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Extended Infusions of Meropenem for Febrile Neutropenia

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Abstract:

Background: Neutropenic fever is an oncologic emergency that requires quick intervention with anti-pseudomonal beta-lactam antibiotics, such as meropenem. Previous literature suggests that extended infusions of beta-lactam antibiotics may improve clinical outcomes. To date, there are 3 prior studies utilizing an extended infusion beta-lactam in this population; however, there is only one previous study investigating the use of extended infusion meropenem in patients with febrile neutropenia.

Objective: To describe the outcomes of eight patients receiving extended infusions of meropenem for the treatment of febrile neutropenia.

Methods: A retrospective chart review was completed including adult patients admitted to a community teaching hospital who received extended infusions of meropenem for febrile neutropenia.

Results: In this descriptive study, no patients receiving extended infusions of meropenem failed treatment, were readmitted for an infectious issue within 30 days, or endured inpatient mortality. Additionally, all eight patients defervesced within 48 hours, and four patients had a microbiologically documented infection. One patient incurred *Clostridium difficile* on day 2 of meropenem therapy.

Conclusions: Extended infusions of meropenem may be effective in the treatment of febrile neutropenia. Future studies comparing extended infusions to intermittent infusions of meropenem for febrile neutropenia are warranted.

Introduction

Febrile neutropenia is a complication of cancer treatment and requires the use of broad spectrum antibiotics to treat potentially life-threatening infections. Anti-pseudomonal beta-lactam antibiotics such as cefepime, piperacillin/tazobactam, or meropenem are first-line options in the treatment of febrile neutropenia.[1] In general, efficacy for all beta-lactam antibiotics is enhanced when the concentrations of the antibiotics are four to five times greater than the organism's minimum inhibitory concentration (MIC).[2] In order to achieve favorable clinical outcomes, carbapenems (such as meropenem) require the time above the MIC to be at least 30-40% of the dosing interval.[2] Traditionally, meropenem is given every 6 or 8 hours with a standard 30 minute infusion to achieve this time above the MIC outcome; however, a Monte Carlo simulation in critically ill patients with febrile neutropenia with bacteremia suggests that extended infusions of meropenem increase its time above the MIC and thus the probability of target attainment (PTA) indicating extended infusions may have utility in the febrile neutropenia population.[3]

Although this administration method seems like a promising alternative to the current standard, there is little clinical literature to support its use in the high risk setting of febrile neutropenia. Furthermore, the use of extended infusions renders the intravenous line unavailable for other medications, which is particularly problematic in those receiving several intravenous medications. Previously, a prospective study from 2017 in neutropenic patients compared extended and standard infusions of cefepime and found that there were comparable outcomes in regards to defervescence at 72 hours, clinical success, mortality, and length of stay.[4] Of note, this prospective study demonstrated a potential decrease in the time to defervescence. In another retrospective trial of cefepime, patients receiving extended infusions were more likely to defervesce at 24 hours and time to defervescence was decreased by 14 hours compared to standard 30-minute infusions.[5]

Likewise, piperacillin/tazobactam extended infusions demonstrated increased overall response (resolution of fever, sterile blood cultures, resolution of clinical signs and symptoms, and no need for change in antibiotic regimen) on day 4 in patients with febrile neutropenia.[6] In the only published study evaluating extended infusions of meropenem for febrile neutropenia, treatment success after 5 days of meropenem was higher in those receiving the extended infusion.[7] However, this study was limited to patients undergoing hematopoietic stem-cell transplantation or induction chemotherapy for acute myeloid leukemia (AML). Data in the general oncology population with febrile neutropenia is lacking. The purpose of this retrospective, observational study is to describe the outcomes of extended infusion meropenem in patients with febrile neutropenia due to any cause.

Methods

Study patients

The local Institutional Review Board approved this retrospective, single center study. Adult patients admitted to a community teaching hospital with febrile neutropenia (ANC <500 cells and temperature ≥100.5° F) from August 2013 to March 2017 were included in this study if they received extended infusions of meropenem. Patients were excluded if defervescence occurred before meropenem was initiated. Per hospital protocol, patients receiving extended infusions received their first dose of meropenem over 30 minutes and subsequent doses were administered over 3 hours. If a patient incurred more than one

episode of febrile neutropenia during their hospital stay (i.e., became febrile after meeting criteria for defervescence – see 2.2 Data collection below), only the first episode was included in this analysis.

