Continuous and Prolonged Infusions of Beta Lactams

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Quick Poll...

• How many utilize prolonged or continuous infusion antibiotic regimens at their hospital?

• How many utilize this strategy in ALL patients on select beta lactams? (piperacillin/tazobactam, meropenem, ceftazidime)

Objectives

• Technician Objectives:
  – Explain the rationale for PI/CI of beta lactams
  – List 2 antimicrobials that are not ideal for CI
  – Describe potential downsides of PI/CI of beta lactams

• Pharmacist Objectives:
  – Explain the pharmacokinetic and pharmacodynamics benefits of PI/CI of beta lactams
  – Evaluate clinical literature related to the use of PI/CI
  – Describe clinical situations in which PI/CI of beta lactams may not be ideal

Where to Begin?!

• OVERWHELMING literature
  – Improved “target attainment”?
  – Improved microbiologic clearance?
  – Improved survival?
  – No benefit?
  – Worse clinical outcomes?

• Important disclaimers....

The Fine Print

• Nothing is exact in infectious disease
• BUG vs. DRUG interactions change when you throw in DOUG
• Beta lactam levels not routinely be utilized, so we’re all guessing
• We don’t always have MIC data
• Must combine what we know with our best clinical judgment
  – One size likely does NOT fit all
Outline

- Why even extend beta lactam infusions?
  - Time dependent vs. concentration dependent bacterial killing
- In vitro, simulated patient, and actual patient data
- Most studied beta lactams
- Practical application
  - Special populations

Time-Dependent vs. Concentration-Dependent

- f%T>MIC
  - % of time where free drug concentration exceeds the MIC
  - Minimum inhibitory concentration: minimum amount of drug that inhibits bacterial growth
- Cmax:MIC ratio
  - Ratio of maximum serum concentration to MIC
- AUC₂₄/MIC
  - Total drug exposure in 24 hours that exceeds the MIC

Pharmacodynamics

Examples

- Concentration dependent
  - Fluoroquinolones
  - Daptomycin
  - Aminoglycosides
- Time dependent
  - Metronidazole
  - Linezolid
  - Tetracyclines
  - BETA LACTAMS
    - Penicillins, cephalosporins, carbapenems

Which is Which?

Continuous vs. Intermittent

Mandell, Douglas, and Bennett’s Principles and Practice of Infectious Disease. 7th edition. 2010.
How much time > MIC?

- Depends on the beta lactam
  - Cephalosporins > penicillins > carbapenems
- Generally ~ 50%
  - Some evidence 100% time > MIC may improve clinical and microbiologic outcomes
- Killing maximized at 4-5x MIC

The DALI Study

- DALI= “Defining Antibiotic Levels in ICU patients”
- 248 infected patients, multicenter
  - 16% not achieving 50% fT>MIC → 32% less likely to have positive clinical outcome
    - 7% with prolonged infusion vs. 20% with intermittent
  - 100% fT>MIC associated with improved clinical outcome compared to 50%

Beta Lactams Covered

- Piperacillin-tazobactam
  - Most clinical data
  - “Vitamin Z”
- Carbapenems
  - Meropenem
  - Doripenem
    - Drugs for the bad bugs
- Ceftazidime
  - Early data on continuous infusions
  - Culture directed therapy for Pseudomonas

Achieving Targets in the ICU

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>50% Time &gt; MIC</th>
<th>100% Time &gt; MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperacillin-tazobactam</td>
<td>71.6</td>
<td>91.4</td>
</tr>
<tr>
<td>Meropenem</td>
<td>93.0</td>
<td>93.0</td>
</tr>
<tr>
<td>Doripenem</td>
<td>92.0</td>
<td>93.0</td>
</tr>
</tbody>
</table>

Why Not ALL Beta Lactams?

- Stability too short
  - Ampicillin, ceftaroline
- Not necessary due to long half-life
  - Ertapenem, ceftriaxone
- Other beta lactams given continuously that we won’t cover
  - Cefazolin, penicillin, oxacillin
Piperacillin-tazobactam

- Workhouse Gram negative antimicrobial
  - Standard dosing:
    - 3.375 grams IV every 6 hours OR 4.5 grams IV every 8 hours
    - 4.5 grams IV every 6 hours (nosocomial pneumonia)
    - Infused over 30 minutes
  - Cmax following 4.5 gram dose is ~300 mcg/mL (30% protein bound)
  - Half life ~1 hour

When is Something Pip/Tazo Susceptible?

