Pharmacotherapy IV
Phar 6124

Course sequence: ID, Tox, & Oncology
Course Syllabus and Webpage
Sanford Pocket Guides
Infectious Diseases TA’s
  ∗ Isaac Mitropoulos, Pharm. D.
Aminoglycoside Problem Set
Web CT
  ∗ Quizzes
  ∗ Aminoglycoside Pharmacokinetics Exam
Final Exam

Antibiotic Pharmacodynamics
Bedside Applications

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Case

Patient is a 19 year old male:
  ∗ 94% TBSA thermal burn
  ∗ 5 ft. 9 inches tall
  ∗ 78 Kg (LBW 71 Kg)
Vital Signs:
  ∗ BP = 90/50 mmHg
  ∗ HR - 170 per minute
  ∗ T = 100.8 F
Medication:
  ∗ None & NKDA

PHYSICAL EXAM:
  ∗ 94% partial and full thickness burns of head and
    neck, upper and lower extremities
  ∗ Area spared were the genitalia, scalp, left upper chest
HOSPITAL COURSE:
  ∗ Transferred from North Dakota & admitted to
    Region’s Hospital Burn Unit
  ∗ Intubated and hemodynamically stabilized
  ∗ Escharotomies of upper and lower extremities

Cultures

Sputum:
  ∗ S. aureus (MRSA) Oct. 11, 20, 24, & Nov. 12
  ∗ E. cloacae Oct. 11
  ∗ Staph coag neg. Oct 19, 22 and 24
Blood:
  ∗ S. aureus (MRSA) Oct. 11
  ∗ Flavobacterium sp Oct. 11-26

Cultures & Antibiotic Therapy

<table>
<thead>
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<th>0ct8</th>
<th>11</th>
<th>14</th>
<th>17</th>
<th>20</th>
<th>23</th>
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<th>Nov4</th>
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Peterson Williams, Pharm. D.
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**Flavobacterium spp**

- MIC Profile
  - Oct. 11-26
    - Gentamicin MIC = 4-8 mg/L
    - Piperacillin MIC = 8 mg/L

**October 25**

- Ceftazidime and Ciprofloxacin D/C
- Piperacillin 4Gm Q 6 H
- Gentamicin 160 mg Q 8 H
- Sandoglobulin
  - 35 GM IV 10/25
  - 20 GM 10/26
  - 20 GM 10/29

**October 27**

- Blood culture 10/25 &10/26 grew Flavobacterium spp resulted in consult
- D/C current antibiotics & start
  - Gentamicin 440 mg (~6 mg/kg) Q24H
  - Piperacillin Loading dose 3 Gm 2 hours after Gentamicin dose
  - Then Piperacillin continuous infusion at 500 mg/Hr (12 gm per day)
  - Levels
    - Piperacillin level once at steady state
    - Gentamicin pharmacokinetics per protocol

**Continuous Infusion of Piperacillin**

- Approach to continuous infusion
  - Total Daily Dose/24 hrs
  - Ko = Kd * Vd * Cp-ss
    - Assume T1/2 ~ 1 hr
    - Kd ~0.693/hr
    - Assume Vd ~ 0.2L/Kg * 78 Kg = 15.6L
  - Cpss
    - Suggested Cp-SS = 4 to 10 X MIC
    - Flavobacterium MIC for piperacillin = 8 mg/L
    - Desired Cp-SS = 6 x 8 mg/L = 48 mg/L
    - Ko (mg/Hr) = 0.693 /hr * 15.6 L * 48 mg/L = 518.9 mg/Hr

**Continuous Infusion Piperacillin Results**

- Actual piperacillin Cp-ss = 22 mg/L at Ko = 500 mg/hr
  - Our estimate was Cp-ss = 48 mg/L
  - Actual Cp-ss ~3 X MIC not 6 X MIC
- Cl = KoCpss
- Cl = 500 mg/Hr / 22 mg/L = 22.7 L/hr
  - Our estimate for clearance = 10.8 L/hr
  - Actual clearance ~ 2 X greater than estimate
- Ko = Cl x Cpss
- Ko = 22.7 L/hr x 48 mg/L = 1089.6 mg/hr
  - > 24 Gm / Day Piperacillin or ~ 2X current dose