Data collection

Demographic and clinical characteristics collected from the electronic health record for all eligible patients included age, sex, length of stay, serum creatinine, height, weight, documented past medical history, oncology diagnosis, duration of neutropenia, receipt of prior chemotherapy, use of prophylactic antibiotics, presence of documented mucositis, concomitant intravenous vancomycin usage, granulocyte colony stimulating factor (GCSF) administration, defervescence, time to defervescence, readmission within 30 days for an infectious issue, inpatient mortality, microbiologically documented infection, and antibiotic failure. Defervescence was defined as a temperature ≤100.4° F for at least 24 hours. Time to defervescence was defined as time from initiation of meropenem until defervescence. Antibiotic failure was defined as switching to another antibiotic for any reason other than allergy/intolerance or inpatient mortality due to febrile neutropenia. Additionally, Charlson Comorbidity Index Score and optimal renal dosing were determined for each patient. Optimal renal dosing was defined as meropenem 500 mg every 6 hours for a creatinine clearance ≥50 ml/min, meropenem 500 mg every 8 hours for a creatinine clearance between 25 and 49 ml/min, meropenem 500 mg every 12 hours for a creatinine clearance between 10 and 24 ml/min, and meropenem 500 mg every 24 hours for a creatinine clearance ≤10 ml/min or on dialysis. Creatinine clearance was determined using the Cockcroft-Gault equation.

RESULTS

A total of eight patients were included in this descriptive study. Of these eight patients, five were female and three were male. Patient age ranged from 51 to 76 years and creatinine clearance ranged from 40 to 90 mL/min. Additionally, two patients received prophylaxis with ciprofloxacin, two patients received prophylaxis with sulfamethoxazole/trimethoprim, and the other four patients did not receive antibiotic prophylaxis. One patient received suboptimal renal dosing of meropenem. Additional patient characteristics are described in Table 1. Six of the eight patients had an oncologic diagnosis, one patient had myasthenia gravis, and the other patient had a history of kidney transplant and was receiving immunosuppressants. Table 2 encompasses all patient diagnoses and their chemotherapy regimens, if applicable.

No patients failed antibiotics, were readmitted for an infectious issue, or died during their hospital admission. Length of stay ranged from 4 to 53 days and time to defervescence ranged from 4 to 40.5 hours (average 21.6 hours). Four patients had a microbiologically documented infection, one of which incurred bacteremia. No patients experienced any adverse effects requiring meropenem discontinuation. Further patient outcomes and a description of microbiologically documented infections are described in Table 3 and Table 4, respectively.

Table 1: Patient Characteristics

Patient number	1	2	3	4	5	6	7	8
Sex	Male	Female	Female	Female	Male	Female	Female	Male
Age, years	69	51	65	64	72	60	55	76
Weight, kg	85	72	60	105	92	56	87	96
Baseline CrCl, mL/min	58	71	45	81	69	68	90	40
Optimal renal dosing*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
CCS	2	8	2	1	3	2	2	2
Mucositis	No	No	No	No	No	Yes	No	No
Prior prophylactic antibiotic	None	None	None	None	Cipro	SMX/TMP	Cipro	SMX/TMP
Duration of neutropenia, days	5	11	20	6	5	26	2	4
Concomitant Vancomycin	No	Yes	Yes	Yes	No	Yes	Yes	Yes
Concomitant GCSF	No	Yes	Yes	No	No	No	Yes	Yes

Abbreviations: CCS: Charlson Comorbidity Index Score; Cipro: ciprofloxacin; SMX/TMP: sulfamethoxazole/trimethoprim; GCSF: granulocyte colony stimulating factor

*At the time of drug initiation

Table 2: Diagnosis and current treatment

Patient number	Diagnosis	Chemotherapy regimen
1	Breast cancer	Docetaxel + cyclophosphamide
2	Burkitt's lymphoma	Hyper-CVAD+R
3	B-cell ALL	Hyper-CVAD+R+MTX/ARA-C IT
4	Myasthenia gravis	N/A
5	AML	HiDAC
6	AML	7+3
7	Breast cancer	Docetaxel + cyclophosphamide
8	Kidney transplant	N/A