- Enterobacteriaceae
  - MIC ≤16 mcg/mL
- Pseudomonas aeruginosa
  - MIC ≤16 mcg/mL
  - Previously ≤64 mcg/mL
  - Increased clinical failures for Paeruginosa isolates with MICs 32-64 mcg/mL

What Changes with PI?

- 4.5 grams IV every 8 hours as a 4 hour infusion
  - 13 hospitalized patients
    - 7 ICU
    - Age ~50, weight ~80kg
    - Cmax: 108.2 mcg/mL (+/- 31.7)
    - Cmin: 27.6 mcg/mL (+/- 26.3)
  - PD target attainment (50% FT>MIC) rates
    - 100% at MICs <16 mcg/mL

Do PIs Improve Outcomes?

- Cohort study of 194 patients
- Pip/tazo 3.375 grams every 4 or 6 hours vs. 3.375 grams every 8 hours as a 4 hour infusion
- 14 day mortality significantly lower with PI for patients with APACHE II ≥17
  - 12.2% vs. 31.6% (p<0.04)
- Shorter median hospital LOS in PI arm

Achieving PD Targets

TABLE 1 STEADY STATE MEAN PLASMA CONCENTRATIONS IN ADULTS AFTER 
30-MINUTE INTRAVENOUS INFUSION OF PIPERACILLIN/TAZOBACTAM EVERY 6 
HOURS

<table>
<thead>
<tr>
<th>Piperacillin</th>
<th>Plasma Concentrations** (μg/mL)</th>
<th>AUC** (μg•h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose*</td>
<td>No. of Evaluables</td>
<td>30 min</td>
</tr>
<tr>
<td>2.25 g</td>
<td>8</td>
<td>134 (14)</td>
</tr>
<tr>
<td>3.375 g</td>
<td>6</td>
<td>242 (12)</td>
</tr>
<tr>
<td>4.5 g</td>
<td>8</td>
<td>298 (14)</td>
</tr>
</tbody>
</table>


Infect Dis 2007; 44: 357


Pip/Tazo: CI vs II in Sepsis

- Retrospective cohort study
- 173 propensity score matched pairs
  - 16 grams piperacillin/24 hours
- Similar mortality rates
  - ICU
    - CI vs. II: 23.7% vs. 20.2% (p=0.512)
  - In hospitl
    - CI vs. II: 41.6% vs. 40.5% (p=0.913)


Time for a Pause

- TONS of literature on clinical outcome with pip/tazo prolonged/extended/continuous infusions
- No benefit vs. improved outcomes
  - Is there a difference or not??

Evaluation of Clinical Trials

Figure 4. The summary of the current limitations and fixed associated with the available clinical trials.


Meropenem

- Standard dose= 500 mg- 2 grams every 8 hours
- Peak serum concentration after 30 minute infusion
  - ~25 mcg/mL for 500 mg dose
  - ~50 mcg/mL for 1 gram dose
- Very low protein binding
- Half life ~ 1 hour
- Short stability at room temperature
  - ~4 hours (per manufacturer)
- Post antibiotic effect (PAE) seen


What’s Considered Susceptible?

- Enterobacteriaceae
  - ≤1 mcg/mL
  - Based on a dose of 1 gram every 8 hours
- Pseudomonas aeruginosa
  - ≤2 mcg/mL
  - 1 gram every 8 hours
- 500 mg every 6 hours appears to be similar to 1 gram every 8 hours


Mero PI and CI

- Continuous (4 grams/24 hours)
  - Not so fast... stability issues
  - Higher clinical cure rates than intermittent infusion in Gram-negative VAP (90.5% vs 59.6%, OR 6.44, 95% CI 1.97-21.05, p<0.001)
  - Similar clinical cure with higher microbiologic clearance in septic patients
- Prolonged
  - Typically over 3 hours due to stability
  - Shown to have equal or improved clinical outcomes when compared to intermittent infusions

Mero PI Kinetics

Figure 1. Mean steady-state serum concentration-time profile of meropenem 0.5 g (O) and 2 g (D) administered as a 3-hour infusion.


Practical Uses of Meropenem

- Empiric therapy in patients at high risk of infections with resistant organisms
- Culture-directed therapy
  - MDR pathogens
- Pneumonia, bacteremia, intra-abdominal infections... but what about meningitis?

