Ertapenem or ticarcillin/clavulanate for the treatment of intra-abdominal infections or acute pelvic infections in pediatric patients

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 Abstract

Background: Ertapenem, a group I carbapenem antibiotic, has been shown to be safe and effective in treating adults with complicated intra-abdominal (cIAI) or acute pelvic infection (API). This study evaluated ertapenem for treating these infections in children.

Methods: In an open-label study, children aged 2 to 17 years with cIAI or API were randomized 3:1 to receive ertapenem or ticarcillin/clavulanate. Children 13 to 17 years of age received 1 g parenterally daily, and those 2 to 12 years of age received 15 mg/kg twice daily. Patients <60 kg received ticarcillin/clavulanate 50 mg/kg 4 to 6 times daily and 3.1 g 4 to 6 times daily for those ≥60 kg. Patients were assessed for safety and tolerability throughout the study and for efficacy after the completion of therapy.

Results: One hundred five patients, 72 (69%) with cIAI, received 1 dose of study drug and were included in the safety analysis. Eighty-one patients were treated with ertapenem. Infusion site pain was the most common drug-related adverse event in both groups. In the modified intent-to-treat analysis, the age-adjusted posttreatment clinical response rates were 87% (43/50 patients) and 100% (25/25 patients) in the cIAI and API patients, respectively, for ertapenem and 73% (11/15 evaluable patients) and 100% (8/8 evaluable patients), respectively, for ticarcillin/clavulanate. Overall age-adjusted response rates were 91% (68/75 evaluable patients) for ertapenem and 83% (19/23 evaluable patients) for the comparator.

Conclusions: This study suggests that ertapenem is generally safe and efficacious for treating cIAI or API in pediatric patients. © 2007 Published by Excerpta Medica Inc.

Keywords: Ertapenem; Pediatric; Intra-abdominal; Acute pelvic infection

Complicated intra-abdominal infections (cIAIs), caused primarily by ruptured or gangrenous appendicitis with or without peritonitis, are important causes of morbidity in children [1,2]. Acute pelvic infections (APIs), similar to cIAIs, are often mixed infections caused by enteric pathogens. These include postpartum or obstetrical surgery infectious complications in adolescent females [3]. Previous well-controlled, adequately powered trials have shown the safety and efficacy of ertapenem for treatment of cIAI and API in adults [4–6]. Because the pathophysiologic processes and pathogens involved in cIAI and API are similar in adults and children, children should respond similarly to treatment with ertapenem when infections are caused by susceptible bacteria. Ertapenem, a group 1 carbapenem, is active in vitro against most pathogens likely to be encountered in the treatment of cIAI (ie, infections requiring both operative drainage and antimicrobial therapy) including Escherichia coli and other Enterobacteriaceae, Clostridium clostridioforme, Eubacterium lentum, Peptostreptococcus species,
and Bacteroides spp including Bacteroides fragilis. In acute pelvic infections, such as postpartum endomyometritis, septic abortion, and postsurgical gynecologic infections, eraptapenem is effective against pathogens such as Streptococcus agalactiae, E. coli, B fragilis, Porphyromonas asaccharolytica, Peptostreptococcus species, and Prevotella bivia. Unlike the group 2 carbapenems, imipenem and meropenem, eraptapenem has substantially less activity against nonfermentative gram-negative bacteria and thus is not indicated in the treatment of infections caused by Pseudomonas aeruginosa or Acinetobacter species. Like other currently approved beta-lactam agents, eraptapenem is not active against methicillin/oxacillin-resistant staphylococci [7–9].

The aims of this study were to evaluate the safety, tolerability, and efficacy of eraptapenem versus a comparator ticarcillin/clavulanate control group in pediatric patients (3 months–17 years of age) with cIAI or API caused by susceptible pathogens.

Methods
Study design
This was a prospective, multicenter, randomized, open-label, comparative-controlled study conducted from March 2002 to January 2004 at 15 sites in the United States, Mexico, and Brazil (12 sites in the United States). The protocol was approved by each center’s institutional review committee. Written informed consent was obtained for each patient from his/her parent or guardian according to the guidelines of each institution.

