Cephalosporins in Obesity

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Disclosure

Conflicts of Interest: None
Sponsorship: None

Objectives

• Discuss the effects of obesity (BMI >30) on cephalosporin pharmacokinetics
• Examine dose regimen options for cephalosporins in obese patients
• Apply these principles to cephalosporin treatment using a patient case
Patient Case

- 19 yo male  GSW to face and abdomen
  - Emergent to OR and intubated on Day 1
  - Admitted to the surgical ICU

- PMH: None
- Wt =175 kg, Ht =185 cm
  - BMI = 51

- Issues weaning off ventilator
- SCr = 1.23 mg/dL, CrCl > 90 ml/min
- CXR = atelectasis, pneumonia
- Cultures obtained: Mini-BAL, blood, urine
- Started on ceftriaxone 2000 mg IV daily

<table>
<thead>
<tr>
<th>Vital or Lab</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>138</td>
<td>133</td>
<td>140</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>38.8</td>
<td>39.0</td>
<td>38.7</td>
</tr>
<tr>
<td>WBC (k/µL)</td>
<td>14.0</td>
<td>15.4</td>
<td>19.0</td>
</tr>
</tbody>
</table>

Cephalosporins

- Beta-lactam antibiotics
  - More stable to beta-lactamase producers than penicillins
  - Broad spectrum of activity

- Semi-synthetic derivatives cephalosporin C
  - Compound produced by fungus Cephalosporium

Pharmacodynamics

- Bind penicillin binding proteins $\rightarrow$ inhibition of peptidoglycan $\rightarrow$ inhibition cell wall synthesis
- Bactericidal
- Time dependent

**Generation** | **Coverage** | **Examples**
--- | --- | ---
**First** | Gram positives (streptococcus/staphylococcus) Gram negatives (Proteus, E. coli, Klebsiella) | Cefazolin, Cephalexin
**Second** | More Gram negative (Haemophilus, Enterobacter, Neisseria) | Cefuroxime, Cefotetan
**Third** | Streptococcus, respiratory gram negatives $\rightarrow$ H. flu, N. meningitidis Pseudomonas (ceftazidime) | Cefdinir, Ceftriaxone
**Fourth** | Extended spectrum $\rightarrow$ more stability to hydrolysis | Cefepime
**Fifth** | MRSA | Ceftaroline

Pharmacokinetics Review

**Distribution:**
- Hydrophilic, Vd <0.3 L/kg, limited adipose solubility
- Penetrate most body fluids/tissues [kidneys, lungs, joints, bone, soft tissues, biliary tract]
- Poor penetration into the CSF (prior to third generation)
- Degree of plasma-protein binding is variable

**Metabolism:** Minimal, specific per agent
**Excretion:** Primarily renal (with exceptions)
Pharmacokinetics in Obesity

Obese = BMI > 30
- ↑ Vd
- ↓ adipose tissue perfusion
- ↑ Cl
- ↑ protein binding
- Leads to lower plasma and serum concentrations
- Morbid Obesity = BMI > 40 - blood and tissue cefazolin concentrations 50% of normal patients


Cefoxitin tissue penetration

- 27 patients, BMI > 30 compared to ≤ 25, undergoing abdominal or pelvic surgery


Patient Case

- 175 kg, BMI = 51
- Ceftriaxone 2000 mg daily enough for sepsis?
  - Life threatening
- Achieve adequate concentrations to stay above MIC?
Dose Regimens Strategies in Obesity

• Increase dose or frequency

• Extended infusions

• Continuous infusions

Increased Dose or Frequency

• Doubling dose or dose adjust according to BSA

• Increase dosing frequency to stay above MIC
  - Patient case – giving ceftriaxone Q12h

• Study compared normal weight vs BMI >46
  - Received a single dose of cefazolin
  - 1g (normal weight), 1g (obese), or 2g (obese)
  - Serum concentrations obese patients received 2-g similar to normal weight group

• AJHP recommends 3g of cefazolin for surgical prophylaxis in patients weighing ≥120 kg


Extended Infusions

• Doubling the dose ↑ time above MIC by one half-life of the drug, ↑ frequency ↑ total daily dose

• Continuous infusions take up vascular access and consider stability of the product

• Prolonging the infusion time (e.g. to 3–4 h) can ↑ time above MIC and ↓ total daily dose

**Extended Infusions**

- Compared extended infusion cefepime vs short on outcomes of adults with bacteremia or pneumonia due to *Pseudomonas aeruginosa*
- Mortality in the standard infusion was 20% vs. 3% extended infusion
- Aim study demonstrated effectiveness at elevated MIC, apply this principle to obese


**Continuous Infusion**

- Potentially ↓ total daily dose
- Slower infusion rate = slower diffusion into the CNS
  - ↓ CNS toxicity including seizures
- Provides more stable serum levels and higher tissue penetration


**Patient Case**

BAL = non-lactose fermenting GNR
Broadened to cefepime 2000 mg Q8h

- Speciation = *Pseudomonas*
  - Pan-sensitive
- Treated for 10 days with Cefepime
- Discharged to LTAC Day 24

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Clinical Pearl

- Pharmacokinetic properties in obese patients
  - ↑ volumes of distribution
  - ↓ adipose tissue perfusion
  - Leads to ↓ tissue and plasma concentrations

- Strategies to overcome issues:
  - Increase dose/frequency
  - Extended infusions
  - Continuous infusions

- No single strategy shown to be best. PK alterations still pertain to PO depending on bioavailability

- Take into consideration patient specific factors and monitor for clinical response

References


Questions?

Additional questions:
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