Pharmacokinetics and Pharmacodynamics of Antimicrobials in Sepsis

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Objectives
1) Review the goals and terminologies of pharmacotherapy of antimicrobials in sepsis.
2) Describe how altered physiology in sepsis can impact antimicrobial pharmacokinetic (PK) and pharmacodynamic (PD) properties, with an emphasis on augmented renal clearance and renal dysfunction.
3) Characterize PK/PD targets of different antimicrobial classes.
4) Evaluate benefits and limitations of PK/PD strategies used to optimize antimicrobials in sepsis.

Goals of Pharmacotherapy
- Optimize PK/PD
- Adequate concentration at site of infection
- Avoid toxicity
- Minimize unintended side effects
- Low serum concentrations
- Increased cardiac index
- Leaky capillaries and/or altered protein binding
- End-organ dysfunction (e.g., renal or hepatic)
- Increased clearance
- Increased volume of distribution
- Decreased clearance
- High serum concentrations

Key Terminologies
- Pharmacokinetics (ADME): Processes conducted by the body on the drug
- Pharmacodynamics: Describes the pharmacologic response resulting from drug at the site of action
- Pharmacogenomics: Patient-specific differences in PK/PD through genetic polymorphisms

Pathophysiologic Changes in Sepsis
- Increased cardiac index
- Leaky capillaries and/or altered protein binding
- End-organ dysfunction (e.g., renal or hepatic)
- Increased clearance
- Increased volume of distribution
- Decreased clearance
- Low serum concentrations

Augmented Renal Clearance

- Increased glomerular filtration
- Role of tubular secretion and reabsorption
- Possibly a natural response to critical illness in patients with greater physiologic reserve
- No standard definition
  - Creatinine clearance (CrCl) > 120 – 150 mL/minute
  - Requires urine creatinine collection for diagnosis
  - Prevalence of 30-65% general ICU population
  - Peaks between ICU day 4-5, normalizes around ICU day 7

- Increased perfusion to kidneys

ICU factors
- Increased cardiac output
- Increased blood flow to major organs
- Fluid resuscitation
- Afferent arteriole

Patients with greatest risk
- Early phase sepsis
- Major trauma
- Traumatic brain injury
- CNS infection
- Ventilator associated pneumonia
- Burn
- Major surgery
- Hematologic malignancy
- Pregnancy

Acute Kidney Injury (AKI)

- Kidney Disease: Improving Global Outcomes (KDIGO) society guidelines
  - Chronic kidney disease: adjust doses based on FDA-approved labeling
  - AKI: for hydrophilic medications
    - Administer loading dose 25-50% greater than normal
    - Provide normal or near normal maintenance dosage
  - Guidance on dosing of specific medications not provided for AKI in FDA-approved labeling or KDIGO society guidelines

CLINICAL JUDGEMENT REQUIRED

PK/PD Goals of Antimicrobials

- Antibacterial
  - Aminoglycosides
  - Metronidazole
  - Azithromycin
  - Tetracyclines
  - Glycopeptides
  - Fluoroquinolones
  - Beta-Lactams
  - Linezolid
  - Clarithromycin
  - Clindamycin

- PK/PD Goal
  - Concentration dependent
  - AUC/MIC
  - Concentration and time dependent
  - MIC
  - T>MIC

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Continuous or Extended Infusion β-Lactams

High Dose Extended Interval Aminoglycosides
- Aminoglycosides frequently given to cover multi-drug resistant Gram negative infections
- Relationship between $C_{\text{max}}$ and MIC most important for efficacy
  - Optimal efficacy when $C_{\text{max}}$ $\geq$ 8X - 10X $\geq$ MIC
  - Also consider site of infection
- $C_{\text{min}}$ most important for toxicity
- Optimal dosing strategy → high dose extended interval aminoglycosides

Antimicrobial Levels at Site of Infection
- Must assess whether drug is appropriate for site of infection
- Volume of distribution ($V_d$)
- Ability of drug to concentrate at site?
- Site of infection difficult to penetrate?
- If suboptimal PK/PD match for site of infection, must identify ways to optimize

Loading Doses in Critically Ill

To be fractionated
Loading Doses
Vancomycin Example

- $V_d$ (wide range) $0.4 - 1$ L/kg
- Critically ill patients, consensus statements suggest loading dose of $25 - 30$ mg/kg (based on actual body weight)
  - Facilitates rapid achievement of target trough concentration
  - Overcomes increased $V_d$ observed in sepsis

Conclusions

- An understanding of PK/PD concepts is vital to optimal dosing of antimicrobials in septic patients
- Sepsis can cause changes in distribution and clearance of antimicrobials, based on the underlying pathophysiology for each individual patient and drug class
- Loading doses, continuous or extended infusions, and high doses given at extended intervals are examples of strategies to optimize PK/PD parameters of antimicrobials in patients with sepsis

Interprofessional Education Module to Learn, Teach, and Optimize the Treatment of Sepsis

- Jeffrey P. Gonzales, PharmD
- Nirav G. Shah, MD
- Renee Dixon, MD
- Joan M. Davenport, RN, PhD
- Mojdeh S. Heavner, PharmD
- Samuel A. Tisherman, MD
- Tracey Wilson, DNP
- Sia Yan Amy Yeung, PharmD
- Nimeet Kapoor, RN
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