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REVIEW ARTICLE

A Review of Clinical Outcomes Associated with Two Meropenem Dosing Strategies

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Abstract Meropenem is a carbapenem antibiotic that
exhibits time-dependent bactericidal activity, traditionally
dosed intravenously at 1 g every 8 h. In order to maximize
its pharmacodynamic activity and reduce costs, an alter-
native regimen employed by many institutions is 500 mg
every 6 h. The objective of this review was to summarize
and evaluate published literature comparing clinical out-
comes associated with these two meropenem dosing regi-
mens. The literature was searched up to October 2016
using the MEDLINE, EMBASE, and Google Scholar
databases. Three retrospective cohort studies were identi-
fied that compared clinical outcomes in general infectious
disease patients (two studies) and patients with febrile
neutropenia (one study). All studies reported no difference
in clinical outcomes (clinical success, time to defeves-
cence, sign or symptom resolution, length of stay, mor-
tality, need for other antibiotics, and seizure rates). One
study reported reduced economic costs with the alternative
dosing. Interpretation of findings was primarily limited by
small sample sizes and generalizability. Based on the data
reviewed, the alternative dosing regimen of meropenem
500 mg intravenously every 6 h could be considered a
therapeutic option. Future studies are needed to confirm the
findings of this review, especially in high-risk populations
such as immunocompromised patients or those with severe
infections.

Key Points

Meropenem dosing of 500 mg every 6 h did not
differ in clinical outcomes with a dosing strategy of
1 g every 8 h.

The alternative dosing strategy may result in
institutional cost savings due to lower drug
acquisition costs.

1 Introduction

Appropriate use of antibiotics is a major target for health
systems worldwide [1]. It is well known that antimicrobial
overuse can contribute to poor patient outcomes, through
promotion of antibiotic resistance, increased adverse
events, and prolonged length of hospital stay [2]. These
considerations can be detrimental to patients, as fewer
agents are being developed to combat resistant infections
[3]. Additionally, antibiotic-associated resistance is a major
expenditure for institutions and is resulting in a heavy
global economic burden [4]. The clinical, epidemiological,
and economic burdens of antibiotic overuse must be
addressed to preserve the effectiveness of drug therapy and
sustainability of health systems. Aside from antimicrobial
stewardship, other strategies can be employed to improve

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the use of antibiotics and minimize associated costs. Optimization of dosing strategies, route of administration, and duration of therapy are considerations that can decrease overuse and wastage of targeted agents [5].

Meropenem, a carbapenem antibiotic that exhibits broad-spectrum activity, is an agent that has sparked clinical controversy regarding the most appropriate dosing strategy [6]. Traditionally, intravenous meropenem is dosed at 1000 mg given every 8 h. Alternative regimens have been studied in pre-clinical and pharmacokinetic studies, in order to determine equivalence through pharmacokinetic and pharmacodynamic perspectives [7]. For meropenem, its bactericidal activity is unrelated to plasma concentrations, but is instead dependent on the percentage of time the plasma concentrations are maintained above the minimum inhibitory concentration of the pathogen ($\%T > MIC$) [8]. Therefore, theoretically, lower doses given at more frequent intervals would optimize its killing activity. More specifically, a dose of 500 mg given every 6 h is purported to demonstrate the same $\%T > MIC$ to the traditional dosing regimen of 1000 mg every 8 h, and therefore is speculated to provide similar clinical effects. Although studies have assessed this alternative dosing strategy through a pharmacokinetic–pharmacodynamic perspective, clinical outcomes and comparison data between these different dosing regimens are lacking [9–11]. However, studies do suggest that this alternative dosing strategy will likely result in adequate pharmacodynamic endpoints to treat most non-severe infections.

Even though previous reviews have attempted to provide a better understanding of meropenem dosing strategies [6, 8], no review has been published that comprehensively compares the two dosing regimens mentioned above from an evidence-based clinical perspective. Therefore, the objective of this review is to evaluate and summarize the published literature comparing the clinical outcomes between administration of intravenous meropenem dosed at 1000 mg every 8 h and 500 mg every 6 h.

