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A Randomized Prospective Study of Cefepime Plus Metronidazole with Imipenem-Cilastatin in the Treatment of Intra-abdominal Infections

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Abstract

Background: Presumptive antimicrobial therapy is an important aspect of the management of intra-abdominal infections. Together with surgery, antimicrobial combinations are still widely used to achieve the required spectrum of activity. The aim of this study was to evaluate the efficacy of parenteral cefepime + metronidazole vs imipenem-cilastatin for the treatment of intra-abdominal infections in adult patients.

Methods: Patients with a clinically confirmed diagnosis of intra-abdominal infection were randomized to one of two treatment regimens: cefepime 2 g iv/12 h plus metronidazole 500 mg/8 h or imipenem-cilastatin 500 mg iv/6 h. The primary measure of clinical response was the decline of pre-treatment signs and symptoms of infection. The duration of follow-up was 30 days. Treatment failure was defined as either a lack of improvement or a worsening of pre-treatment signs and symptoms of infection. Surgical management of the infection was determined by the surgeon-in-charge.

Results: Of the 122 intended-to-treat patients included in the study, 60 patients (33 men) were randomized to cefepime + metronidazole and 61 (27 men) to imipenem-cilastatin. Cefepime + metronidazole treatment was successful in 52 (87%) patients and imipenem-cilastatin in 44 (72%) patients (p = 0.004). Microbiological eradication was established in similar proportions in both groups (cefepime + metronidazole, 43; imipenem-cilastatin, 38).

Conclusion: Further studies are warranted to confirm the better results with the cefepime + metronidazole regimen for the treatment of intra-abdominal infections.

Infection 2007; 35: 161–166
DOI 10.1007/s15010-007-6237-2

Background

Presumptive antimicrobial therapy is an important aspect of the management of intra-abdominal infections, together with surgery and supportive care. Antimicrobial regimens must be active against *Enterobacteriaceae* and anaerobes (particularly *Bacteroides fragilis*) [1]. While the presence of enterococci may increase the rate of infectious postoperative complications or treatment failure [2], it has been shown that polymicrobial intra-abdominal infections involving *Enterococci* can be successfully treated with surgical drainage and antibiotics that are not active against enterococci [3].

Antimicrobial combinations are still widely used to achieve the required spectrum of activity. Formerly, a combination of clindamycin or metronidazole with an aminoglycoside was considered as a standard therapy for peritonitis [4–6]. However, aminoglyosides are associated with a risk of nephrotoxicity and ototoxicity [7] and, furthermore, resistance of *B. fragilis* to clindamycin has been observed. The availability of carbapenem, broad-spectrum cephalosporins, or fluoroquinolones, with the addition of metronidazole when necessary, has led to the replacement of aminoglycosides, thus resulting in less potential toxicity.

In several trials in patients with peritonitis, carbapenem monotherapy has been reported to be as effective as standard combinations in this setting [8–11]. *Solomkin* et al. [12] reported that imipenem-cilastatin was shown to be even more effective than a combination of clindamycin and tobramycin in patients with secondary peritonitis. Imipenem-cilastatin has been suggested as the treatment of choice for peritonitis with clinical efficacy rates close to 83% [12–14]. The combination of a broad-spectrum cephalosporin plus an anti-anaerobic agent has been shown to be an alternative to imipenem-cilastatin in the treatment of severe intra-abdominal infections in different published series. In the study by *Berne* et al. [15], cefepime + metronidazole was compared to clindamycin-gentamicin in the treatment of patients with peritonitis. Clinical and bacteriological cure rates were higher for the cefepime + metronidazole arm (94%/97%) than for the clindamycin-

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Received: August 31, 2006 • Revision accepted: January 22, 2007

gentamicin arm (77%/88%); satisfactory clinical response rates were 94% and 77%, respectively [15]. A study of the treatment of biliary tract infections requiring surgery showed a satisfactory clinical response rate of 97% in the cefepime + metronidazole arm vs 92% in the gentamicin + mezlocillin arm. Bacteriological eradication rates were 97% and 92%, respectively [16]. Another study of complicated intra-abdominal infections which compared cefepime + metronidazole with imipenem-cilastatin showed that 88% of patients treated with cefepime + metronidazole were deemed clinically cured vs 76% ($p = 0.02$) of those treated with imipenem-cilastatin [17]. A study with a new carbapenem, ertapenem, compared with a combination of ceftriaxone + metronizadole demonstrated also an equivalent efficacy in the treatment of intra-abdominal infections [18].