Children between 3 months and 17 years of age were eligible to participate if they were diagnosed with cIAI with rupture and extension into the peritoneal cavity or API (in the absence of pelvic inflammatory disease) that was likely to be treatable with 3 to 14 days of parenteral therapy and was not complicated by preexisting conditions that could confound the evaluation of the study drugs. Patients with intra-abdominal infection were either enrolled postoperatively after visual confirmation of established intra-abdominal infection including appendicitis complicated by perforation and/or abscess or were enrolled preoperatively based on the need for surgical intervention and the presence of each of the following criteria: (1) evidence of systemic inflammatory response (at least 1 of the following: fever [oral temperature >38.5°C], white blood cell [WBC] count >15,000/mm³, drop in blood pressure, increased pulse and respiratory rate, hypoxemia, or altered mental status), (2) localized physical findings including pain/tenderness and rigidity consistent with intra-abdominal infection, and (3) supportive radiologic findings in the abdomen such as detection of an intraperitoneal abscess detected on computed tomography scan or ultrasound. Patients found to have simple appendicitis or gangrenous appendicitis without rupture into the peritoneal cavity were excluded from enrollment. Patients with acute pelvic infection were required to have each of the following for a clinical diagnosis: (1) either vaginal delivery, cesarean section, or gynecologic surgery >24 hours and within 1 month before enrollment (or within 24 hours if oral temperature at least 38.6°C) or a diagnosis of septic abortion requiring at least 3 days of parenteral antibacterial therapy; (2) pelvic, abdominal, or uterine pain or cramping or tenderness or sonographic/radiographic evidence suggesting a pelvic abscess; and (3) either fever (oral temperature >38°C), WBC >10,500/mm³, or a WBC differential with >10% band forms.

Enrollment was limited to immunologically competent patients. Because specific eraptapenem dosing guidelines for pediatric patients with renal insufficiency are not available, children with significant renal impairment (serum creatinine >1.25 times the upper limits of normal) were excluded from the study.

Interventions
For children 3 months to 12 years of age, eraptapenem was administered twice daily as a 15-mg/kg parenteral dose to a maximum total daily dose of 1 g. Children 13 years of age or older received 1 g of eraptapenem as a single daily dose. Treatment was always initiated with a 30-minute intravenous (IV) infusion, but intramuscular dosing could be used if the patient met protocol-defined criteria (hemodynamically stable and no coagulopathy). Dosing was based on preliminary results from a single-dose pharmacokinetic study in pediatric patients and was chosen to approximate the exposure and pharmacokinetic/pharmacodynamic efficacy determinants of 1 g daily dosing in adults [10].

The comparator antibiotic regimen, IV ticarcillin/clavulanate (50 mg/kg, based on the ticarcillin component), was administered 4 or 6 times a day (for patients <60 kg) or 3.1 g (3 g of ticarcillin and 100 mg of clavulanic acid) 4 or 6 times a day (for patients ≥60 kg). Each infusion was administered over a 30-minute period. These doses are approved for pediatric use in children 3 months of age and older for the indications of intra-abdominal infection and pelvic infections, including endometritis.

Study therapy could be completed in the hospital, an outpatient clinic, or with home infusion after at least 2 days of in-hospital or clinic-based infusion therapy. Treatment was to be continued for a minimum of 5 days for cIAI and 3 days for API. The maximum suggested duration of therapy was 14 days. All therapy was to be administered parenterally; the protocol did not allow for a switch to oral follow-up treatment. In addition to the antibiotic therapy, medical and surgical treatment of the infectious process was performed according to guidelines established by the participating institution and was consistent with the investigator’s usual clinical practice. Culture and sensitivity assays of appropriate bacterial specimens was requested at baseline, at any time that there was clinical or laboratory evidence of persistence or progression of the infectious process (including persistent fever, elevated white blood cell count, or significant changes in the patient’s clinical condition), and at the time of any surgical or drainage procedure.