Meropenem PI for CNS Infections

- Effective in cases of severe Gram negative infections in the CNS
- MICs fairly low in all cases


Ceftazidime

- Anti-Pseudomonal cephalosporin
- Commonly utilized agent for pulmonary exacerbations of cystic fibrosis
- Standard dose= 1-2 grams every 8 hours
  - 8 grams/day has been used in severe Gram negative infections
- Half life ~2 hours in healthy volunteers
- Largely replaced by cefepime in many institutions


Table 1. Average Serum Concentrations of Ceftazidime

<table>
<thead>
<tr>
<th>IV Dose</th>
<th>0.5 hr</th>
<th>1 hr</th>
<th>2 hr</th>
<th>4 hr</th>
<th>8 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 mg</td>
<td>42</td>
<td>25</td>
<td>12</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>1 g</td>
<td>60</td>
<td>39</td>
<td>23</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>2 g</td>
<td>129</td>
<td>75</td>
<td>42</td>
<td>13</td>
<td>5</td>
</tr>
</tbody>
</table>

- What’s susceptible?
  - Enterobacteriaceae
    - ≤4 mcg/mL
    - Based on a dose of 1 gram every 8 hours
  - Pseudomonas aeruginosa
    - ≤8 mcg/mL
    - 1 gram every 6 hours


Ceftazidime: CI vs II

- 12 critically ill patients
- PK/PD analysis
- 7/12 patients achieved target ceftazidime steady state levels with CI
  - *4 patients with sub-therapeutic levels**
  - No clinical outcome data

A Little More Ceftaz Never Hurt Anyone

- 18 critically ill patients randomized to one of two regimens
- 6 grams/24 hours CI vs. 2 grams every 8 hours
- 8/9 patients in CI arm maintained serum levels 4-5x MIC


Clinical Outcomes > PK/PD

- Ceftazidime II vs. CI in ICU patients with VAP
  - II= 2 grams every 12 hours
  - CI= 1 gram load followed by 4 grams CI/24 hours
  - Average MIC= 2 mcg/mL
  - CI associated with greater clinical cure rate
    (OR 12.2, 95% CI 3.47-43.21; p<0.001)


Some Take Home Points... So Far

- Know what you’re treating
- Know you’re patient
- Recognize variations in dosing schemes used in clinical trials/reports of prolonged and continuous infusions

CI/PI in Pediatrics

- Differences in children and adults
  - Larger Vd
  - Increased renal elimination
    - Particularly true in patients with cystic fibrosis
- Similar results to adult studies
  - Improved target attainment with PI/CI
  - Surprisingly poor target attainment with standard doses of many beta lactams
- Loading doses encouraged
- Would not recommend dropping total daily dose

Some Take Home Points... So Far

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- Know you’re patient
- Recognize variations in dosing schemes used in clinical trials/reports of prolonged and continuous infusions

A Point of Caution?

A randomized trial of 7-day doripenem versus 10-day imipenem-cliastatin for ventilator-associated pneumonia

- Doripenem 1 gram every 8 hours as a 4 hour infusion vs. imipenem 1 gram every 8 hours as a 1 hour infusion
- Stopped prematurely- didn’t mean non-inferiority margin
  - Lower clinical cure rate in doripenem arm
  - Higher mortality in patients with VAP due to _P. aeruginosa_ treated with doripenem


Is It Just Dori?

- Before and after study at Barnes Jewish
- Prolonged (3 hour) infusion vs. intermittent infusion
  - Cefepime (51%), meropenem, piperacillin/tazobactam
- NO loading doses given
- No difference in treatment success rates, in hospital mortality, length of stay
  - Longer time to mortality in intermittent infusion group (36 vs. 19 days, p <0.001)
Implementation of Pip/Tazo PI

- 4.5 grams every 8 hours as a 4 hour infusion
- What’s good for the goose may not be good for the gander...
  - Obese patients (>100 kg)
  - Young patients with expected rapid renal elimination
    - Lower than expected levels with CrCl >100 mL/min
  - Critically ill
  - Not currently recommended by cystic fibrosis guidelines

Not All Patients Are Created Equally

- Healthy volunteers are not patients

- Critically ill patients are not regular patients
  - Variations in volumes of distribution
  - Alternations in renal clearance
  - Decreased protein binding
    - More free drug to be cleared

- Children are not small adults


Where I Would Use PI/CI

- Critically ill patients

- Culture-directed therapy for pathogens with elevated MICs

- Patients with rapid renal elimination
  - Be cautious of dropping the total daily dose too much

- First dose should be a load

QUESTIONS? COMMENTS?