This study was conducted to compare the efficacy and safety of cefepime + metronidazole with imipenem-cilastatin for the treatment of patients with intra-abdominal infections and to confirm if the conclusions of the study conducted by *Barie* et al. [17] were still applicable.

Methods

This prospective, randomized, comparative, clinical trial in adult patients with intra-abdominal infections was conducted in a tertiary care university hospital. The study protocol was reviewed and approved by the institutional review committee prior to implementation. All patients provided written informed consent prior to receiving the first dose of the study drug.

Eligible patients were allocated to one of the two regimens according to a random computer-generated list using a random block size of six, which allowed equal numbers of patients in each treatment arm. The antibiotic treatment was initiated after the double-blinded randomization envelope had been opened by an independent study collaborator.

Patients received either cefepime (Maxipime®, Bristol-Myers Squibb, Baar, Switzerland) administered intravenously at a dose of 2 g twice daily over a period of 30 min plus metronidazole (Flagyl®, Aventis-Pharma, Zurich, Switzerland) administered separately at a dose of 500 mg intravenously every 8 h, or imipenem-cilastatin (Tienam®, Merck Sharp Dohme-Chibret, Glattbrugg, Switzerland) administered at a dose of 500 mg/500 mg intravenously every 6 h over a period of 30 min. All drugs were dose-adjusted for patients with impaired renal function.

The minimal duration of treatment with the study drug was 5 days (10 doses of cefepime + metronidazole or 20 doses of imipenem–cilastatin for patients whose dosage had not been adjusted for renal impairment). The recommended duration of therapy was between 7 and 15 days and depended upon the physician's assessment of the severity of infection and the clinical response. The duration of follow-up of all patients was 30 days.

Adult patients (≥ 18 years of age) presenting with a clinically diagnosed intra-abdominal infection were eligible for enrolment. The diagnosis was confirmed by surgery and in the cases where surgery was not performed, a computed tomography (CT) scan was performed to confirm the diagnosis (e.g. diverticulitis). Patients with sigmoid diverticulitis presented the following signs and symptoms: muscle guarding; rebound tenderness localized to the left iliac fossa or left flank, white blood cells > 10 g/l or white blood cells < 4 g/l; and fever ≥ 38 °C. The diagnosis of intra-abdominal infection involved all patients with localized or generalized peritonitis. Randomization was performed intra-operatively after confirmation of a diagnosis of peritonitis by the surgeon and specimens obtained for bacteriological cultures during the surgical procedure. In some situations where surgical intervention had to be deferred for more than 1 h, some patients were randomized pre-operatively if presenting with clinical signs and symptoms of peritonitis.

Exclusion criteria were pregnant or lactating women; expected survival of less than 48 h; known allergy to study drugs; positive HIV test; concomitant infection other than intra-abdominal; infection with microorganisms known to be resistant to the study drugs; patients already treated with an antibiotic dose for more than 24 h for the same condition within 7 days prior to study entry; and serum transaminases, alkaline phosphatase and bilirubin greater than or equal to three times the upper normal limit. The use of concomitant systemic antimicrobials in addition to the study drugs was not permitted.

Clinical and Bacteriological Assessment

Clinical response at the test-of-cure visit was defined as cured when local and systemic clinical signs and symptoms of infection that were present during the treatment period had resolved or sufficiently improved so that no additional surgical procedures or additional or alternative antimicrobial therapy were required. Non-responders were defined as patients who fulfilled the following conditions: relapse or failure to respond.