2 Methods

A search of MEDLINE (1948–October 2016), EMBASE (1980–October 2016), and Google Scholar was conducted using combinations of the following search terms: "meropenem" or "carbapenem" with "dosage," "pharmacodynamics," and "clinical outcomes." The search was limited to English-language studies in human subjects. Articles were included in the review if they compared traditional (1000 mg every 8 h) dosing with alternative (500 mg every 6 h) dosing. Appropriately adjusted dosing for each regimen was allowed for compromised renal function if patients were analyzed as a whole. Articles were excluded if they were solely in patients with compromised renal function or in those receiving renal replacement therapy, or if no clinical outcomes were described. Clinical outcomes were defined as any outcome measure relating to efficacy or safety of drug therapy, including clinical success, mortality, length of hospital stay, duration of therapy, time to resolution of symptoms, or adverse events. Two investigators independently completed the literature search and assessed articles for inclusion. Discrepancies were resolved through discussion and consensus. Data were extracted as reported from the studies, and no further statistical analyses were performed. The quality of articles was assessed using the Critical Appraisal Skills Programme (CASP) Cohort Study Checklist [12].

3 Results

A total of 1107 articles were identified. Thirty-two articles remained after title and abstract screening. After full-text review, three articles met the inclusion criteria [13–15]. Reasons for exclusion of other articles were lack of reporting of clinical outcomes or composition of study population with all renal insufficient patients. All included studies were retrospective and single-centered, and are summarized in Table 1. Table 2 provides the overall results of each study, and the quality analysis is displayed in Table 3. More detailed study evaluations are provided below.

Arnold et al. [13] conducted a retrospective cohort study to evaluate the use of imipenem-cilastatin 500 mg every 6 h, meropenem 1000 mg every 8 h, and meropenem 500 mg every 6 h in adult febrile neutropenic patients with intolerances to or failure on cefepime after at least 3 days of therapy [13]. Data were collected over a 2-year period (September 1, 2005 to August 31, 2007), and 127 patients were identified that met inclusion criteria (Table 1). Of these patients, 40 received imipenem-cilastatin, 29 received traditional meropenem dosing (1000 mg every 8 h), and 58 received alternative meropenem dosing (500 mg every 6 h). A total of 76% of all patients received concurrent vancomycin, and there was a statistically significant ($p = 0.04$) difference in empiric antifungal use between the imipenem–cilastatin, traditional meropenem, and alternative meropenem groups (40, 76, and 64%, respectively).

Results of this study are presented in Table 2. No differences were found in the primary outcomes of time to defervescence, need for additional antibiotics, or time to addition of first antibiotic. Secondary outcomes were also not significant with regards to duration of treatment, mortality, and seizure activity; all being similar or the same between all groups. The authors concluded that the study

Table 1 Description of studies assessing meropenem dosing regimens of 1 g q8h and 500 mg q6h

Study	Year	Objective	Design	Population	Exclusion	Comparator groups
Arnold et al. [13]	2009	To compare clinical outcomes between neutropenic fever patients treated with imipenem 500 mg q6h, meropenem 1 g q8h, or meropenem 500 mg q6h following failure or intolerance to cefepime	Retrospective, single-center, observational cohort	Adults (>18 years) with hematological malignancy and neutropenic fever failing or intolerant to cefepime therapy; minimum 3 days carbapenem therapy	Received cefepime for <3 days prior to carbapenem initiation or received inappropriate carbapenem dose for renal function for >24 h	Imipenem-cilastatin IV 500 mg q6h Meropenem IV 1 g q8h Meropenem IV 500 mg q6h
Patel et al. [14]	2007	To compare outcomes and cost for the traditional US FDA-approved dosing regimen for meropenem vs. an alternative dosing regimen providing similar pharmacodynamic exposure with a lower total daily dose	Retrospective, single-center, observational cohort	Historical controls: patients receiving meropenem 1 g q8h or q12h between Jan 1 and Sep 30, 2004 Alternative dosing: patients receiving meropenem 500 mg q6h or q8h between Oct 1, 2004 and Sep 30, 2005	Patients <18 years old; pregnancy; neutropenia, meningitis; cystic fibrosis; CrCl <25 mL/min; doses >1 g q8h or <1 g q12h; if alternative patients received >1 dose of 1 g, patients converted to traditional dosing; patients receiving inappropriate dose for renal function >1 day; patients with initial organism resistant to meropenem	Meropenem IV 1 g q8h (CrCl >50 mL/min) or 1 g q12h (CrCl 25–49 mL/min) Meropenem IV 500 mg q6h (CrCl >50 mL/min) or 500 mg q8h (CrCl 25–49 mL/min)
Kotapati et al. [15]	2004	To compare the clinical and economic outcomes of administering meropenem 500 mg q6h vs. 1000 mg q8h	Retrospective, single-center, observational cohort	All patients receiving at least one dose of meropenem (Jan 2002–Dec 2002)	Received more than 1 day of antibiotics previously (unless unresponsive to that therapy); received higher dose than 1000 mg q8h or 500 mg q6h; isolated organism resistant to meropenem at initiation; if CrCl <25 mL/min; previous hospitalization treated with meropenem for same indication	Meropenem IV 1 g q8h Meropenem IV 500 mg q6h

