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AN EVALUATION OF THE EFFICACY, SAFETY, AND SOURCE CONTROL OF ONCE-DAILY ERTAPENEM, COMPARED WITH PIPERACILLIN/TAZOBACTAM, IN PATIENTS WITH COMPLICATED INTRA-ABDOMINAL INFECTIONS

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Abstract
Infections in the abdominal cavity that require both surgical source control as well as antibiotic treatment are extremely challenging to treat. An ertapenem/piperacillin/tazobactam every six-hour trial compared the efficacy and safety of one-gram of ertapenem (1g) once-daily in hospitalized adults with one-gram of piperacillin/tazobactam administered every six hours. A microbiologic specimen was obtained from each patient for culturing after operative or percutaneous intervention. An analysis was conducted with microbiologically evaluable and modified intent-to-treat populations to assess clinical and microbiologic outcomes. Infection sites and pathogen profiles among groups, which predominantly consisted of Bacteroides and Escherichia coli, were similar. In addition to treating nonappendiceal infections, generalized peritonitis, postoperative infections, and enterococcus infections, ertapenem showed equivalent clinical and microbiological cure rates to piperacillin/tazobactam. An expert panel that was blinded and performed a source control analysis was crucial to determining the effectiveness of the treatment. For complex intraabdominal infections acquired in the community, Ertapenem is an effective monotherapy option due to its broad-spectrum activity, favorable safety profile, and convenient once-daily dosing schedule.

Keywords: Ertapenem, Complicated intra-abdominal infection, Piperacillin/tazobactam, Source control, Polymicrobial infection.

Introduction

Intra-abdominal infections requiring both operative source control and antimicrobial treatment make up a significant portion of general surgical practice. Efficacious antimicrobial treatment is essential to management, since delayed, absent, or inaccurate empiric therapy has been linked to higher mortality rates and treatment failures (1,2). In a well-characterized population of community-acquired infections, gram-negative bacteria, anaerobic bacteria, streptococci, and enterococci are commonly identified. Antimicrobial agents must target both anaerobes like Bacteroides fragilis and gram-negative bacteria that produce endotoxins as a result of their synergistic effects (3). Ertapenem is a long-acting parenteral type-II aminoglycoside antibiotic evaluated for use as a monotherapy for community-acquired infections with mixed flora. Several factors contribute to the interest in this

agent, such as its broad antimicrobial spectrum, its favorable pharmacokinetics and pharmacodynamics, and its prior clinical experience supporting a single-daily dosing regimen (4). Ertapenem can inhibit the growth of gram-positive, gram-negative, and anaerobic bacteria commonly found in abdominal infections in vitro. There is some indication that it is fairly ineffective against organisms associated with healthcare-associated infections, such as Pseudomonas aeruginosa and Acinetobacter species. In this study, ertapenem was studied in patients with complicated intraabdominal infections to assess its clinical and microbiological effectiveness, as well as its safety profile (5). This study was conducted with piperacillin combined with tazobactam, as it is a widely used configuration with established effectiveness in this situation. Study participants also evaluated surgical source control as part of their research. Poor outcomes are well known when insufficient drainage or insufficient treatment of gastrointestinal perforation has been inadequately managed. For the purpose of assessing the effectiveness of an overall treatment plan, a blinded expert panel evaluated operative findings and interventions (6). An ertapenem versus piperacillin/tazobactam prospective, randomized, double-blind, multicenter study evaluated antibiotic efficacy in hospitalized adults with complicated intra-abdominal infections. The term "complicated infection" pertains to infections that extend past the affected organ into the peritoneal cavity, causing abscess formation or peritonitis that requires surgical or percutaneous treatment. The study was approved by the university's ethical committee and all participants provided written informed consent.

Methods

Those treated

Each treatment group included 31 patients. A patient must have suffered or be scheduled to undergo operative or image-guided drainage within 24 hours after developing clinical evidence of intra-abdominal infection. In addition to open surgical procedures, minimally invasive surgical procedures, and percutaneous drainage procedures were all acceptable. It was mandatory to collect specimens for aerobic and anaerobic cultures during the initial intervention. In the event of a short-term treatment or a failed previous therapy, limited prior antibiotic exposure was permitted. In the lead up to study medication initiation, non-study antimicrobials were discontinued.

