A Retrospective Analysis of the Incidence of Clostridium Difficile Associated Diarrhea with Meropenem and Piperacillin-tazobactam

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Abstract

Introduction: Meropenem and piperacillin-tazobactam have similar indications, spectrum of antimicrobial actions, and cost. When selecting between two antibiotics with similar efficacy, one may want the antibiotic with the least harm, such as *C. difficile* associated diarrhea (CDAD).

Aim & Objectives: This study tested the hypothesis that patients on piperacillin-tazobactam had a lower incidence of CDAD than patients on meropenem.

Methods: A retrospective analysis was performed that included patients who received meropenem or piperacillin-tazobactam during their admissions to Ridge Meadows Hospital, Canada from September 2007 to August 2009. This study had a subgroup analysis on patients with risk factors of developing CDAD: male, over 65 years old, staying longer than 28 days in healthcare settings, receiving concurrent risk factor medications, not on *Saccharomyces boulardii* in the previous two months, and not on oral metronidazole, intravenous metronidazole, or oral vancomycin in the previous two months.

Results: There were 168 patients in the meropenem group and 122 patients in the piperacillin-tazobactam group. No significant difference was found between meropenem and piperacillin-tazobactam with respect to incidence of CDAD (3.57% and 4.92%, respectively; p=0.5676), two-month in-hospital mortality (34.52% and 36.89%, respectively; p=0.7102), and composite outcome of CDAD and two-month in-hospital mortality (37.50% and 40.16%, respectively; p=0.7142). All subgroup analyses showed no difference in incidence of CDAD between the two antibiotics.

Conclusions: There was no evidence to support patients on piperacillin-tazobactam had a lower incidence of CDAD or mortality than patients on meropenem. Further research is still needed to help selecting the safest antibiotic for patients.

Keywords: meropenem, piperacillin-tazobactam, *Clostridium difficile*, diarrhea, mortality, *Saccharomyces boulardii*

Introduction

Clostridium difficile is the most clinically relevant bacteria known to cause antibiotic-associated diarrhea and is responsible for 15-25% of cases of antibiotic-associated diarrhea.[1] The incidence of *C. difficile* associated diarrhea (CDAD) in hospitalized patients is approximately 8% and accounts for 20-30% of cases of hospital-acquired diarrhea.[2]

Meropenem and piperacillin-tazobactam are time-dependent killing, β-lactamase-resistant antibiotics that are active against gram-negative aerobes, gram-positive aerobes, and anaerobic bacteria.[3,4] Both meropenem and piperacillin-tazobactam are indicated for treatment of lower respiratory tract, intra-abdominal, gynecologic, and skin infections.[5,6] Both drugs have similar costs, and review of their respective drug monographs suggests that adverse effect profiles are very similar.[5,6] Because both antibiotics have similar indications and adverse effect profiles, selecting one antibiotic over the other can be difficult. When selecting between two antibiotics with similar efficacy, one may want the antibiotic with the least harm, such as CDAD. Knowing the prevalence of CDAD with meropenem and piperacillin-tazobactam may help health institutions in reducing incidence of antibiotic associated diarrhea.

It has been demonstrated that piperacillin-tazobactam inhibits growth and toxin production of *C. difficile*.[7] In two institutions, CDAD rates increased by 200% or more during a shortage of piperacillin-tazobactam.[8,9] However, piperacillin-tazobactam has also been associated with CDAD. In one institution, the incidence of CDAD decreased by 47% during the same piperacillin-tazobactam shortage period.[10] However, there is currently no information on the prevalence of CDAD in subjects exposed to meropenem.

The present study was designed to test the hypothesis that patients on piperacillin-tazobactam had a lower incidence of CDAD than patients on meropenem. This study also compared the incidence of in-hospital mortality within two months of meropenem or piperacillin-tazobactam use.

Methods

This study was a retrospective analysis of all patients who received meropenem or piperacillin-tazobactam during their admissions to Ridge Meadows Hospital, Canada from September 2007 to August 2009. There was no protocol in place in choosing between the two antibiotics. The data was obtained using the health record software Meditech Version 3.26 (Westwood, Massachusetts, USA) and patients' chart records in the hospital. CDAD was defined as having more than 2 documented unformed or watery stools in 24 hours plus a positive assay for toxin B in a stool sample.[2,11] The episode of CDAD was attributed to the use of meropenem or piperacillin-tazobactam if the *C. difficile* toxin was found during, or within two months of, the antibiotic therapy.