Assessment
Safety and tolerability of the parenteral therapy were evaluated daily while patients were receiving study therapy and for 14 days after therapy. The primary objective of the study was to assess the incidence of any serious drug-related clinical and/or laboratory adverse experiences during the study drug therapy period and 14-day posttherapy follow-up. Secondary safety objectives for the study included eval-
uating the incidence of any drug-related clinical and/or laboratory adverse experiences, incidence of moderate-to-severe administration site reactions.

For the evaluation of efficacy, patients were assessed by the investigator for clinical signs and symptoms of infection at baseline, at the discontinuation of parenteral study therapy, and at the 2- to 4-week posttreatment follow-up visit for API and 3 to 5 weeks for cIAI patients. Bacterial cultures were to be obtained from appropriate infected material at baseline and subsequently if clinically indicated. Overall, clinical and microbiologic outcome evaluations were made at the discontinuation of parenteral study therapy and at the posttreatment follow-up assessment. Clinical outcome included an assessment of “cure,” “failure,” or “indeterminate.” At all investigative sites, patients were considered cured if there was complete resolution or substantial improvement in the baseline signs and symptoms (including pelvic, abdominal, or uterine pain/tenderness, nausea/vomiting, fever, and elevated WBC) of the index infection with no previous assessment of failure and no further antimicrobial therapy indicated. A microbiologic response was assessed for each baseline pathogen. For patients in whom follow-up cultures were not performed, microbiologic responses for baseline pathogens were presumed based on the clinical response. The overall microbiologic response was considered favorable if all baseline pathogens were eradicated or presumed eradicated. Emergent pathogens were considered “superinfections” if first isolated during therapy and “new infections” if isolated after completing therapy.

Sample size and power calculations

Based on estimates obtained from 2 adult phase IIb/III clinical trials of cIAI [4] and API [6], the pooled average rate of ertapenem patients having any clinical and/or laboratory drug-related serious adverse experiences was 2% with a range per study of 1% to 2%. It was anticipated that the experience in pediatric patients would parallel that of adults. Assuming a total of 75 patients in the ertapenem group in this trial, if the observed incidence rate of any clinical and laboratory drug-related serious adverse experience during study therapy and 14-day follow-up period was 3%, approximately equal to the highest observed rate in the adult studies, the 95% confidence interval (CI) about an incidence rate of 3% would be 0.4% to 10%. If a specific clinical or laboratory drug-related serious adverse experience was not observed in the 75 patients of the ertapenem treatment group, the true incidence rate of that clinical or laboratory drug-related serious adverse experience would be <5% with 95% confidence.

Blinding and randomization

The study drugs were administered in an unblinded manner. Because ertapenem and ticarcillin/clavulanate have different dosing frequencies, the design of the study was by necessity open label so that matching placebo infusions would not have to be administered to acutely ill pediatric patients.

Patients were randomized 3:1 to receive ertapenem or ticarcillin/clavulanate to obtain as much safety and efficacy data as possible on ertapenem and still maintain a reasonably sized sample in the comparator treatment arm. Enrollment was stratified based on indication (cIAI or API) and, within the IAI indication, by age category (3–23 months, 2–12 years, or 13–17 years) to ensure comparability and unbiased enrollment between treatments. Within each stratum, patients were randomized in a 3:1 ratio according to computer generated allocation schedules provided by the sponsor to a centralized randomization service. Screening and consent activities were completed before randomization. No study site personnel had access to the centrally held randomization schedules.