Abbreviations: Hyper-CVAD: cyclophosphamide, mesna, vincristine, doxorubicin, dexamethasone; R: rituximab; MTX+ARA-C: methotrexate and cytarabine; IT: intrathecal; HiDAC: high dose cytarabine; 7+3 7 days of cytarabine and 3 days of idarubicin

Table 3: Patient Outcomes

Patient number	1	2	3	4	5	6	7	8
Length of stay, days	10	53	26	17	11	47	5	4
Readmission for an infectious issue within 30 days	No	No	No	No	No	No	No	No
Inpatient mortality	No	No	No	No	No	No	No	No
Time to defervescence, hours	32	14	40.5	5.5	40	27	9.5	4
Duration of antibiotics, days	2	6	8.3	3	4.3	11	3	2
Antibiotic failure	No	No	No	No	No	No	No	No

Table 4: Microbiologically documented infections

Study number	Organism	Culture site	Resistance
1	*Clostridium difficile*	Stool	Pan-susceptible
2	*Pseudomonas aeruginosa*	Abscess	Pan-susceptible
3	N/A		
4	*Staphylococcus aureus*	Wound	Pan-susceptible
5	N/A		
6	*Streptococcus viridans*	Blood	Pan-susceptible
7	N/A		
8	N/A		

Discussion

Neutropenic fever is an oncologic emergency that requires swift intervention with broad spectrum antibiotics. Meropenem is commonly used for febrile neutropenia, especially as a step up therapy after other antibiotics (e.g. cefepime, piperacillin/tazobactam) have failed or in patients at risk for or with a history of resistant organisms. Previous literature has tried to optimize meropenem dosing based on its pharmacokinetic and pharmacodynamic profile. When compared to meropenem 1000 mg every 8 hours over 30 minutes, meropenem 500 mg every 6 hours over 30 minutes achieved higher PTA for susceptible pathogens in a pharmacokinetic study from 2005.[8] Additionally, meropenem 500 mg every 6 hours administered over 30 minutes produced similar outcomes to meropenem 1000 mg every 8 hours administered over 30 minutes in a study applying population pharmacokinetic and Monte Carlo simulations.[9] A separate Monte Carlo simulation evaluated 1 g of meropenem administered over either 30 minutes or 3 hours.[3] When aiming for a time over the MIC of 40%, the PTA for pathogens with a MIC of 4 was 75.7% with intermittent infusions and 99.2% with extended infusions.[3] When looking at the same outcome for a MIC of 8, the study demonstrated a PTA of 17.8% with intermittent infusions and 78.8% with extended infusions.[3] This increased PTA is especially important for organisms harboring resistance mechanisms, such as *Pseudomonas aeruginosa* and *Acinetobacter spp.*.[3,10,11] The previously mentioned Monte Carlo simulation also demonstrated a marginal increase in PTA with extended infusions of meropenem for both *Pseudomonas aeruginosa* (77.1% v. 79.3%) and *Acinetobacter spp.* (75.8% v. 78%) infections.[3] In the current study, meropenem 500 mg every 6 hours infused over 3 hours was administered to patients with febrile neutropenia.

Beta-lactam antibiotics have previously shown benefit in other patient populations by extending the infusion time over a period of three or four hours compared to a standard 30-minute infusion.[12-16] However, subgroup analyses of carbapenems have not shown benefit in ICU patients or patients with pneumonia.[13-15,17] In a meta-analysis of continuous or extended infusions of carbapenems or piperacillin/tazobactam for pneumonia or infections in ICU patients, carbapenems did not significantly reduce the risk of mortality (RR 0.66, 95% CI 0.34 – 1.30).[13] Additionally, another meta-analysis of continuous or extended infusions of beta-lactam antibiotics in ICU patients indicated extended infusions of carbapenems did not reduce mortality (RR 0.74, 95% CI 0.42 – 1.28) or increase the rate of clinical success (RR 1.16, 95% CI 0.93 – 1.46).[14] In the same fashion, a meta-analysis of patients with nosocomial pneumonia receiving continuous or extended infusions of anti-pseudomonal beta-lactam antibiotics showed no statistical increase in clinical cure (OR 2.01, 95% CI 0.48 – 8.37) or statistical decrease in mortality (OR 0.92, 95% CI 0.57-1.47) when using extended infusions of carbapenems.[15] Moreover, a meta-analysis of randomized controlled trials including any hospitalized patient receiving extended infusions of a beta-lactam antibiotic showed no benefit for extended infusions in either mortality (RR 0.92, 95% CI 0.61 – 1.37) or clinical cure (RR 1.00, 95% CI 0.94 – 1.06).[17] Again, further subgroup analyses found no benefit with extended infusions of carbapenems in regards to mortality (RR 1.08, 95% CI 0.64 – 1.82) or clinical cure (RR 1.00, 95% CI 0.92 – 1.10).[17]

