

IRB Proposal : A Retrospective Study of an Alternative Meropenem Dosing Strategy for Treatment of ESBL infections

Research Question

Is meropenem dosed at the revised regimen of 500 mg q6 equally as effective as the traditional dosing of 1 gm q8?

Scientific Abstract

The carbapenem antibiotic meropenem was initially approved by the FDA in 1995 with the dosing regimen of 1 g to be administered every 8 hours. Subsequent studies involving mathematical modeling of pharmacokinetic behavior of this antibiotic proposed a smaller effective dose of 500 mg given every 6 hours, resulting in a lower total daily dose by 1 g. Three previous clinical studies evaluating this revised dosing regimen of meropenem demonstrated similar clinical efficacy.^{1, 2, 3} Two of these studies also specifically evaluated costs associated with the alternative dosing regimen, and found a significant cost reduction due to decreased drug acquisition.^{1, 2} Based on these prior studies, CUMC phased in alternative dosing scheme in 2008. We would like to perform a retrospective study of the clinical efficacy of meropenem dosing in treating documented infections caused by bacteria containing extended spectrum beta-lactamases (ESBLs), for which carbapenems, including meropenem, are the treatment of choice. To our knowledge, no prior studies have specifically compared the two dosing regimens of meropenem in treating ESBL infections. By analyzing clinical outcomes data from patients prior to and following this dosing switch, we hope to improve understanding of optimal treatment of ESBL infections and support the current clinical understanding of optimal meropenem dosing.

Lay Abstract

We will conduct a retrospective clinical outcomes analysis of an alternative dosing scheme of the antibiotic meropenem for treatment of a type of resistant bacterial infection, caused by bacterial containing a special enzyme to inactivate many classes of antibiotics, known as extended-spectrum beta lactamase enzyme (ESBL). We would like to study clinical and microbiological outcomes of patients with documented ESBL infections treated with meropenem at FDA-approved dosing (1 g IV q8h) at CUMC prior to 2008 compared to those in patients treated with the alternative dosing regimen (500 mg IV q6h) implemented after 2008. Studies have shown similar efficacy of meropenem dosing through the traditional and revised dosing regimen, but thus far no study has compared outcomes in this particular type of resistant infection. Along with the benefits of overall lower drug exposure in the patient and decreased overall cost, we suspect that there is a benefit to avoiding high levels of drug exposure in already resistant strains of bacteria. levels of antibiotics, thus the revised dose would be beneficial in this setting. Available clinical and microbiological data will be collected to compare treatment outcomes. All relevant patient information will

be obtained through retrospective chart review.

Study Purpose and Rationale

Initial clinical trials for antibiotics generally standardize administration through a single dose and dosing interval.⁴ Subsequent studies using population models of pharmacokinetics allow insight into the probability that a given antibiotic dosing regimen will obtain a pharmacodynamic target.⁵

The Food and Drug Administration approved meropenem in 1995, with a standard dosing regimen of 1,000 mg administered every 8 hours. Like other beta-lactam antibiotics, the bactericidal activity of meropenem is a function of the amount of time the free or unbound drug exceeds the minimum inhibitory capacity, or fT>MIC. The precise fT>MIC varies amongst beta-lactam antibiotics. Through population pharmacokinetic modeling, it was found that an alternate dosing regimen of meropenem, of 500 mg given every 6 hours, optimized the fT>MIC.⁵ This alternative dosing regimen results in a lower total daily dose by 1 g per patient per day.⁵ Further studies indicated that this revised meropenem dosing is associated with a decrease in total infusion time, decreased adverse effects and a cost savings of \$40,000 a year.⁵