Failure occurred under any of the following conditions: insufficient resolution of a majority of clinical signs and symptoms of acute infection; worsening of one or more clinical signs and symptoms of infection; requiring alternative antimicrobial therapy or an additional surgical procedure. Treatment response was assessed by an independent surgeon and infectious diseases specialist.

Bacteriological response was based on the results of the appropriate cultures when available. At the test-of-cure visit, bacteriological outcomes were categorized as eradication: absence of baseline pathogen on culture; presumed eradication: absence of evaluable culture in a patient with clinical cure (absence of signs and symptoms of infection); failure: presence of baseline pathogen in a patient with no clinical response.

All cultures were from intra-abdominal samples. Conventional bacteriological cultures were performed according to recommended procedures [19] and the antimicrobial susceptibility of bacteria was determined according to the most recently available National Committee for Clinical Laboratory Standards (NCCLS) [20].

Time of eradication was considered after the patient had received at least 5 days of study treatment. Then, the physician considered that the patient was cured in the absence of signs and symptoms of infection and if cultures were available and showed the absence of pathogens.

Safety and Tolerability

Patients were evaluated by physical examination and standard serial renal, hepatic, and hematologic laboratory tests. Adverse events occurring during post-therapy and serious adverse events and deaths (30 days) occurring before the test-of-cure visit period were recorded. Adverse event relationship to the study drug was categorized by the investigator and ranked as "probable", "possible", "unlikely", or "none". Serious adverse events included a

life-threatening situation, death, a temporary or permanent disability, or a need for prolonged hospitalization.

Statistical Methods

All statistical analyses were done using SPSS v11.5 (SPSS Inc., Chicago). All tests were based on a significance level of $\alpha = 0.05$. For continuous variables, the independent sample t-test was used where the statistical assumptions for such tests were not violated. Otherwise, the non-parametric Mann-Whitney tests were applied. For the categorical variables, Fisher's exact test was used.

The primary efficacy analysis (clinical and bacterial responses) at test-of-cure was based on a non-inferiority test [21] with the non-inferiority margin delta set to $\delta = 0.1$ (10%). If for the non-inferiority test the null hypothesis (H_0: $A - B \leq -\delta$) was rejected, a step-down superiority test for the null hypothesis, H_0: $A - B = 0$, was subsequently added. A logistic regression model was used to investigate the association of prognostic factors with the likelihood of response. A stepwise forward selection method was applied to retain the most contributing prognostic factors using as selection criteria at $p < 0.05$.

Results

A total of 122 patients were enrolled in the study with 61 allocated to each treatment arm; one patient in the cefepime + metronidazole arm was excluded due to a protocol violation. The intention-to-treat (ITT) population consisted of 60 patients in the cefepime + metronidazole group and 61 patients in the imipenem-cilastatin group.

Treatment groups were comparable with respect to age distribution, gender and comorbidities (Table 1). All patients presented with abdominal pain and tenderness at study entry, and the majority also had abdominal guarding and nausea. An inflammatory process was present in all patients in each group consisting primarily of bowel perforation, appendicitis, inflammatory bowel disease, colonic-diverticulitis, or ulcer disease. The distribution of all surgical infections (infections requiring surgery in addition to the antibiotic treatment, n = 84) and no surgical infections (without surgical procedure, n = 37) were similar in both study groups.

Vital signs, mean APACHE II score, hematology and serum chemistries at study entry and pre-treatment were comparable between the two groups. In each group, 63% of the patients received a single pre-operative dose within 24 h prior to study entry. Sixty-nine percent of the microbial isolates were aerobic organisms and 54% were gram negative. The distribution of the microorganisms between the two groups is shown in table 2. No infections with microorganisms resistant to the study drugs were observed. However, in a minority of cases of peritonitis, *Enterococcus* spp. was found in the microbiologic cultures. These organisms have not been clinically interpreted as the responsible pathogens since there was no case involving secondary or tertiary peritonitis and cure was finally achieved without anti-enterococcal medication. Only two patients had positive blood cultures (blood cultures were performed in all patients), but 10% of patients presented signs compatible with Systemic Inflammatory Response Syndrome (SIRS) [22].

