokinetics

The authors of this study used population pharmacokinetic modeling to develop a profile of oxycodone pharmacokinetics in children between 6 months and 7 years of age. Using data from several small studies, the data were fit to a two-compartment linear model. Weight was found to have a significant affect on clearance and volume of distribution, confirming the need for weight-based dosing in young children. El-Tahtawy A, Kokki H, Reidenberg BE. Population pharmacokinetics of oxycodone in children 6 months to 7 years old. **J Clin Pharmacol** 2006;46:433-42.

There was no P&T Committee meeting in May.

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