A retrospective review by Kotapati et al. compared meropenem regimens of 500 mg every 6 hours with 1,000 mg every 8 hours and found no significant differences regarding clinical success of the antibiotic (78% versus 82%, respectively, p=0.86) while patients received a significantly lower dose overall (13 g versus 18 g, p=0.012).¹ A similar comparative study by Patel et al. evaluated patient records at a community hospital where meropenem dosing was changed from the standard 1,000 mg every 8 hours to the revised dosing of 500 mg every 6 hours. The authors retrospectively compared 100 patient records predating the switch to 192 patients who received the revised regimen. They found similar clinical success (91% versus 92%, respectively, p=0.72), with an estimated per patient cost savings of \$205 with the new regimen.² By some estimates, this alternative small dose administration of meropenem saves approximately \$38 per patient per day.⁶ Finally, a recent study compared clinical outcomes of patients receiving the alternative meropenem dosing strategy with those of patients receiving imipenem-cilastatin or the traditional meropenem dosage in febrile neutropenic patients. The study concluded that the alternative meropenem dosing strategy yielded similar clinical outcomes in this select group of patients.

Based on the available literature demonstrating similar clinical outcomes and the benefit of significant cost savings, NewYork-Presbyterian, Columbia University Medical Center adopted the revised meropenem dosing strategy to be administered in all infections where meropenem was indicated in late 2008. To date, no studies have specifically evaluated the efficacy of the revised dosing regimen for the treatment of ESBL infections. Infections with ESBL-producing organisms are predominantly nosocomial, and carbapenems, such as meropenem, are considered the treatment of choice.⁷ Through this proposed study, we would like to assess clinical efficacy of treating ESBL infections with the alternative meropenem dosing regimen.

Study Design

A retrospective study of patients who received meropenem for treatment of documented infections due to ESBL-producing bacteria at NewYork-Presbyterian Hospital, Columbia University Medical Center (NYP-C) will be conducted. Once identified, a chart review will be performed for all study subjects, including the following:

- Demographics
- Characteristics at time of infection
- Microbiology/susceptibilities
- Hospital course
- Treatment course
- Labs/vitals

Outcomes Assessment

Outcomes of interest will include:

- Primary
 - Clinical response at end of treatment (EOT) or discharge, whichever came first
 - Success
 - Complete
 - Resolution of leukocytosis, temperature, and clinical signs and symptoms of infection
 - Partial
 - Improvement or stability of leukocytosis, temperature, and clinical signs and symptoms of infection
 - Failure
 - Persistence of signs and symptoms of infection

- Intolerance to meropenem
 - Death
- Indeterminate
 - Patients without leukocytosis, elevated body temperature, or clinical signs and symptoms of infection prior to initiation of meropenem therapy
- Secondary
 - Time to defervescence
 - Need for addition of aminoglycoside therapy
 - Treatment duration
 - Hospital length of stay (LOS)
 - In-hospital mortality
 - Microbiologic response at EOT or discharge, whichever came first
 - Eradication
 - Presumed eradication
 - Persistence

Inclusion criteria

The following patients will be included in this study:

- Age ≥ 18 years
- ESBL-positive organism isolated from urine, blood, sputum, tracheal aspirate, or BAL from September 2007 to September 2009
- Treatment groups
 - Received traditional meropenem dosing regimen (1 g q8h or renally adjusted equivalent)
 - Received alternative meropenem dosing regimen (500 mg q6h or renally adjusted equivalent)
- Received meropenem therapy for at least 3 full days

Exclusion criteria

- Received inappropriate dose of meropenem for renal function for >24 hours
- Suspected or documented meningitis
- Patients who initially received >1 dose of 1 g
- Patients converted from alternative dosing to traditional dosing during hospitalization

Statistical Analysis

This review will encompass patients treated between September 2007 to September 2009. It is estimated that approximately 5% of all *E. coli*, *K. pneumoniae*, and *P. mirabilis* isolates per year are ESBL-positive at NewYork-Presbyterian. In 2009 there were approximately 6100 isolates of *E. coli*, *K. pneumoniae*, and *P. mirabilis*, making about 305 ESBL-positive. We estimate that about 200 patients per year will be eligible for this study based on our inclusion and exclusion criteria, ultimately evaluating approximately 200 patients during in each group during the specified time period.