**SDD Pharmacokinetic Studies**

<table>
<thead>
<tr>
<th>Day &amp; Date</th>
<th>Cp-x (mg/L)</th>
<th>T1/2 (hr)</th>
<th>Vd (L/Kg)</th>
<th>Cp-X: MIC</th>
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<tbody>
<tr>
<td>1 Oct. 27</td>
<td>17.2</td>
<td>1.9</td>
<td>0.28</td>
<td>4.3</td>
</tr>
<tr>
<td>2 Oct. 28</td>
<td>14.6</td>
<td>1.7</td>
<td>0.32</td>
<td>3.7</td>
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<tr>
<td>4 Oct. 30</td>
<td>15.7</td>
<td>1.8</td>
<td>0.32</td>
<td>3.9</td>
</tr>
<tr>
<td>5 Oct. 31</td>
<td>14.1</td>
<td>0.9</td>
<td>0.31</td>
<td>3.5</td>
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<td>6 Nov. 1</td>
<td>20.6</td>
<td>1.1</td>
<td>0.22</td>
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<tr>
<td>8 Nov. 3</td>
<td>14.5</td>
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<td>0.33</td>
<td>3.6</td>
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<tr>
<td>30 Nov. 27</td>
<td>20.1</td>
<td>1.5</td>
<td>0.25</td>
<td>5.0</td>
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</table>
Case Summary

- Flavobacterium spp cleared from blood in 24 hr
  - Result of our intervention
    - Was the outcome because of the continuous infusion of piperacillin, the SDD approach with gentamicin, or both?
    - Did the gentamicin strategy contribute at all?
  - Result of combination immunoglobulin &/or previous therapy
- Ultimate outcome patient survived

Therapeutic Goals

ATS HAP/VAP/HCAP Guidelines 2005

- Select most potent class agent
  - Optimize pharmacodynamic outcome parameter by selecting class agent with lowest MIC
    - Example: *P. aeruginosa*: Piperacillin, Cefepime, Imipenem/Meropenem, Tobramycin, & Ciprofloxacin/Levofloxacin
  - Use hospital and ward specific antibiogram data

- Strategy for combination therapy
  - Use antibiotics of different chemical class
  - Use antibiotics with different MOA
  - Use antibiotics with different PD profile
    - Concentration dependent vs independent killers

Therapeutic Goals

- Sequence the antibiotic combination
  - Use concentration dependent agent first
    - Example: Aminoglycoside, fluoroquinolone, etc.
    - Quickly & significantly reduce initial bacterial burden
      - Reduce bacterial burden by > 3 logs of CFU/ml in compromised host
  - Follow with concentration independent agent
    - Example: Beta-lactam
    - Loading dose followed by continuous infusion
    - Suppress emergence of resistance &/or regrowth

Therapeutic Goals

- Optimize the value of the pharmacodynamic (PD) outcome parameter for each agent
  - Most potent class agent for better MIC profile
  - Dose will affect AUC & Cp-max but MIC can double or half PD outcome parameter value
- Example
  - *P. aeruginosa* vs Tobramycin or Gentamicin
    - MIC
      - Gentamicin MIC = 1mg/L vs Tobramycin MIC 0.5mg/L
    - Peak Concentration
      - Gentamicin Cmax 8mg/L vs Tobramycin Cmax 8 mg/L
    - Peak/MIC Ratio
      - Gentamicin = 8 vs Tobramycin = 16
    - Same dose, same peak concentration but peak/MIC ratio doubled

Therapeutic Goals

- Unclear Two vs One Antibiotic But:
  - Infection associated with high morbidity/mortality
  - Increase odds of providing at least 1 effective agent
  - Possible synergy or additive effect
  - Suppress emergence of resistant mutants
  - Suppress release of endotoxin
  - Suppress glycocalyx production
  - Recommended to start with two and then streamline therapy

Case Report

- 53 year old male involved in MVA with multiple head & abdominal injuries. Admitted 12 days ago to SICU placed on respirator 8 days ago
  - Short exposure to several different antibiotics including vancomycin, F/I, imipenem, gentamicin, & ciprofloxacin in different combinations
  - Patient spikes temperature to 103.5 F
  - WBC’s increase to 21,000/mm3 & CXR demonstrates new infiltrate
  - Following culture results are returned from BAL specimen obtained ~24 hours ago
Antibiotic Resistant P. aeruginosa

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>P. aerug #1</th>
<th>P. aerug #2</th>
<th>MIC (mg/L)</th>
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<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>&gt;4</td>
<td>&gt;4</td>
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<tr>
<td>Ceftazidime</td>
<td>&gt;32</td>
<td>32</td>
<td>(≥32)</td>
</tr>
<tr>
<td>Imipenem</td>
<td>16</td>
<td>8</td>
<td>(≥16)</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>&gt;16</td>
<td>&gt;16</td>
<td>(≥16)</td>
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<tr>
<td>Gentamicin</td>
<td>&gt;16</td>
<td>&gt;16</td>
<td>(≥16)</td>
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Role of Pharmacodynamics in Developing Antibiotic Dosing Strategies

Can we reinvent Colistin?