CrCl creatinine clearance, *FDA* Food and Drug Administration, *IV* intravenous, *q6h* every 6 h, *q8h* every 8 h, *q12h* every 12 h

did not provide any evidence that the alternative meropenem dosing strategy resulted in any adverse effects, but safety and efficacy of the regimen could not be confirmed. Limitations included a small sample size, which may have resulted in insufficient power to detect differences in clinical outcomes, a highly specific patient population (use of cefepime prior to carbapenem), and the use of concurrent medications which may have confounded the results. Despite these limitations, this study did not provide any signal or hypothesis-generating data that counter the use of the alternative meropenem dosing strategy in febrile neutropenic patients failing treatment with cefepime.

Patel et al. [14] conducted a retrospective cohort study to determine if an alternative meropenem dosing strategy (500 mg every 6 h) results in similar clinical outcomes to traditional dosing and whether this regimen is associated with any pharmacoeconomic impact [14]. Patient records for traditional dosing were obtained between January 1 and September 30, 2004. Traditional dosing was defined as 1000 mg every 8 or 12 h (if creatinine clearance was 25–49 mL/min). Patient records for alternative dosing were obtained from October 1, 2004 and September 30, 2005, if they received 500 mg every 6 or 8 h (if creatinine clearance was 25–49 mL/min). All infectious indications that required meropenem therapy were included aside from febrile neutropenia and cystic fibrosis. Other exclusion criteria are listed in Table 1. A total of 100 patients met the inclusion criteria for the traditional dosing arm, and 192 patients for the alternative dosing arm. Baseline characteristics were similar between groups, including use of

Table 2 Results of studies assessing meropenem dosing regimens of 1 g every 8 h and 500 mg every 6 h

Study	Outcome	Meropenem 500 mg every 6 h	Meropenem 1 g every 8 h	Significance
Arnold et al. [13]	Median time to defervescence (days)	3 (n = 44)	2 (n = 22)	HR 0.881, 95% CI 0.511–1.519
	Need for additional antibiotics	8/58 patients (13.8%)	5/29 patients (17.2%)	NS
	Median (range) time to addition of first antibiotic (days)	1 (1–6) (n = 58)	2 (1–22) (n = 29)	HR 0.645, 95% CI (0.208–1.998)
	Median (range) duration of treatment (days)	8 (3–35) (n = 58)	8 (3–25) (n = 29)	HR 1.124, 95% CI 0.685–1.845
Patel et al. [14]	In-hospital mortality	11.5% (n = 192)	8% (n = 100)	p = 0.238
	Median (range) meropenem-related length of stay (days)	9 (1–67) (n = 192)	7 (1–44) (n = 100)	p = 0.141
	Median (range) duration of therapy (days)	4 (1–27) (n = 192)	5 (2–22) (n = 100)	p = 0.055
	Success rate	92.1% (n = 192)	90.9% (n = 100)	p = 0.72
Kotapati et al. [15]	Clinical success rate (evaluable patients)	28/36 (78%)	32/39 (82%)	p = 0.862
	Clinical success rate (monotherapy)	24/29 (83%)	17/21 (81%)	p = 1.000
	Microbiological success rate	19/30 (63%)	19/24 (79%)	p = 0.334
	Rate of response (days to normalization of temperature)	3 (n = 36)	3 (n = 39)	p = 0.476
	Rate of response (days to normalization of lymphocyte count)	4 (n = 36)	4.5 (n = 39)	p = 0.927
	Meropenem-related length of stay (days) [IQR]	7 [4.8–13] (n = 45)	7.5 [4–10] (n = 40)	p = 0.891