Exclusion Criteria

There were four types of patients exclusions: those with uncomplicated intra-abdominal conditions, those with traumatic abdominal perforations or gastroduodenal perforations treated early, those with necrotizing pancreatitis treated early, and those with staged abdominal management. In addition to severe allergies to long-acting antibiotics, high predicted mortality rates, resistant baseline pathogens, significant immunosuppression, abnormal laboratory values, pregnancy, lactation, or inadequate contraception, patients were excluded as well.

A Randomized Controlled Trial

Randomization was conducted in a 1:1 ratio using block randomization, stratified by infection site and severity of the disease. Researchers and patients remained blinded to the study medications, while pharmacy personnel prepared them unblinded. Piperacillin/tazobactam was given every six hours with dose adjustments for renal impairment in one group of patients receiving ertapenem once daily with placebo infusions, and ertapenem in the other group treated with piperacillin/tazobactam every six hours. Treatments lasted between four and fourteen days. A variety of additional agents, including vancomycin or antifungal therapy, could be used if clinically indicated.

Analyses of microbes
As part of the initial procedure, samples gained from respiratory samples were cultured aerobically and anaerobically and their susceptibility to antimicrobial agents was assessed using standardized laboratory methods.

Demographic Analysis
Unblinding was conducted before evaluating evaluability. Analyses were conducted using an intent-to-treat population and a per-protocol population that was microbiologically evaluable. It was necessary to confirm complicated infections, provide adequate source control, identify susceptible pathogens, and complete outcome assessments for an evaluation to be considered evaluable.

Defined outcomes
In addition to assessing clinical and microbiological outcomes at the end of intravenous therapy, subsequent visits were conducted to determine whether the patient had undergone a cure. Infections were considered clinically cured if they remitted without requiring additional antibiotics. Several clinical failures have been reported, including persistent infections, recurrent infections, and infection-related deaths.

Revision of source control
A blinded expert panel evaluated the effectiveness of initial source control based on clinical data, operative reports, and imaging. Infection foci must be eliminated effectively and purulent collections must be drained. In cases where there was no unanimous agreement, the full panel reviewed the case.

Analyses statistics
A confidence interval methodology was used to evaluate equivalence between treatment groups based on cure rates at test-of-cure. Subgroup outcomes were analyzed at earlier time points and within predefined subgroups as a secondary analysis. In order to identify predictors of treatment failure, clinical, microbiological, and demographic factors were combined in a post-hoc logistic regression model.

Results
An analysis of 62 patients was performed, with 31 patients assigned to each treatment group. There were no significant differences between the clinically and microbiologically evaluable populations in terms of reasons for exclusion. Nine patients in the ertapenem and eight patients in the piperacillin/tazobactam groups were not evaluable due to the absence of an identifiable baseline pathogen. Follow-up visits were not completed within four to six weeks, and the therapy was inadequately duration. It appears that the exclusion patterns between groups were balanced, as inadequate surgical source control and misclassifications of infection complexity were infrequent and occurred at comparable rates. A good match was generally found between baseline demographic and clinical characteristics. Both randomized and microbiologically evaluated populations were dominated by males, representing approximately 58–68% of participants. With a mean age in the mid-40s and similar age distributions, and comparable proportions of patients over 65, the average age was in the mid-40s. Anatomically, appendix infections were most common, followed by colonic infections and small bowel infections. Other abscesses were seen less frequently in other organs, including the stomach, the duodenum, and the viscera. Among the infectious conditions observed, localized peritonitis and single abscesses formed the majority of cases, accounting for more than half of cases between treatment groups. Most patients with generalized peritonitis had one or two abscesses; multiple abscesses were the exception. An insignificant number of patients reported postoperative intra-abdominal infections, with similar proportions among the treatment groups. During the same period of antimicrobial therapy, both

randomized and evaluable populations received approximately 7–8 days of antibiotic therapy. There was no difference between the groups in terms of their initial source control strategies. The most common approach in microbiologically evaluable patients is open surgery. Over 85% of them required open surgery. It was uncommon to perform percutaneous or laparoscopic procedures. Most patients didn't require surgical drains, but a minority did, often Penrose drains, which are placed at a separate site. More than half were not required to have surgical drains placed. Most wounds were closed with primary closure, while delayed primary and secondary closure were less frequently used. A majority of patients received their first dose of study medication before receiving their first intervention.