The mean duration of antibiotic treatment was 8 days (range 5–15 days) in the cefepime + metronidazole group and 9 days in the imipenem-cilastatin group (standard deviation 2.83 vs 2.67, respectively; p = 0.28; 95% CI 1.517–0.445). The maximum duration of therapy was 15 days in both treatment arms.

Table 1
Patients' demographic characteristics.

	Cefepime + metronidazole	Imipenem-cilastatin
Patients (n)	60	61
Age, y (SD)	63 (18)	57 (16)
Gender		
Male, n (%)	33 (45)	27 (45)
Female, n (%)	27 (44)	34 (56)
APACHE II score (SD)	6.15 (4.13)	5.48 (2.9)
Body mass index (kg/m²)	37.97	35.94
Comorbidities, n (%)		
Gastrointestinal	38 (64)	31 (51)
Cardiovascular	32 (53)	30 (49)
Endocrinology	13 (22)	15 (25)
Neurology	9 (15)	3 (5)
Urogenital disorder	8 (13)	15 (25)
Pulmonary	7 (12)	10 (17)
Hematological disorder	6 (10)	3 (5)
Skin	3 (5)	4 (7)
Hepatic	1 (2)	3 (5)
Laboratory results		
White blood cells, G/l (range)	11.8 (3.9–29.8)	13.0 (4.8–22.8)
Platelets, G/l (range)	250 (57–554)	252 (22–512)
Creatinine, µmol/l (range)	91 (51–401)	85 (8–178)
Clinical findings at day 1		
Fever, °C (range)	37.4 (35.7–39.1)	37.3 (35.4–39.0)
Pulse rate, /min (range)	86 (60–140)	85 (50–130)
Arterial blood pressure, mmHg	130/78	133/76
Respiratory rate, /m (range)	20 (12–36)	22 (12–48)

All results for age, APACHE II score, laboratory results, hematological and blood chemistry values show no significant difference between the two treatment groups (tested with Mann-Whitney tests, t-test, or Fisher's exact tests)
n = number; SD = standard deviation

Table 2
Type of infection and microbiology.

	Cefepime + metronidazole	Imipenem-cilastatin
Type of infection (%)		
Diffuse peritonitis	21 (52)	23 (54)
Diverticulitis	12 (31)	12 (29)
Appendicitis	5 (12)	5 (13)
Perforated ulcer	1 (2)	1 (1)
Cholecystitis	2 (3)	2 (3)
Microbiology (%)		
Bacteroides fragilis	10 (24)	15 (25)
Escherichia coli	7 (17)	23 (37)
Pseudomonas aeruginosa	6 (14)	4 (6)
Streptococcus alpha hemolyticus	4 (10)	4 (6)
Enterococcus spp.	3 (7)	4 (6)
Bacteroides stercoris	2 (3)	–
Bacteroides uniformis	2 (3)	–
Proteus mirabilis	2 (3)	–
Propionibacterium spp.	2 (3)	4 (6)
Streptococcus spp.	2 (3)	

All operated patients had positive cultures (one or more microorganisms)

Among the study population, clinical cure was obtained in 87% of the cefepime + metronidazole group and 73% of the imipenem-cilastatin group (non-inferiority test $\delta = -0.1$, $p < 0.001$; 95% CI 0.066–0.2913). A subsequent step-down superiority test resulted in a significant difference for the treatments ($p = 0.004$). The primary reason for treatment failure was worsening of symptoms or the appearance of new symptoms associated with the original infection. Of these, eight cases occurred in the cefepime + metronidazole arm vs 16 in the imipenem-cilastatin arm. In the latter group, one case was an early death and one case was an inadequate clinical diagnosis. Analysis revealed a similar APACHE II score in both groups and it was not considered as a significant independent predictor of treatment failure. A logistic regression model was used to investigate the association of prognostic factors with the likelihood of the response. The stepwise method applied to retain the most contributing factors showed a significant difference in the final model ($p = 0.004$, Chi-square = 15.181). Treatment was a significant parameter (odds ratio (OR) = 4.79 and 95% CI for OR, 1.51–15.22). In addition, dichotomized APACHE II scores [14] (< 3 and ≥ 3) and the peak body temperature were found to be valuable prediction factors (APACHE II scores: $p = 0.041$, OR 0.267; 95% CI 0.077–0.922; peak body temperature: $p = 0.047$, OR 0.994; 95% CI 0.262–1.010). An APACHE II score equal or higher than 3 changed the odds for becoming a responder by a factor of 0.267; thus indicating that a patient with an APACHE II score less than 3 is more likely to become a responder.