Statistical analyses

Both the clinical modified intent-to-treat (cMITT) and evaluable per protocol (EPP) populations were determined before analyses using prespecified criteria. The overall clinical response was assessed by the investigator at the posttreatment follow-up visit. To include as many randomized patients as possible in these analyses, the principal evaluation of efficacy was based on the cMITT population, which included all treated patients meeting baseline clinical diagnosis criteria. A microbiologic MITT population was also defined and consisted of all cMITT patients with a baseline pathogen. The MITT efficacy analyses took into consideration all posttreatment assessments and was based on assessments within the protocol defined test-of-cure window. If available, (2 to 4 weeks after treatment for API patients and 3- to 5 weeks after treatment for cIAI patients) or were otherwise based on the last assessment available after the completion of study therapy. Patients missing a posttreatment assessment were excluded from these analyses unless they had previously failed, in which case their outcome was unfavorable. Analyses were also done on the EPP population, which excluded patients with potential confounders likely to have affected outcome in accordance with applicable regulatory guidelines and accepted industry standards [11,12]. To be included in the EPP analyses, efficacy was required to have been assessed by the investigator within the protocol defined test-of-cure window. Patients with 1 or more baseline pathogens were included in the EPP analyses if at least 1 baseline pathogen was susceptible to both parenteral study therapies.

The primary efficacy response for both cIAI and API patients was based on the clinical efficacy assessment. A favorable clinical response (clinical cure) at the posttreatment assessment visit was prospectively defined as a complete resolution or substantial improvement in the signs and symptoms of the index refraction with no previous assessment of failure and no further antimicrobial therapy indicated.

The efficacy summary statistics were computed adjusting for age within each stratum and adjusting for age “overall” (where strata were combined).

Results

Patient accounting

One hundred twelve patients were randomized (Fig. 1). One hundred five patients (cMITT population) received ≥1 dose of study therapy and were included in the safety
evaluation. Eighty-one and 24 patients were treated with ertapenem and ticarcillin/clavulanate, respectively. Overall, 94% of the patients randomized were included in the cMITT population, and 72% (n = 81) of all randomized patients were included in the EPP population.

**Baseline characteristics**

Baseline characteristics for all treated patients (cMITT population) are reported in Table 1. The study included 47 patients 2 to 12 years of age and 58 patients 13 to 17 years of age. All 33 patients in the API stratum were females between 13 and 17 years of age. Although patients between 3 months and 17 years of age were eligible to participate, only patients 2 years of age and older were actually enrolled. This age distribution accurately reflects the age ranges for the infectious diseases under study in children.

One cIAI patient had a perforated Meckel’s diverticulum with localized peritonitis. All other cIAI patients had a ruptured appendix at presentation; more than 30% of these patients in each treatment group had ≥1 intra-abdominal abscess, and 62% in each treatment group had evidence of peritonitis. Seventy-five percent or more of the cIAI patients in each treatment group were initially managed by an open surgical procedure; approximately 20% in each group had laparoscopic surgery, and the remaining patients were managed by a percutaneous procedure only. The most common pathogens isolated during surgery in both treatment groups were *E coli* and *Bacteroides* species, including *B fragilis* and *Bacteroides thetaiotaomicron*. Two patients in the ertapenem group were bacteremic at baseline, 1 each with *B fragilis* and *Streptococcus constellatus*. In the ticarcillin/clavulanate comparator group, 1 patient was bacteremic with a *Bacillus* species at baseline.

In the API stratum, approximately half of the patients in each treatment arm had a diagnosis of endomyometritis associated with an obstetrical procedure; the remainder had a diagnosis of septic abortion. The most commonly isolated pathogen in both treatment groups was *E coli*. There were no bacteremic API patients in either treatment group at baseline.

**Duration of treatment**

The duration of treatment for each treatment group by disease indication is provided in Table 2. No patient in either treatment group missed a day of study therapy. Both treatment groups appear similar with respect to extent of exposure. Although the protocol allowed investigators the option to administer ertapenem by the intramuscular (IM) or IV route, only 1 patient in the study received IM therapy (for 2 days).

**Incidence of adverse events**

As shown in Table 3, 48 patients (46%) had 1 or more clinical adverse experiences as assessed by the investigator: 32 (39%) in the ertapenem group and 16 (67%) in the comparator group.