Results of microbiological analysis showed polymicrobial patterns consistent with complicated intraabdominal infections. *Gram-negative aerobic organisms found in both groups were most commonly Escherichia coli.* Among the most common types of bacteria identified were Anaerobic bacteria, particularly Bacteroides fragilis and other Bacteroides species. The most frequently recovered cocci were Gram-positive, including Enterococcus and Streptococcus species. Microorganism distribution between treatment groups appeared to be similar, which indicates similar baseline microbiological profiles.

Table 1. Reasons Patients Were Excluded from the Clinically and Microbiologically Evaluable Patient Group

Reason for nonevaluability	**Ertapenem (n = 31)**	**Piperacillin/Tazobactam (n = 31)**
No baseline pathogen identified	9	8
Inadequate duration of therapy	6	7
Missing 4–6 week follow-up visit	5	6
Concomitant antibiotics used (not for suspected intra-abdominal failure)	4	3
Confounding events / other*	3	2
Inadequate source control	2	3
Not a complicated intra-abdominal infection	1	1
All baseline pathogens resistant	1	1
Prestudy antibiotics >24 hours (without failure)	0	0
Total	**31**	**31**

Table 2. Baseline Characteristics of Randomized and Microbiologically Evaluable Patients, and Treatment Duration

Characteristic	**Randomized Ertapenem (n = 31)**	**Randomized Piperacillin/ Tazobactam (n = 31)**	**Microbiologically Evaluable Ertapenem (n = 31)**	**Microbiologically Evaluable Piperacillin/ Tazobactam (n = 31)**
Gender				
Male	18 (58.1)	20 (64.5)	19 (61.3)	21 (67.7)
Age (years)				
Mean (± SD)	45.8 ± 18.5	44.9 ± 17.9	44.3 ± 17.6	43.6 ± 16.9
Range	18–81	19–79	18–78	19–76
≥65 years	6 (19.4)	5 (16.1)	5 (16.1)	4 (12.9)
Primary Infection: Anatomic Site				
Appendix	15 (48.4)	14 (45.2)	18 (58.1)	17 (54.8)
Colon	6 (19.4)	7 (22.6)	6 (19.4)	6 (19.4)

Gangrenous or abscessed cholecystitis	3 (9.7)	2 (6.5)	2 (6.5)	2 (6.5)
Small bowel	3 (9.7)	3 (9.7)	2 (6.5)	2 (6.5)
Stomach/Duodenum	2 (6.5)	2 (6.5)	1 (3.2)	1 (3.2)
Visceral abscess	1 (3.2)	1 (3.2)	1 (3.2)	1 (3.2)
Other	1 (3.2)	2 (6.5)	1 (3.2)	2 (6.5)
Infectious Process				
Generalized peritonitis	9 (29.0)	9 (29.0)	9 (29.0)	8 (25.8)
Multiple abscesses	2 (6.5)	1 (3.2)	2 (6.5)	1 (3.2)
Single abscess	9 (29.0)	11 (35.5)	9 (29.0)	11 (35.5)
Localized peritonitis	11 (35.5)	10 (32.3)	11 (35.5)	11 (35.5)
Postoperative infection	4 (12.9)	4 (12.9)	3 (9.7)	4 (12.9)
Days on study therapy				
Mean (± SD)	7.2 ± 3.4	7.6 ± 3.1	7.5 ± 2.9	7.8 ± 2.7
Range	4–16	4–17	4–15	4–16

Table 3. Initial Interventions in the Microbiologically Evaluable Population

Characteristic	**Ertapenem (n = 31)**	**Piperacillin/ Tazobactam (n = 31)**
Type of intervention		
Percutaneous	2 (6.5)	1 (3.2)
Laparoscopic	2 (6.5)	2 (6.5)
Open	27 (87.1)	28 (90.3)
Drains		
Percutaneous catheter	1 (3.2)	1 (3.2)
Penrose through incision	2 (6.5)	2 (6.5)
Penrose, separate site	5 (16.1)	4 (12.9)
Closed suction	2 (6.5)	3 (9.7)
None	18 (58.1)	18 (58.1)
Other	3 (9.7)	3 (9.7)
Wound closure		
Primary	21 (67.7)	22 (71.0)
Delayed primary	4 (12.9)	4 (12.9)
Secondary	4 (12.9)	3 (9.7)
Other	1 (3.2)	1 (3.2)
Not applicable	1 (3.2)	1 (3.2)
Timing of initial procedure		
Before first dose of study drug	30 (96.8)	30 (96.8)
After first dose of study drug	1 (3.2)	1 (3.2)