Bacteriological eradication rates were 71.6% for the cefepime + metronidazole arm and 62.3% in the imipenem-cilastatin arm (non-inferiority test, $\delta = 0.01$, $p = 0.032$; 95% CI –0.0827–0.1955). The mean time to eradication was 9 days in both study groups. Susceptibility profiles of the aerobic bacteria isolated from patients in each treatment group were similar; no *in vitro* resistance to either cefepime or imipenem-cilastatin was observed, and susceptibility profiles for anaerobic bacteria were sensitive to metronidazole. These susceptibility results are in accordance with the microbiologic epidemiologic data in the institution. Less than 2% of patients presented a surgical wound infection at the end of the study which is in accordance with the low rate (< 2%) of wound infections observed in our institution.

Both drug regimens were well tolerated. Safety data are described for cefepime + metronidazole and for imipenem-cilastatin (Table 3) A total of 29 patients had at least one adverse event; 15 in the cefepime + metronidazole arm and 14 in the imipenem-cilastatin arm. As shown in table 3, no significant difference was noted between the treatment groups with regard to adverse events (Fischer's exact test: $p = 0.834$). Among the most frequent adverse events were metabolic and nutritional disorders, gastrointestinal system disorders, and liver and biliary disorders (Table 4). In all cases, the adverse event was not interpreted as being a side-effect directly related to the study medication. One patient died at the 30-day follow-up period in each study group. The deaths were not related to the study drugs adverse events but to the patients' underlying diseases (1 cardiovascular and 1 respiratory disease).

Discussion

This study focused on intra-abdominal infections for which an operative procedure or a systemic antibiotic treatment was required. The demographic profile of the patients was representative of the population at risk for these infections. Randomization resulted in comparable distribution of the patients' demographic characteristics, although more men than women were enrolled in the cefepime + metronidazole arm.

In the present study, there was no trend toward more severe illness as evidenced by the APACHE II scores of the two study groups and as observed in other series [23–25]. This may be due to the low APACHE II scores in our study.

Patients with a large variety of abdominal diseases were enrolled. The diagnosis was confirmed by surgery or if surgery was not performed, a CT scan confirmed the diagnosis. Infections originating from the appendix occurred in 12% of all surgical patients. The causal factor was primarily an inflammatory process, but 53% of patients entered the study due to peritonitis for which a surgical procedure was necessary.

Aerobic organisms were isolated in 31% of cases with *Escherichia coli* being the most frequently isolated.

The local epidemiology during the study period showed that *Pseudomonas aeruginosa* had an MIC_{90} of 3.5 mcg/ml

Table 3
Patients with at least one adverse event cross-tabulation.

	Patients with at least one adverse event			Total
	No	Yes	N° of episodes	
Cefepime + metronidazole				
Count	45	15	24	60
Expected count	45.6	14.4	–	60.0
Imipenem-cilastatin				
Count	47	14	20	61
Expected count	46.4	14.6	61.0	61.0
Total				
Count	92	29	44	121
Expected count	92.0	29.0	–	121.0

Table 4
Adverse events experience by patients in both study groups.