In patients with febrile neutropenia, limited data exists supporting the use of extended infusion beta-lactams or carbapenems. A prospective study of febrile neutropenia compared extended and intermittent infusions of cefepime 2 g every 8 hours and observed no difference in defervescence at 24, 48, or 72 hours or time to defervescence.[4] Only 63% of patients receiving extended infusions of cefepime defervesced at 48 hours and the median time to deferevescence was 19 hours. Of note, this prospective study only included hematologic malignancies and stem cell transplant patients. Additionally, patients were excluded if they met diagnostic criteria for sepsis or had a creatinine clearance <50 mL/min. In a retrospective study of cefepime extended infusions in oncology patients with febrile neutropenia, those receiving extended infusions were more likely to defervesce at 24 hours and time to defervescence was decreased by 14 hours.[5] Upon multivariate analysis, the odds of defervescence at 24 hours were quadrupled with extended infusions. Extended infusion piperacillin/tazobactam was also studied prospectively in patients with febrile neutropenia while undergoing hematopoietic stem cell transplant or induction/consolidation therapy for acute leukemia.[6] In that study, extended infusion piperacillin-tazobactam increased the likelihood of overall response (resolution of fever, sterile blood cultures, resolution of clinical signs and symptoms, and no need for change in antibiotic regimen) (74.4% extended infusion vs. 55.1% standard infusion, $p = 0.044$).

In the only published study of extended infusion meropenem in the setting of febrile neutropenia, patients undergoing hematopoietic stem-cell transplantation or induction chemo-therapy for AML were more likely to achieve treatment success (resolution of fever for ≥ 24 h, resolution or improvement in clinical signs and symptoms of infection, absence of persistent or breakthrough bacteremia, and no additional antibiotics prescribed) at 5 days if they received extended infusions (68.4% extended infusion vs. 40.9% standard infusion, $p<0.001$).[7] In addition, patients receiving extended infusion meropenem had a more prompt defervescence ($p=0.021$). In the current study, extended infusions of meropenem appeared to be effective in all eight patients. All patients defervesced within 48 hours of meropenem administration and the median time to defervescence was 20.5 hours. Additionally, no patients required an escalation in antibiotic therapy, were readmitted for an infectious issue within 30 days of discharge, or passed away during their hospital stay. Although febrile neutropenia most commonly occurs in the leukemic populations, patients in this study had a variety of oncologic diagnoses including AML, ALL, Burkitt's lymphoma, and breast cancer. Furthermore, one patient had myasthenia gravis and another was on chronic immuno-suppression for a past kidney transplant. The variety of diagnoses demonstrates that extended infusions of meropenem may be effective in diverse patient populations who incur febrile neutropenia. Additionally, four patients had a microbiologically documented infection, one of which was *Clostridium difficile* and

occurred while on day 2 of meropenem. No resistance patterns were identified in any of the documented infections. Of note, in the prior study of meropenem extended infusion, 55% of the patients with microbiologically documented infections had meropenem-resistant microorganisms compared to none in the current descriptive study.[7] To the authors' knowledge, this is the first description of meropenem extended infusion in the general population with febrile neutropenia.

Conclusion

Febrile neutropenia has traditionally been treated with intermittent infusions of beta-lactam antibiotics. Due to the potential life-threatening nature of this oncologic complication, it is important to identify effective interventions, including optimal antibiotic administration techniques. In this descriptive study, extended infusions of meropenem appeared to be effective for the treatment of febrile neutropenia, without any instances of antibiotic failure. Further comparative studies with intermittent infusions in this general population of patients with febrile neutropenia are warranted.