One patient treated with ertapenem experienced a serious drug-related clinical adverse experience. This was a 3-year
old Asian male with a cIAI and moderate diarrhea before enrollment who developed progressively more frequent diarrhea over a 4-day course of ertapenem therapy resulting in discontinuation. *Clostridium difficile* testing was negative in this patient. On study day 5, the diarrhea resolved, and the patient was discharged from the hospital. Because the diarrhea prolonged hospitalization, it was considered a serious adverse event. This was the only patient to discontinue ertapenem therapy because of a drug-related adverse experience. Diarrhea was reported as a drug-related adverse event with a similar frequency in the 2 treatment groups and with a similar frequency to that reported in previous adult studies [4,5].

In total, 4 patients discontinued therapy because of adverse clinical experiences, 2 in each group. The other patient in the ertapenem group had an abdominal abscess and discontinued therapy on day 10. In the comparator group, 1 patient developed a rash and discontinued therapy on day 28, and the other, with a wound infection, discontinued therapy on day 9.

Eleven patients (14%; 95% CI, 7.0–23.0) in the ertapenem group and 8 patients (33%; 95% CI, 15.6–55.3) in the comparator group reported drug-related clinical and/or laboratory adverse experiences. Infusion-site pain was the most common drug-related adverse experience reported in both treatment groups: 6 (7%) patients in the ertapenem treatment group and 3 (12%) patients in the comparator group.

Overall, 103 (98%) treated patients had laboratory test postbaseline during study therapy and the 14-day follow-up period. Of these, 10 (10%) had laboratory adverse experiences. Five patients (3 in the ertapenem group and 2 in the comparator group) had drug-related laboratory adverse experiences. However, none of the laboratory adverse experiences was serious or resulted in study discontinuation. All of the drug-related laboratory adverse experiences reported occurred during parenteral therapy.

**Tolerability**

Assessment of tolerability (eMITT population) at the IV and IM study drug infusion-site was performed daily while the patient was on study therapy. Of the 105 treated patients, 9 (11%; 95% CI, 5.2–20.0) in the ertapenem group and 6 (25%; 95% CI, 9.8–46.7) in the comparator group experienced local reactions of any intensity at the infusion/injection site (data not shown). Two patients (2%; 95% CI, –8.6) in the ertapenem group and 2 (8%; 95% CI, 1.0–27.0) in the comparator group experienced ≥1 local reactions of...
moderate to severe intensity at the infusion/injection site. All of the tolerability symptoms reported were from patients receiving IV therapy. One patient received ertapenem IM therapy for 2 days with no injection site reactions reported.

**Efficacy**

The proportion of patients in the cMITT and EPP populations and within each study drug group with a favorable clinical response assessment (cure but not failure or indeterminate) at the post treatment visit are shown in Table 5. Clinical efficacy response rates in the EPP population were consistent with the cMITT results; overall response rates were 89% (59/66 evaluable patients) for ertapenem and 73% (11/15 evaluable patients) for the comparator. Comparable rates were seen across each of the age groups studied. Although both drugs had 100% efficacy in the API stratum in both cMITT and EPP populations, the lack of difference in clinical efficacy between treatments may be because of the relatively small number of patients in the cMITT and EPP populations of this stratum. Clinical efficacy in the cMITT population of the cIAI stratum was 87% (95% CI, 77%–96%) for ertapenem versus 73% (95% CI, 45%–92%) for the comparator. The overall age adjusted response rate in these patients was 68/75 patients (91%; 95% CI, 85%–98%) for ertapenem and 19 of 23 patients (83%; 95% CI, 1%–95%) for the comparator. In both treatment groups, some-
what lower response rates were observed in the EPP analysis. This resulted primarily from the exclusion of patients whose final assessment of “cure” in the cMITT analysis occurred before the test-of-cure window. Consistent with the results of the cMITT analysis, however, the overall response rates observed in the EPP analysis were also higher in the ertapenem treatment group.

Microbiological efficacy of treatments against the major pathogens identified (E coli and Bacteroides species) in the cMITT population are shown in Table 6. Ertapenem was effective against these pathogens in both disease strata, with favorable responses ranging from 83% (E coli in cIAI) to 100% (E coli in API). The comparator had favorable responses between 67% (B thetaiotaomicron in cIAI) and 100% (E coli in API).