The following patients were excluded from the study: patients under 18 years of age, patients who received both piperacillin-tazobactam and meropenem in a two-month period, patients who developed CDAD in the two months prior to the use of meropenem or piperacillin-tazobactam, and patients with gastrointestinal tract colonization of pathogens also known to cause infectious diarrhea (Figure 1).

The primary outcome of this study was the incidence of CDAD. The secondary outcomes were two-month in-hospital mortality, and composite outcome of CDAD or two-month mortality. This study also looked at a subgroup of patients with risk factors for developing CDAD: male gender[12,13], above 65 years of age at the end of meropenem or piperacillin-tazobactam therapy[14], prolonged (> 28 days) stay in health-care settings in the previous 6 years[15], use of risk factor medications that were given within two months of meropenem or piperacillin-tazobactam (antineoplastic agents[16], tacrolimus[17], histamine 2-receptor antagonists[18], proton pump inhibitors[18], non-steroidal anti-inflammatory drugs[19], and systemic antibiotics except vancomycin and metronidazole), and no exposure to oral *Saccharomyces boulardii,* oral vancomycin, oral metronidazole, or intravenous metronidazole within two months prior to meropenem or piperacillin-tazobactam use.

The incidence of CDAD with piperacillin-tazobactam was predicted to be 7%. This was based on a study that compared incidence of CDAD in patients on piperacillin-tazobactam and cefotaxime (7% vs. 53%).[20] There is no published data on the incidence of CDAD with meropenem. We estimated that the CDAD incidence rate of meropenem was between that of the piperacillin-tazobactam and cefotaxime (7% vs. 53%). Because meropenem is active against the clinical isolates of *C. difficile*[21], we did not foresee that its incidence of CDAD could be as high as 53%. The incidence of CDAD with meropenem was arbitrarily set at 22%, which was 15% higher than the estimated piperacillin-tazobactam rate (7%). A sample size calculation with dichotomous outcome variables, a two-tailed alpha of 5%, and a beta of 80% was used.[22] A minimum of 86 patients was needed per group to detect a difference of 15% between the two groups.

The two-sided Fisher's exact test was used to compare data from two treatment groups. The criterion of statistical significance was set at $p < 0.05$. Statistical tests were performed using the computer software GraphPad Prism version 4.00 for Windows, (GraphPad Software, San Diego, California USA).

Results

Medical records were reviewed for a total of 333 patients (Figure 1). Thirty-five patients in the meropenem group and 32 patients in the piperacillin-tazobactam group were excluded. There were a total of 168 meropenem-treated patients and 122 piperacillin-tazobactam-treated patients included in the analysis. The sample size was sufficient to detect an effect difference of about 12% between the two groups. The demographic data showed that the piperacillin-tazobactam group had a higher percentage of males than the meropenem group (Figure 2; 61.48% and 47.62%, respectively; $p = 0.0235$).

Table 2 showed no significant difference between meropenem and piperacillin-tazobactam groups with respect to incidence of CDAD (3.57% and 4.92%, respectively; p = 0.5676), two-month in-hospital mortality (34.52% and 36.89%, respectively; p = 0.7102), and composite outcome of CDAD and two-month in-hospital mortality (37.50% and 40.16%, respectively). In each subgroup analysis in Table 3, the piperacillin-tazobactam group had a slightly higher CDAD incidence than the meropenem group. However, the difference did not reach statistical significance.

Discussion

Overall, the present study showed that piperacillin-tazobactam did not have a significantly lower incidence of CDAD than meropenem (Table 2). The results should not warrant the use of one antibiotic over the other to reduce the incidence of CDAD. The two-month in-hospital mortality rate was also not significantly different between the meropenem and piperacillin-tazobactam groups (Table 2). The lack of significance was speculated to be due to a lack of statistical power. The composite outcome of incidence of CDAD or two-month in-hospital mortality was measured to improve the statistical power. The results should not warrant the use of one antibiotic over the other to reduce *C. difficile* related mortality. It is important to note that the severity of diseases could be different between the two antibiotic groups, and thereby offset the difference in mortality rates, though this possibility was not explored in this study.