CI confidence interval, HR hazard ratio, IQR interquartile range, NS non-significant ($p > 0.05$)

Table 3 Quality evaluation of identified studies according to the CASP-UK Cohort Study Checklist [12]

Question	Arnold et al. [13]	Patel et al. [14]	Kotapati et al. [15]
Did the study address a clearly focused issue?	Yes	Yes	Yes
Did the authors use an appropriate method to answer their question?	Yes	Yes	Yes
Was the cohort recruited in an acceptable way?	Yes	Yes	Yes
Was the exposure accurately measured to minimize bias?	Yes	Yes	Yes
Was the outcome accurately measured to minimize bias?	Can't tell	Can't tell	Yes
Have the authors identified all important confounding factors?	Yes	Yes	Yes
Was the follow-up of subjects complete enough?	Yes	Yes	Yes
What are the results of this study?	Table 2	Table 2	Table 2
How precise are the results?	No	Can't tell	Can't tell
Do you believe the results?	Can't tell	Can't tell	Can't tell
Can the results be applied to the local population?	No	Can't tell	Can't tell
Do the results of this study fit with other available evidence?	Yes	Yes	Yes

CASP Critical Appraisal Skills Programme

other concurrent medications and the source of infection. Intra-abdominal and respiratory infections were most commonly reported.

Results are given in Table 2. Clinical outcomes of meropenem-related length of hospital stay, in-hospital mortality, and duration of therapy did not significantly differ between the two arms. Overall clinical success (complete or partial resolution of leukocytosis, temperature, and clinical signs and symptoms of infection) rates were also similar, yet the median time to resolution of infection was shorter in the alternatively dosed patients (n = 156) versus the traditionally dosed ones (n = 87) (1.5 vs. 3 days, $p < 0.0001$, respectively). Pharmacoeconomic analyses demonstrated a decrease in drug acquisition costs with the alternative dosing strategy. Specifically, median cost per patient for the duration of therapy was US$439.05 for traditional dosing and US$234.08 for alternative dosing ($p < 0.0001$). The authors estimated that within the 1 year

of data collection, a saving of approximately US$40,000 occurred for the 192 patients treated. Limitations of the study include the small sample size and the single-centered design. In addition, a high percentage of concomitant antimicrobial therapy was observed in all patients (56% traditional group vs. 66% alternative group). Despite these limitations, this study does not report evidence of harm using the alternative regimen, and the regimen may result in institutional cost savings.

Kotapati et al. [15] completed a retrospective cohort study to assess the clinical and economic outcomes associated with meropenem 1000 mg every 8 h and 500 mg every 6 h [15]. Study characteristics are given in Table 1. Patients were included if they received at least one dose of meropenem between January and December 2002. Patients were grouped according to the same traditional and alternative dosage groups as per Patel et al. [14], and were excluded if they previously received antibiotics, except in the case of antibiotic failure. Patients were included in the pharmacoeconomic analysis if they received 1 full day of meropenem and were considered clinically evaluable if they received at least 3 days. A total of 85 patients (40 traditional dosing and 45 alternative dosing) met the inclusion criteria for the pharmacoeconomic analysis, and 75 (39 traditional dosing and 36 alternative dosing) were clinically evaluable. Baseline characteristics were similar between groups. The most common site of infection was the lung.

Results are presented in Table 2. No difference in clinical outcomes was observed among groups. These included clinical success rate (acute or partial resolution of acute signs and symptoms of infection at end of meropenem therapy or discharge), microbiological success rate, response rate (days to normalization of temperature or lymphocyte count), and length of stay. Pharmacoeconomic analyses favored the alternative dosing regimen. Specifically, drug acquisition costs per patient were lower in the alternative dosing group compared with the traditional dosing group (US$576 vs. US$982, respectively, $p = 0.009$). Acquisition costs plus all costs associated with concomitant antibiotics and treatment of adverse effects per patient were also significantly reduced in the alternative dosing group compared with traditional dosing (US$1035 vs. US$1797, respectively, $p = 0.008$). However, these costs in addition to meropenem-related length of stay costs were not significantly different between both groups (US$19,934 vs. US$16,087, respectively, $p = 0.420$). The authors concluded that the two regimens were similar from a clinical perspective, but the alternative regimen was advantageous from an economic perspective. Limitations included the small sample size (i.e., lack of power to detect differences) and the lack of generalizability of economic data outside of the study center. Despite these limitations,

this study did not provide any evidence of harm and suggested that drug acquisition costs are likely lower with the alternative dosing regimen.