### Comments

Guidelines from both the Infectious Diseases Society of America and the Surgical Infection Society support and recommend the use of ertapenem as an empirical treatment option for adult patients with community-acquired cIAI [13,14]. The results of this small randomized, controlled study extend the available data on the safety, tolerability, and efficacy of ertapenem in a pediatric population. These data are consistent with the results obtained previously for these indications in adults [4–6].

Clinical and microbiological efficacy response rates were comparable in this study between pediatric patients treated with ertapenem and patients treated with ticarcillin/clavulanate. Patients treated for intra-abdominal infection were required to have had a ruptured viscous; all but 1 patient had a ruptured appendicitis with extension of infection into the peritoneal space. Similar to the study in adults, approximately 63% of patients had evidence of generalized or localized peritonitis and approximately one third had one or more intra-abdominal abscesses identified at the time of surgery. A slightly higher percentage of adult patients (89%) were managed with open surgical intervention as compared with approximately 76% of patients in this pediatric study. The difference may be a reflection of the fact that virtually all patients in the pediatric study were treated for infectious complications of a ruptured appendix, whereas this represented only about half of the patients treated in the adult study (the remainder having infections originating from the colon or other intra-abdominal site) [4]. Adolescent patients treated for acute pelvic infection had either septic abortion or postpartum endomyometritis. Overall, the efficacy results observed for ertapenem in this pediatric study were consistent with that observed previously in adult patients treated with ertapenem for these indications [4–6].

Ertapenem was generally well tolerated in pediatric patients. Only 1 ertapenem patient reported a serious drug-related clinical adverse experience (moderately intense diarrhea) which required discontinuation. There were no serious drug-related laboratory adverse experiences reported in any patient receiving ertapenem therapy, and no patients discontinued ertapenem therapy as the result of a laboratory adverse experience. There were no deaths reported in any patient during the study, and overall the rate of serious adverse experiences was low and of the type generally expected in hospitalized pediatric patients treated for these types of infectious diseases.

The overall and the drug-related incidence of clinical and laboratory adverse experiences was low and similar in the 2
treatment groups. The overall safety profile for ertapenem in pediatric patients in this study was similar to that described for adults.

The drug-related adverse experiences were generally mild and considered of minimal clinical significance. The most commonly reported drug-related clinical adverse experiences during ertapenem parenteral therapy and 14-day follow-up period included infusion site pain and diarrhea, similar to the experience in adult patients receiving ertapenem [4–6]. The incidence of both of these adverse experiences was less in the ertapenem group than in the comparator group. No seizures were reported, and no patients discontinued ertapenem therapy because of a drug-related rash. Overall, the incidence of rash was low in both treatment groups.

Drug-related laboratory abnormalities were uncommon in both treatment groups, and none were considered serious. The most commonly reported drug-related laboratory adverse experiences were mild transaminase elevation, occurring in 2 patients in the ertapenem group and 1 patient in the comparator group. These resolved on discontinuation of study drug at completion of treatment. There were no reports of decreased neutrophil counts as an adverse experience, and other drug-related laboratory adverse experiences were also uncommon. Overall, the laboratory safety profile of ertapenem in pediatric patients was similar to that of ticarcillin/clavulanate and to that reported in adults treated with ertapenem [4–6].

Similar proportions of patients in both treatment groups reported drug-related infused vein complications during study therapy. In a separate assessment designed to examine local tolerability, similar proportions of patients in the treatment groups had signs or symptoms of local intolerance, most of which were considered mild. Overall, infusion of ertapenem appeared to be at least as well tolerated as ticarcillin/clavulanate.

In summary, results from this study, similar to those observed in adults, show that ertapenem administered 1 g parenterally per day to children 13 to 17 years of age or 15 mg/kg twice daily to children 2 to 12 years of age is a safe and effective therapeutic regimen for treating cIAI or API.

References