Factors that increased the risk of developing CDAD included the following: advanced age, prolonged duration of stay in healthcare settings, concurrent risk factor medications, and no previous exposure to oral *S. boulardii,* oral vancomycin, oral metronidazole, or intravenous metronidazole. The demographic data showed no significant difference in the above noted risk factors between the meropenem and piperacillin-tazobactam groups (Table 1). It suggested that the lack of difference of CDAD rates between the two groups was unlikely due to the confounding variables. However, the meropenem group had significantly more male patients than the piperacillin-tazobactam group. Two studies found that male patients were more prone to have CDAD than female patients, although the mechanism is still unclear.[12,13] In contrast, two studies showed female patients were more prone to have CDAD than male patients.[23,24] It is inconclusive therefore, whether gender is a risk factor for CDAD.

In any events, the subgroup analysis showed no significant difference in incidence of CDAD between the meropenem and piperacillin-tazobactam groups in male patients (Table 3). The subgroup analysis also showed no significant difference in incidence of CDAD between the two antibiotics in patients at higher risk of developing CDAD. It suggested that selecting piperacillin-tazobactam over meropenem did not reduce the incidence of CDAD in high-risk patients.

It is interesting to note that the incidence of CDAD in the piperacillin-tazobactam group was lower than the rate reported in the study by Settle *et al* (4.92% and 7%, respectively).[20] Differences in settings, demographics, and study designs might have contributed to the difference in the incidence. It is important to note that the study by Settle *et al.* was conducted in geriatric wards. In the piperacillin-tazobactam group in

the current study, the incidence of CDAD in elderly patients was 6.67% (Table 3), which was comparable to the rate in the study by Settle *et al*.

The present study had its limitations. The first limitation was that there was a relatively small sample size (a total of 290 patients after exclusion), and thus lacked statistical power to detect small differences between the meropenem and piperacillin-tazobactam groups. The absolute difference in incidence of CDAD between the two groups was 1.35% (Table 2), which was much smaller than the estimated difference used in the sample size calculation (15%). It appeared that the current study overestimated the difference between the incidence of CDAD with meropenem and piperacillin-tazobactam. To detect an absolute difference of 1.35%, a sample size of 3500 patients would be needed per group. This would require the patient data in the hospital in the last 40 years. The hospital lacks the available data.

The second limitation was that the present study was performed at a single centre. We had no access to patient medical information prior to admission. Moreover, this study was retrospective, and thus could not eliminate all confounders. For example, it did not screen each patient for all possible pathogens for infectious diarrhea. Nasogastric tube feeding[25], peri-partum (4 weeks before to 4 weeks after delivery)[11], serious underlying illness-comorbidities, immune-compromising conditions, and gastrointestinal surgery and disorders have also been related to development of CDAD.[26] Therefore, the incidence of CDAD in this study might not be exclusively related to meropenem or piperacillin-tazobactam usage alone. Despite that, the objective of this study was to investigate incidence of antibiotic associated diarrhea but not diarrhea caused by antibiotics. Increase in incidence of CDAD might still suggest an indirect relationship with meropenem or piperacillin-tazobactam.

The third limitation was that the present study used *C. difficile* toxin B test and the number of unformed or watery stool to diagnose CDAD. The toxin test was reported to be only 70-80% sensitive.[27] Other published diagnostic methods include positive stool culture for *C. difficile*, positive assay for toxin A in a stool sample, characteristics of *C. difficile* infection on colonic biopsy, and pseudomembranous colitis observed on lower gastrointestinal endoscopy.[27] In addition, certain diets and medications might have caused constipation and masked the number of loose stools per day, which is important for the diagnosis of CDAD. Therefore, the incidence of CDAD observed in the current study could be an underestimate.