References

1. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. *Clin Inf Dis*. 2011;52(4):e56-93. doi:10.1093/cid/cir073.
2. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Inf Dis*. 1998;26:1-10. doi:https://doi.org/10.1086/516284.
3. Jaruratanasirikul S, Limapichat T, Jullangkoon M, Aeinlang N, Ingviya N, Wongpoowarak W. Pharmacodynamics of meropenem in critically ill patients with febrile neutropenia and bacteremia. *Int J Antimicrob Agents*. 2011;(38):231-236. doi:10.1016/j.ijantimicag.2011.04.019.
4. Wrenn RH, Cluck D, Kennedy L, Ohl C, Williamson JC. Extended infusion compared to standard infusion cefepime as empiric treatment of febrile neutropenia. *J Oncol Pharm Pract*. 2017; 0(0)1-6. doi:10.1177/1078155216687151.
5. Przybylski DJ, Reeves DJ. Extended versus intermittent infusions of cefepime for the treatment of febrile neutropenia. *Infect Dis Clin Pract*. 2018;26(3):154-158. doi:10.1097/IPC.0000000000000600.
6. Ram R, Halavy Y, Amit O, et al. Extended versus bolus infusion of broad spectrum β-lactams for febrile neutropenia: an unblinded randomized trial. *Clin Inf Dis*. 2018.67(8):1153-1160. doi:10.1093/cid/ciy258/4956068.
7. Feher C, Rovira M, Soriano A, et al. Effect of meropenem administration in extended infusion on the clinical outcome of febrile neutropenia: a retrospective observational study. *J Antimicrob Chemother*. 2014;69(9):2556-2562. doi:10.1093/jac/dku150.
8. Arianao RE, Nyhlen A, Donnelly JP, Sitar DS, Harding GKM, Zelenitsky SA. Pharmacokinetics and pharmacodynamics of meropenem in febrile neutropenia patients with bacteremia. *Ann Pharmacother*. 2005;39(1):32-38. doi:10.1345/aph.1E271.
9. Lodise TP, Lomaestro BM, Drusano GL; Society of Infectious Diseases Pharmacists. Application of antimicrobial pharmacodynamic concepts into clinical practice: focus on beta-lactam antibiotics: insights from the Society of Infectious Diseases Pharmacists. *Pharmacotherapy*. 2006;26(9):1320-32. doi:10.1592/phco.26.9.1320.
10. Theuretzbacher U. Pharmacokinetic and pharmacodynamic issues for antimicrobial therapy in patients with cancer. *Clin Inf Dis*. 2012;5(12):1785-92. doi:10.1094/cid/cis210.
11. MacGowan A. Revisiting beta-lactams - PK/PD improves dosing of old antibiotics. *Curr Opin Pharmacol*. 2011;11:470-476. doi:10.1016/j.coph.2011.07.006.
12. Yang H, Zhang C, Zhou Q, et. al. Clinical outcomes with alternative dosing strategies for piperacillin/tazobactam: a systematic review and meta-analysis. *PLoS One*. 2015;10(1):e0116769. doi:10.1371/journal.pone.0116769.
13. Falagas ME, Tansarli GS, Ikawa K, Vardakas KZ. Clinical outcomes with extended or continuous versus short-term intravenous infusion of carbapenems and piperacillin/tazobactam: a systematic review and meta-analysis. *Clin Inf Dis*. 2013;56(2):272-82. doi:10.1093/cid/cis857.
14. Teo J, Liew Y, Lee W, Kwa AL. Prolonged infusion versus intermittent boluses of β-lactam antibiotics for treatment of acute infections: a meta-analysis. *Int J Antimicrob Agents*. 2014;43:403-411. doi:10.1016/j.ijantimicag.2014.01.027.
15. Lal A, Jaoude P, El-Solh AA. Prolonged versus intermittent infusion of β-lactams for the treatment of nosocomial pneumonia: a meta-analysis. *Infect Chemother*. 2016;48(2):81-90. doi:10.3947/ic.2016.48.2.81.
16. Bauer KA, West JE, O'Brien JM, Goff DA. Extended-infusion cefepime reduces mortality in patients with Pseudomonas aeruginosa infections. *Antimicrob Agents Chemother*. 2013;57(7):2907-2912. doi:10.1128/AAC02365-12.
17. Tamma PD, Putcha N, Suh YD, Van Arendonk KJ, Rinke ML. Does prolonged β-lactam infusions improve clinical outcomes compared to intermittent infusions? A meta-analysis and systematic review of randomized, controlled trials. *BMC Infect Dis*. 2011;181(11):1-13. doi:10.1186/1471-2334-11-181.