Efficacy and Safety of Ertapenem Versus Piperacillin-Tazobactam for the Treatment of Intra-Abdominal Infections Requiring Surgical Intervention

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Complicated intra-abdominal infections usually mandate prompt surgical intervention supplemented by appropriate antimicrobial therapy. The aim of this study was to demonstrate that ertapenem was not inferior to piperacillin-tazobactam for the treatment of community-acquired intra-abdominal infections. A randomized open-label active-comparator clinical trial was conducted at 48 medical centers on four continents from December 2001 to February 2003. Adult patients with intra-abdominal infections requiring surgery were randomized to receive either ertapenem 1 g daily or piperacillin/tazobactam 13.5 g daily in 3–4 divided doses. The primary analysis of efficacy was the clinical response rate in clinically and microbiologically evaluable patients at the test-of-cure assessment 2 weeks after completion of therapy. All treated patients were included in the safety analysis. Patient demographics, disease characteristics, and treatment duration in both treatment groups were generally similar. The most commonly isolated pathogens at baseline were \textit{E. coli} (greater than 50% of cases in each group) and \textit{B. fragilis} (~9%). Favorable clinical response rates were 107/119 (90%) for ertapenem recipients and 107/114 (94%) for piperacillin/tazobactam recipients. The frequencies of drug-related adverse events, most commonly diarrhea and elevated serum alanine aminotransferase levels, were similar in both treatment groups. Six of 180 ertapenem recipients (3%) and two of 190 piperacillin/tazobactam recipients (1%) had serious drug-related adverse experiences. In this study, ertapenem and piperacillin/tazobactam were comparably safe and effective treatments for adult patients with complicated intra-abdominal infections.

KEY WORDS: Intra-abdominal infection, ertapenem, piperacillin-tazobactam

Complicated intra-abdominal infections are common problems for general surgeons and emergency medicine physicians.\(^1\) Complicated intra-abdominal infections are common problems for general surgeons and emergency medicine physicians.\(^1\) The mainstay of appropriate management is timely surgical intervention combined with antimicrobial therapy to eradicate any residual infection. Empirical antibacterial therapy should cover the most likely pathogens, which include gram-positive and gram-negative aerobic and anaerobic bacteria that comprise the usual flora of the gastrointestinal tract.\(^5,7\) All antimicrobial regimens recommended by the Surgical Infection Society and the Infectious Disease Society of America have broad activity against Enterobacteriaceae and the \textit{B. fragilis} group.\(^3,5\)

Ertapenem is a long-acting parenteral Group I carbapenem active in vitro against most aerobic and anaerobic bacteria generally associated with community-acquired infections.\(^7,13\) Ertapenem is not active against most \textit{Pseudomonas aeruginosa} or enterococci, but coverage of these organisms is not routinely required for successful treatment of intra-abdominal infections.\(^3,5,16,17\) In two earlier double-blind randomized clinical trials, ertapenem was comparably effective and as well tolerated as piperacillin-tazobactam.\(^16\)
or ceftriaxone plus metronidazole in the treatment of complicated intra-abdominal infections. The present study was undertaken to confirm the utility of ertapenem as once daily monotherapy for community-acquired intra-abdominal infections requiring surgical intervention.

METHODS

Study Design

This prospective, multicenter, open-label study was conducted at 48 centers on four continents from December 2001 to February 2003. The institutional review board at each site approved the protocol, and written informed consent was obtained from all participants. Hospitalized patients ≥18 years of age with clinical evidence of an intra-abdominal infection requiring open or laparoscopic surgery were eligible for the study if the infection extended beyond the wall of a hollow organ. For patients enrolled preoperatively, signs and symptoms suggestive of an intra-abdominal infection had to include at least one of the following: fever, leukocytosis, hypotension, tachycardia and tachypnea, or altered mental status. Exclusion criteria included pregnancy or lactation; history of serious allergy or intolerance to either study drug; rapidly progressive or terminal illness; chronic immunosuppressive therapy; known infection with human immunodeficiency virus; APACHE II score greater than 30; concurrent infection that could interfere with evaluation of response to study therapy; ischemic bowel disease; uncomplicated cholecystitis; acute necrotizing pancreatitis; traumatic bowel perforation if surgery was performed within 12 hours of perforation; perforated gastroduodenal ulcer if surgery was performed within 24 hours of perforation; any primarily noninfectious intra-abdominal process; need for peritoneal or hemodialysis; acute hepatic failure; serum alanine or aspartate aminotransferase levels greater than six times the upper limit of normal; bilirubin or alkaline phosphatase levels greater than three times the upper limit of normal; and systemic antimicrobial therapy for greater than 24 hours in the 72-hour period immediately before study entry unless the patient had failed that therapy. Patients were withdrawn from the study if surgical intervention did not occur within 24 hours after diagnosis or all pathogens were resistant to either study drug. For polymicrobial infections, patients could remain in the study if at least one isolate was susceptible to both study drugs.

Patients were randomized in a 1:1 ratio to receive ertapenem 1 g once a day or piperacillin-tazobactam 3.375 g q6h or 4.5 g q8h using a computer-generated allocation schedule via an interactive voice recognition system that kept the treatment assignment blinded. Both drugs were infused intravenously over 30 minutes. After 2 days of intravenous therapy, ertapenem could be administered intramuscularly. Other than vancomycin or teicoplanin to treat infections caused by resistant gram-positive pathogens, concomitant antibacterial agents were not allowed. The suggested length of treatment was 4–14 days, but the exact duration for individual patients was determined by the site investigator.

Aerobic and anaerobic cultures of blood and intraoperative specimens were obtained at baseline and processed in the clinical microbiology laboratory of the participating hospitals. Aerobic and facultatively anaerobic isolates were tested for susceptibility to ertapenem and piperacillin-tazobactam by disk diffusion or microtiter dilution according to guidelines of the National Committee for Clinical Laboratory Standards (NCCLS). Routine susceptibility testing of strict anaerobes was not required per protocol.

Assessments of Efficacy and Safety

Clinical parameters were assessed daily during study therapy, at discontinuation of study therapy, and at 2 and 4 weeks post-therapy. The primary efficacy end point was designated a priori as the proportion of clinically and microbiologically evaluable patients with a favorable clinical assessment at the test-of-cure (TOC) visit 2 weeks after completion of all study therapy. The 4-week post-therapy evaluation could be accomplished by telephone contact if laboratory testing was not necessary and a clinic visit was not feasible.

The three clinical response categories were cure (complete resolution or significant improvement of all signs and symptoms related to the index infection such that no further antimicrobial therapy or surgical intervention for infection was necessary), failure (persistance or recurrence of the index infection; death attributable to intra-abdominal infection; the need for a second surgical procedure; or the occurrence of a postoperative wound infection), or indeterminate (data insufficient for evaluation of efficacy or cause of death). Patients with indeterminate clinical responses were excluded from the primary analysis. Microbiological responses were recorded for each baseline pathogen. Favorable microbiological responses included eradication of the pathogen(s) that was either documented or presumptive (no material available for culture in clinically cured patients); unfavorable microbiologic responses included persistence of the pathogen(s),