Based on prior studies, the anticipated success rate of meropenem in treating these infections is approximately 90%. Prior research shows no differences in outcomes between groups treated with the original and revised dosing regimen.¹ In order to design the study to demonstrate non-inferiority between the two groups, we would like to be able to detect a decrease in efficacy from 90% to 80%. Therefore, in order to obtain 80% power in the study, we would need to collect data from 221 subjects within each group. We would be able to obtain this number by studying patients for approximately 1 year before and after the switch. The dates under observation may be expanded slightly in order to obtain the correct number of patients. Primary outcomes will be subsequently analyzed by a chi-squared test. Subsequent control for covariates (for example, age or hospital length of stay) will be done by logistic regression.

Study Drugs or Devices

Not applicable

Study Instruments

Not applicable

Study Subjects

Adult patients hospitalized at NewYork-Presbyterian Hospital between January 2008 - July 2010 with ESBL-positive infections treated with traditional meropenem dosing or alternative meropenem dosing.

Recruitment

Not applicable

Consent Form Waiver/Alteration Request

Please consider for expedited review. A waiver of consent is requested as this protocol will only evaluate existing data. There is minimal risk to subjects. It is impractical to conduct this study without the waiver, as we are reviewing prior data and some patients may be deceased or no longer in contact with this institution.

Informed Consent Process

Not applicable. This is a retrospective chart review.

Confidentiality of Study Data

All patients will be coded to ensure confidentiality. A list of patient name and MRN will be coded to a subject number that will be maintained during the study and destroyed at the end of the study. This will be an electronic file that will be password protected. Subject numbers will then be used with data collected from patient charts. These will be stored on paper and kept in a locked-file cabinet in a locked office for only study personnel to access. Study data will only be made available to study investigators.

Privacy Protections

Not applicable.

Potential Risks

None as this is a retrospective review.

Data and Safety Monitoring

Not applicable

Potential Benefits

Potential benefits of this study include identifying optimal meropenem dosing strategies for ESBL-producing organisms. Data from this study may optimize future patient outcomes.

Alternatives

N/A

Research at External Sites

N/A

Columbia as Lead Institution

N/A

References

¹Kotapati S, Nicolau DP, Nightingale CH, Kuti JL. Clinical and economic benefits of a meropenem dosage strategy based on pharmacodynamic concepts. *Am J Health Syst Pharm.* 2004;61:1264-70.

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³Arnold HM, McKinnon PS, Augustin KM, et al. Assessment of an alternative meropenem dosing strategy compared with imipenem-cilastatin or traditional meropenem dosing after cefepime failure or intolerance in adults with neutropenic fever. *Pharmacotherapy* 2009;29:914-23.

⁴Ambrose PG, Bhavnani SM, Rubino CM, Louie A, Gumbo T, Forrest A, Drusano GL. Pharmacokinetics-pharmacodynamics of antimicrobial therapy: it's not just for mice anymore. *Clin Infect Dis.* 2007 Jan 1;44(1):79-86. Epub 2006 Nov 27.

⁵Lodise TP, Lomaestro BM, Drusano GL. Application of antimicrobial pharmacodynamic concepts into clinical practice: focus on beta-lactam antibiotics. *Pharmacotherapy.* 2006 Sep;26(9):1320-32.

⁶Kuti JL, Maglio D, Nightingale CH, Nicolau DP. Economic benefit of a meropenem dosage strategy based on pharmacodynamic concepts. *Am J Health Syst Pharm.* 2003 Mar 15;60(6):565-8.

⁷Paterson DL. Recommendation for treatment of severe infections caused by Enterobacteriaceae producing extended-spectrum beta-lactamases (ESBLs). *Clin Microbiol Infect.* 2000 Sep;6(9):460-3.