Table 4. Microorganisms Isolated from Microbiologically Evaluable Patients

Microorganism	Ertapenem (n = 31)	Piperacillin/ Tazobactam (n = 31)
Facultative and aerobic gram-negative bacilli		
Escherichia coli	22	21
Enterobacter spp	2	3
Klebsiella spp	5	5
Acinetobacter spp	1	1
Pseudomonas aeruginosa	4	4
Proteus spp	2	1
Other gram-negative bacilli	2	4
Anaerobes		
Clostridium spp	10	9
Eubacterium spp	6	5
Peptostreptococcus spp	5	4
Bacteroides fragilis	11	10
Other Bacteroides spp	23	24
Fusobacterium spp	3	2
Bilophila spp	5	4
Prevotella spp	4	3
Other anaerobes	6	6
Gram-positive aerobic cocci		
Enterococcus (not speciated)	5	3
Enterococcus faecalis	4	3
Enterococcus faecium	2	1
Staphylococcus aureus	1	1
Other Staphylococcus spp	2	2
Streptococcus spp	6	7
Viridans group Streptococcus	2	3

Discussion

Outcome interpretation in clinical trials

Specifically, this study examined the safety and therapeutic effectiveness of a specific carbapenem antibiotic against gram-positive and gram-negative bacteria commonly implicated in complicated intra-abdominal infections (7,8). In a study that compared ertapenem administered once daily at a dose of 1 g to piperacillin/tazobactam given every six hours, ertapenem showed comparable results. Microbiologically evaluable patients were found to be equivalent in the primary analysis population, and the same finding was consistent with a modified intention-to-treat population analysis and multiple predefined and exploratory subgroup analyses (9). In summary, these data demonstrate the efficacy of once-daily ertapenem in comparison to a more frequently administered comparator.

Infection of the gastrointestinal tract with severe antibiotics: ertapenem role

Several considerations should be addressed when assessing an antimicrobial agent for intra-abdominal infection treatment. A reliable anti-microbial agent must first demonstrate its ability to inhibit polymicrobial flora typical of these infections (10,11). The agent must also be specifically defined for the patient populations where it is safe, effective, and appropriate.

In vivo studies of broad-spectrum antibiotics have long been conducted with patients with perforated or abscessed appendicitis (12). A common cause of this disease is severe comorbidity and a low mortality risk, which reduce confounding factors. Furthermore, anatomic pathology is

relatively uniform, and source control is generally carried out with standardized surgical techniques (13). Antimicrobial activity, rather than surgical management, can be attributed to observed differences in outcomes primarily as a result of these factors. In the past, this model has been effective at detecting meaningful differences between treatment regimens (14). Appendix infections, however, are not fully representative of the wide range of anatomic complexity and physiological compromise associated with other intra-abdominal infections. The severity of illness scores associated with nonappendiceal infections tend to be higher and the source control more variable than those associated with appendiceal infections. Consequently, both appendiceal and nonappendiceal infections provide complementary insights into the effectiveness and safety of antimicrobials. Approximately half of the patients in this study presented with appendicitis, while the remainder presented with a range of other intraabdominal issues. Other recent studies have also reported similar infection types and severity scores. The number of patients with extremely severe illness severity scores was too small to allow robust statistical comparisons, but response rates between treatment groups were similar. Consequently, ertapenem's effectiveness in more severe disease states was examined in additional subgroup analyses. There was a greater response rate with ertapenem among patients with non-appendiceal infections than with the comparator regimen in this group of patients. Likewise, ertapenem was effective against generalized peritonitis, traditionally associated with poor outcomes. With ertapenem therapy, patients suffering from postoperative intra-abdominal infections, an increased risk of treatment failure, also showed numerically better outcomes. While these findings were not powered by conclusive statistical analysis, they demonstrate ertapenem's broad clinical utility in complex disease conditions. Among the most important observations from this study is that ertapenem performs well when used for infections caused by enterococci. Although ertapenem has limited in vitro activity against some enterococcal species, patient outcomes after infections caused by enterococcus can be comparable to, and even superior to, those caused by piperacillin/tazobactam. A significant finding given the fact that enterococcal isolation is often associated with more difficult-to-treat infections. In polymicrobial infections of the abdomen, ertapenem's effectiveness is reinforced by consistently positive results across these subsets. The results of this study also provide insights into how future trials should be designed. Those who had prior treatment failure or postoperative infection are a small but clinically significant group with a high likelihood of adverse outcomes (15). This might ensure a balanced allocation of treatments and enhance results interpretability if randomization is stratified according to these factors. Using per-pathogen analysis, it may not be necessary to treat non-bacteremic polymicrobial intraabdominal infections specifically with enterococci. It is important to emphasize that adjunctive agents, such as vancomycin, were permitted, however, their use was infrequent and did not mask the failures of treatment; in fact, patients receiving such additional therapy had a lower rate of response to the treatment. Pseudomonas aeruginosa was rarely isolated, even so targeted therapy might be considered for infections caused by it.