Conclusions

Based on the information in the current study, there was not enough evidence to support that piperacillin-tazobactam had a lower incidence of CDAD than meropenem. The study lacked evidence to suggest a significant difference in the incidence of in-hospital mortality. The study also failed to show significant difference in incidence of CDAD between the two antibiotics in high-risk patients. The results should not warrant the use of one antibiotic over another to prevent CDAD. Further research, involving larger sample size and prospective study design, is still needed to help selecting the safest antibiotic for patients. Knowing the prevalence of CDAD can

help health institutions in establishing a protocol in choosing between the two antibiotics.

Using the current incidence rate of CDAD in the meropenem and piperacillin-tazobactam groups (3.57% and 4.92%, respectively), researchers can perform a prospective randomized controlled trial to confirm the results of the current study. A sample size calculation with dichotomous outcome variables, a two-tailed alpha of 5%, and a beta of 80% can be used.[22] A minimum of 3500 patients would be needed per group to detect an effect size difference of 1.35%. In addition, the new trial should be a multi-centred study with a sensitive diagnostic test and exclusion of confounders described above. It is necessary to reduce the incidence of this life-threatening diarrhea, which is a huge financial burden for the healthcare system.

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Authors' Contribution

E.Y.H.Y was the lead researcher in this study, responsible for data collection and analysis and preparation of the manuscript. J.G.G. and E.V.A. are the supervisors in the study, responsible for revision of the study design and editing of the manuscript.

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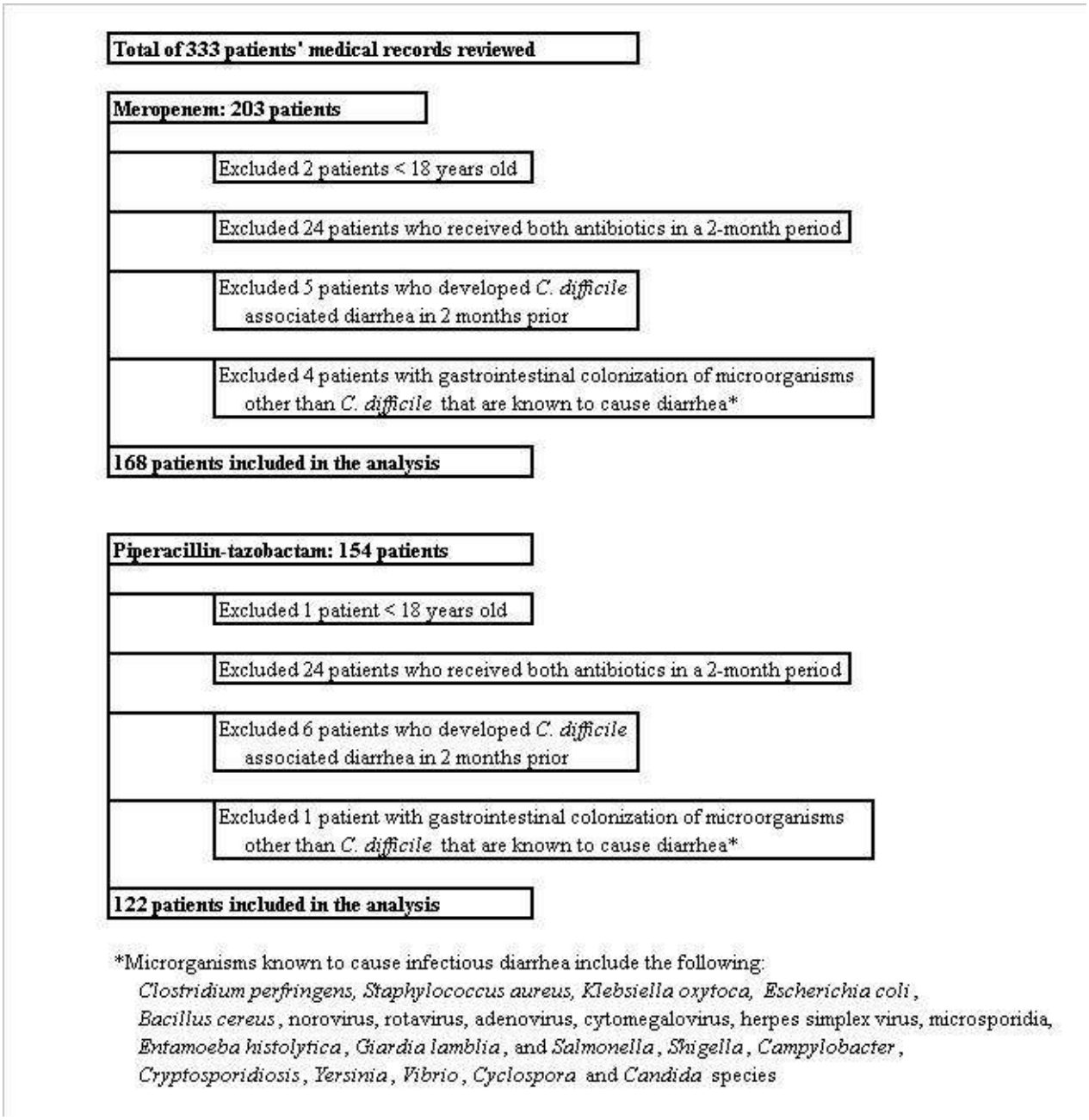