4 Discussion

This paper examined the published literature reporting clinical outcomes associated with two meropenem dosing strategies. Three comparative studies were identified that did not demonstrate any significant differences in clinical outcome between traditional and alternative dosing [13–15]. It was shown, however, that alternative dosing may have economic advantages due to lower drug acquisition costs [14]. Despite identified limitations related to study design, small sample size, and lack of generalizability, the data presented in this review provide insight into an important question facing health institutions worldwide.

The consistent findings among the three studies were that meropenem 500 mg every 6 h did not appear to have any differences in clinical outcomes, as compared to the 1 g every 8 h regimen. Although the small sample sizes likely lacked the power to detect meaningful differences between groups, the similar efficacy can be theoretically supported by meropenem's pharmacokinetic and pharmacodynamic profile [8]. As a time-dependent kill antibiotic, the more frequent dosing interval with the alternate dosing regimen (500 mg every 6 h) would result in the same or higher percentage of time above the MIC as the traditional regime (1 g every 8 h) [9]. Of course, any recommendations to implement alternative dosing must be done cautiously based on the limited evidence, especially for more severe infections.

A potential advantage of the alternative regimen could be the cost savings associated with drug acquisition [14]. Costs of meropenem likely differ worldwide, but the alternative dosing strategy results in a 2-g total daily dose, as compared to 3 g with traditional dosing. This difference of 33% may yield cost savings to health systems, especially in settings with high carbapenem utilization. If clinical outcomes are indeed deemed similar between dosing strategies, institutional switches to the alternative dosing strategy may reduce antimicrobial costs. Any savings, however, must be weighed against indirect costs such as increased workload regarding drug preparation by pharmacy staff and drug administration by nursing staff, and patient quality of life with the receipt of an extra dose per day. It should also be noted that the studies reporting economic outcomes were completed in 2004 and 2007 and drug acquisition costs have likely changed since this time. Therefore, any economic advantage must be studied at the institutional level.

Findings must be interpreted in light of several limitations. The quality analysis identified a few methodological flaws, which should be noted. First, only three studies were identified, and each was limited by the retrospective nature of the study design. However, it is not likely that a prospective study would be conducted to address this particular question, and so this would become the best evidence available. Second, studies were limited by small sample sizes, which likely resulted in decreased power to detect differences between groups. Third, two studies included a broad range of infectious conditions, and thus it is not clear if the results obtained are applicable to a specific population [14, 15]. On the other hand, one study specifically focused on febrile neutropenia patients who were intolerant to or failed on cefepime therapy and therefore lacks generalizability as a whole [13].

Despite the limitations mentioned, conclusions can be drawn from the data obtained. From a clinical perspective, there is no evidence to suggest that an alternative meropenem dosing strategy of 500 mg every 6 h is inferior to traditional dosing of 1 g every 8 h. The alternative strategy could therefore be considered as a potential therapeutic dosing regimen for patients requiring meropenem. Although strong evidence is lacking to support widespread changes to dosing guidelines, it is not likely that well-designed trials will be completed, because of resource limitations. Therefore, those already employing this practice should be encouraged to report long-term outcomes for both efficacy and safety. At the institution level, these clinical outcomes should be studied alongside economic outcomes, in order to determine overall benefits of alternative dosing.

In summary, there are limited data available that support the alternative dosing regimen of meropenem 500 mg intravenously every 6 h. Based on a clinical perspective and on pharmacokinetic/pharmacodynamics principles, this regimen appears to be safe and efficacious. Future studies are needed to confirm the findings of this review, especially in high-risk populations such as immunocompromised patients or those with severe infections.

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