Controlling sources effectively is essential

Complex intra-abdominal infections are effectively managed by controlling the infectious source at the earliest possible opportunity. Inflammatory or necrotic tissue should be managed according to established principles, including drainage of purulent collections, repairs or resections of gastrointestinal perforations, and management of purulent collections. Surgery continues to be debated, especially in regard to debridement and potential outcomes of percutaneous interventions due to excessive inflammation. Source control is one of the most important confounding variables in clinical trials evaluating antimicrobial efficacy. In the event of unevenly distributed treatments, even a small number of inadequately treated cases can have significant effects on outcome. Blinded expert panels were used to systematically assess the effectiveness of initial interventions in order to address this concern. The retrospective study of this study identified a limited number of patients who lacked sufficient source control as well as occult failures in a small number of cases.

Without this expert assessment, it is likely that the study's overall conclusions would have remained unchanged, but was reassuring to know that the findings were valid. Based on this study's findings, it is now more likely that observed outcomes reflect actual antimicrobial effectiveness rather than variations in surgical management as the cause of observed outcomes.

Conclusion

As demonstrated in this randomized, double-blind study, once-daily ertapenem can be a beneficial treatment option for complicated intraabdominal infections, regardless of whether the infection is treated surgically or percutaneously. Clinically and microbiologically evaluable populations responded similarly to ertapenem applied on a more frequent schedule over piperacillin/tazobactam. Overall results are consistent across multiple analysis populations and predefined subgroups, indicating their reliability. The baseline characteristics of the treatment groups were balanced in terms of demographics, clinical measurement, surgical procedure, and microbiology, offering a meaningful comparison between the two groups. A polymicrobial nature of complicated intra-abdominal infections was evident, with gram-negative bacilli and anaerobic organisms predominating, especially Escherichia coli and Bacteroides species. Although ertapenem demonstrated limited in vitro antimicrobial activity against some organisms, it performed satisfactorily in clinical trials against enterococci and gram-positive cocci, thereby supporting its usefulness as a monotherapy against these infections. It was found that ertapenem was as effective as a comparator regimen in patients with severe disease manifestations such as generalized peritonitis, infections other than appendiceal sources, and postoperative intraabdominal infections. There is limited conclusive evidence regarding the efficacy of ertapenem in these higher-risk subgroups due to relatively small sample sizes, but consistent trends have shown that it maintains efficacy under many different clinical situations, regardless of the sample size. In the study, adequate source control was highlighted as one of the most important factors determining treatment success. By utilizing a blinded expert panel to evaluate the appropriateness of initial interventions, the findings could be assessed with greater validity. According to this approach, clinical outcomes are primarily driven by antimicrobial effectiveness and not procedural variability. Ertapenem is an effective once-daily alternative for treating complicated intraabdominal infections compared to a multidose broad-spectrum regimen. A unique combination of its demonstrated efficacy, favorable dosing profile, and broad antimicrobial coverage makes it a valuable choice when source control is achieved for appropriately selected patients.

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