Figure 1. Flow diagram of patient selection.

Table 1. Demographic Characteristics of Patients Treated with Meropenem and Piperacillin-Tazobactam

Characteristic	Number (%) of Patients		*p* value
	Meropenem (*n* = 168)	Piperacillin-tazobactam (*n* = 122)	
Males	80 (47.62)	75 (61.48)	0.0235
Age > 65 years	99 (58.93)	75 (61.48)	0.7162
Stayed > 28 days in health care settings	90 (53.57)	64 (52.46)	0.9053
Had concurrent high risk drugs within 2 months*	163 (97.02)	118 (96.72)	1.0000
Had *Saccharomyces boulardii* in 2 months prior	6 (3.57)	4 (3.28)	1.0000
Had po/iv metronidazole, or po vancomycin in 2 months prior	22 (13.10)	22 (18.03)	0.2515

*High risk drugs: antineoplastic agents, tacrolimus, histamine 2-receptor antagonists, proton pump inhibitors, non-steroidal anti-inflammatory drugs, and systemic antibiotics (except vancomycin and metronidazole)

Table 2. Analysis of *Clostridium difficile* Associated Diarrhea Incidence and Mortality Rates

Outcome	Number (%) of Patients		*p* value	Absolute difference [95% CI]
	Meropenem (*n* = 168)	Piperacillin-tazobactam (*n* = 122)		
Primary				
Had CDAD	6 (3.57)	6 (4.92)	0.5676	1.35% [–3.30% to 6.00%]
Secondary				
Died within 2 months in hospital	58 (34.52)	45 (36.89)	0.7102	2.36% [–8.80% to 13.52%]
Had CDAD or died within 2 months in hospital	63 (37.50)	49 (40.16)	0.7142	2.66% [–8.69% to 14.02%]

CDAD = *Clostridium difficile* associated diarrhea
CI = confidence interval

Table 3. Subgroup Analysis of Patients with Risk Factors for *Clostridium difficile* Associated Diarrhea

Subgroups	Number (%) of Patients				*p* value
	Meropenem		Piperacillin-tazobactam		
	n	With CDAD	*n*	With CDAD	
Males	80	2 (2.50%)	75	5 (6.67%)	0.2646
Age > 65 years	99	5 (5.05%)	75	5 (6.67%)	0.7472
Stayed > 28 days in health care settings	90	5 (5.56%)	64	4 (6.25%)	1.0000
Had concurrent high risk drugs within 2 months*	163	6 (3.68%)	118	6 (5.08%)	0.5667
Not on *Saccharomyces boulardii* in 2 months prior	162	5 (3.09%)	118	5 (4.24%)	0.7471
Not on po/iv metronidazole, or po vancomycin in 2 months prior	146	4 (2.74%)	100	6 (6.00%)	0.3242

*High risk drugs: antineoplastic agents, tacrolimus, histamine 2-receptor antagonists, proton pump inhibitors, non-steroidal anti-inflammatory drugs, and systemtic antibiotics (except metronidazole and vancomycin)
CDAD = *Clostridium difficile* associated diarrhea