By changing the nature &/or magnitude of colistin exposure can we:

- Maximize antibiotic efficacy?
- Minimize antibiotic induced toxicity?

Colistin

- Colistin identified in 1950 (B. colistinus)
- Polycationic peptide ring of 8-10 amino acids with substituted 2, 4-diamino-butyric (DAB) acid residues
- Fatty acid (FA) side chain attached to peptide ring
  - Colistin A (Polymyxin E1) 6-methyl-octanoic acid
  - Colistin B (Polymyxin E2) 6-methyl-heptanoic acid
- Combination of DAB and fatty acid side chain give colistin amphipathic properties
- MW 1200
- First clinical use 1959
- Colistin methanesulfonate introduced in 1961

Polymyxins

- Mechanism of Action
  - Physiochemical action
    - Interacts with LPS and phospholipids of outer membrane & inhibits the release of endotoxin
    - Cause electrostatic interference of outer membrane
    - DAB replace divalent cation (Ca++ and Mg++) bridges that stabilize LPS
    - Overall effect causes leakage, a dysfunctional outer membrane, and cell death

Efflux Pump

- Outperof Membrane
  - Gated Outer Membrane Protein (OprM, J, N)
  - MFP Linker Protein (MexA, C, E, X)
  - RND Exporter Protein (MexK, D, F, Y)

References

Aeschlimann, JR Pharmacothe, 23:916-924, 2003
Simulated Colistin Parameters

<table>
<thead>
<tr>
<th>Cmax (mg/L)</th>
<th>T½ (Hrs)</th>
<th>AUC</th>
<th>AUC/MIC</th>
<th>Cmax/MIC</th>
<th>T&gt;MIC</th>
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<tr>
<td>6 mg/L IM use</td>
<td>3 hours</td>
<td>26 mg hr/L</td>
<td>208</td>
<td>48</td>
<td>70%</td>
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<tr>
<td>18 mg/L IV use</td>
<td>3 hours</td>
<td>78 mg hr/L</td>
<td>624</td>
<td>144</td>
<td>90%</td>
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Colistin vs P. aeruginosa

Colistin QD Dosing

David Smith 2002

- At Methodist Hospital of Indiana multi-drug resistant *P. aeruginosa* and *A. calcoaceticus* baumanii complex isolates remain rare. However, isolates resistant to conventional agents but susceptible to colistin are encountered……..

- Colistin is dosed as: 5 mg/kg q24hr in patients with creatinine clearance > 60 ml/min.
- q36hr in patients with creatinine clearance 40 - 59 ml/min.
- q48hr in patients with creatinine clearance 20 - 39 ml/min.
- q72 - 96 hr in patients with creatinine clearance < 20 ml/min.
Clinical Case

- 12 yr 50Kg male suffered 68% BSA burn
- Hospitalized for 5 months multiple courses of antibiotic including aminoglycosides
  - Scr = 0.9 mg/dl but no lean body mass
  - Previous nephrotoxic episodes with tobramycin
  - Mismatch between age & Scr with tobramycin T1/2
  - Positive blood & sputum cultures for *P. aeruginosa*
  - Amikacin 16mg/L, gentamicin 8mg/L, tobramycin 8mg/L, imipenem >16mg/L, P/T >128/4mg/L, & Ceftazidime >32mg/L
  - Meropenem R, Ceftazidime >128mg/L(Estrip), & colistin 2mg/L

Started on colistin 5mg/Kg loading dose then 2.5 mg/Kg Q24H & ceftazidime loading dose then 250 mg/Hr continuous infusion

- Attempted informed consent from parents
- Colistin pre < 5mg/L, 25 min post 23 mg/L, 
  & 8 hour post < 5 mg/L
- Ceftazidime Cpss = 32 mg/L
- Patient completed ~2wks therapy, although positive blood culture for VRE no further *P. aeruginosa* isolated from blood
- Patient survived

Bedside Application Summary

- General & individualized pharmacodynamic applications
  - Target attainment may prevent or delay the development of antibiotic resistance
  - Focused application may rescue select patients at risk of failure
    - Patient’s with resistant pathogens
    - Patient’s who are hyperdynamic