Adverse event	Cefepime + metronidazole	Imipenem-cilastatin
Hypokalemia	5	3
Nausea	2	–
Diarrhoea	1	3
Duodenum biliar fistula	1[a]	–
Sigmoiditis	–	2[a]
Abscess	1[a]	2[a]
Liver enzyme increased	3	1[a]
Sepsis	–	2[a]
Herpes infection	–	–
Ascites	–	1[a]
Cardiovascular failure	2[a]	–
Periduodenal haematoma	1[a]	–
Mesenteric thrombosis	–	1
Atelectasia	1[a]	–
Arrhythmia	1[a]	–
Vaginitis	1	–
Colon cancer	–	1[a]
Headache	1	1
Renal insufficiency	2[a]	–

[a] Serious adverse event: one patient could experience more than one adverse event

for cefepime and 3.9 mcg/ml for imipenem and *E. coli* strains had an MIC_{90} of 0.05 mcg/ml for cefepime and 0.1 mcg/ml for imipenem. Similarly, all the strains isolated from the patients in the study had the same sensitivity.

In the present study, the isolation rate for *Enterococci* (6%) was comparable between both groups. The role of *Enterococci* as pathogens in intra-abdominal infections remains a subject of debate [3, 26, 27]. They are unlikely pathogens in healthy patients, but they may be pathogens in elderly patients, the critically ill, those undergoing re-operation for surgical complications, or immuno-compromised patients [26–28].

In patients with intra-abdominal infections, it has been shown that monotherapy with imipenem-cilastatin was as efficacious as a combination of imipenem–cilastatin and netilmicin [8]. This demonstrates that broad-spectrum antibiotics such as carbapenem might be sufficient and that combination with an aminoglycoside does not improve outcome and can be replaced by less toxic monotherapy.

Cefepime + metronidazole provides efficacious two-drug antibiotic therapy for complicated intra-abdominal infection due to its broad spectrum of activity against colonic aerobes, in particular *Enterobacteriaceae* [29], and anaerobic coverage. Cefepime has very good penetration into the abdominal cavity, achieving peritoneal fluid levels above the MIC_{90} for *Enterobacteriaceae* for most dosing intervals [30]. Its safety and efficacy have also been demonstrated in previous studies conducted in patients with moderate to complicated intra-abdominal infections [15–17].

By univariate analysis, the clinical response of the patients treated with cefepime + metronidazole was significantly higher than those treated with imipenem-cilastatin. This difference was unexpected as we had anticipated a similar response rate in both treatment arms. The results from the logistic regression model indicate that the likelihood for being a responder is higher with cefepime + metronidazole treatment than with imipenem-cilastatin. A patient with an APACHE II score less than 3 is more likely to be a responder and the lower the peak body temperature at baseline, the more likely a patient will achieve cure. Bacteriological eradication rates were similar to those reported in other series [14]. The situation in our institution regarding extended spectrum beta-lactamase-producing gram-negative rods is not a problem due to the very low incidence, as is the case for vancomycin-resistant *Enterococci* which is less than 0.5%. Both treatments were well tolerated with similar adverse events in each arm. The differences between the two study arms in the present study are difficult to explain but could be attributed more likely to the antibiotic treatment than to the surgical procedures as all procedures were performed by the same group of surgeons.

In the case of peritonitis, surgery to resolve the problem responsible for the disease remains essential. Under some conditions, such as non-perforated diverticulitis, non-surgical treatment and percutaneous drainage in the cases of abscess have become the gold standard treatment. However, for the cases of diffuse peritonitis, surgery and appropriate antibiotic treatment are crucial to cure the patient.

The present randomized study has limitations for its generalizability as it was conducted in a single center study with a relatively small sample size. However, further studies of antibiotic efficacy in intra-abdominal infection are warranted to confirm our results.

In conclusion, our results show that cefepime + metronidazole continues to be a safe and efficacious therapy with a beneficial trend when compared to imipenem-cilastatin in the treatment of intra-abdominal infections.

Acknowledgements

The study was supported by a grant from Bristol-Myers Squibb AG, Baar, Switzerland. The sponsor had no role in study design, data collection, data analysis, data interpretation, or the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication. – The authors declare that they have no competing interests.

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