Individualized Antibiotic dosing in ICU

Gavin M Joynt
The Chinese University of Hong Kong
Bicillin® L-A
(penicillin G benzathine injectable suspension)
Disposable Syringe
for deep IM injection only

WARNING: NOT FOR INTRAVENOUS USE. DO NOT INJECT INTRAVENOUSLY OR IMMOBILIZE WITH OTHER INTRA-
VEINOUS SOLUTIONS. THERE HAVE BEEN REPORTS OF MORTALITY INTRAVENOUS ADMINISTRATION OF
PENICILLIN G BENZATHINE WHICH HAS BEEN ASSOCIATED WITH CARDIORESPIRATORY ARREST AND DEATH.

Prior to administration of the drug, carefully read the WARNINGS, DERMATOREACTIONS, and ORANGE AND
ADMINISTRATION sections of the labeling.

Intramuscular administration is the preferred route. For intramuscular administration, it is recommended that the complete contents of the syringe be injected. DO NOT EXCEED THE MAXIMUM RECOMMENDED DOSE. THIS PRODUCT IS FOR SINGLE USE ONLY. DO NOT REUSE. DO NOT USE IF THE SEAL IS BROKEN.

Bicillin L-A is a sterile penicillin G benzathine suspension in a Roman numerals V-0.025 mL syringe, contains: benzathine penicillin G 500,000 units. Penicillinase-resistant penicillins are generally ineffective against strains of penicillinase-producing staphylococci (e.g., Staphylococcus aureus) and most strains of beta-lactamase-producing streptococci. These infections are usually treated with penicillinase-resistant penicillins (e.g., nafcillin, oxacillin).

CLINICAL PHARMACOLOGY

Bicillin L-A is a sterile penicillin G benzathine suspension in a Roman numerals V-0.025 mL syringe, contains: benzathine penicillin G 500,000 units. Penicillinase-resistant penicillins are generally ineffective against strains of penicillinase-producing staphylococci (e.g., Staphylococcus aureus) and most strains of beta-lactamase-producing streptococci. These infections are usually treated with penicillinase-resistant penicillins (e.g., nafcillin, oxacillin).

Intramuscular administration is the preferred route. For intramuscular administration, it is recommended that the complete contents of the syringe be injected. DO NOT EXCEED THE MAXIMUM RECOMMENDED DOSE. THIS PRODUCT IS FOR SINGLE USE ONLY. DO NOT REUSE. DO NOT USE IF THE SEAL IS BROKEN.
Antibiotic dosing

• In vitro studies
  – MICs
• Animal experiments
  – Effect of blood MICs
• Human observations
  – Healthy (PKs and side effects)
  – Infected (clinical response)
Critically ill

- High volume CRRT
- Residual RF
- Non-renal Clearance
- Augmented Clearance
- Protein binding
- Capillary leakage
- Increased Volume of Distribution
- Low Serum Concentrations
- Organ Dysfunction (AKI, HF)
  - Decreased Clearance
  - High Serum Concentrations
Critically ill

- High volume CRRT
  - Residual RF
- Non-renal Clearance
  - Augmented Clearance
  - Protein binding
  - Capillary leakage
  - Increased Volume of Distribution
  - Low Serum Concentrations
  - High Serum Concentrations

Organ Dysfunction (AKI, HF)
  - Decreased Clearance
  - High Serum Concentrations
Ceftriaxone protein binding in critical illness

[Blood] in a critically ill patient - PKs

- Volume of distribution

\[
\text{Loading dose} = \text{Desired concentration} \times Vd
\]

Antibiotic elimination (MW < 2000Da)

FLOW

Semi-permeable Membrane

Bound Drug

Unbound Drug

Protein

Ultrafiltrate

Antibiotics – small molecules – $Sc \approx 1$
Ceftriaxone 2g 24h

Achieving [Blood] in ICU patients on CRRT

• Augmented renal clearance (ARC)
  – > 130 ml/min/1.73 m²
  – Reported prevalence 30-85% of patients with normal creatinine
    • Multitrauma, traumatic, meningitis, postoperative, burns, VAP

• Measurement of renal clearance
  – 8h CL_{\text{CR}}

Claus BO et al. J Crit Care 2013 doi: 10.1016/j.jcrc.2013.03.003
Ceftazidime 2g 8h

Critically ill

High volume CRRT
Residual RF
Non-renal Clearance
Augmented Clearance

Protein binding
Capillary leakage
Increased Volume of Distribution

Organ Dysfunction (AKI, HF)
Decreased Clearance

Low Serum Concentrations
High Serum Concentrations
One dose size fits all…. NO!

To more accurately dose ICU patients

- Data from critically ill (Vd and CL)
- Within critically ill patient group
  - Dialysis vs no dialysis
  - Dialysis dose
  - Augmented clearance
- Severity of acute illness changes rapidly (within days)
Pharmacodynamic relationships (kill characteristics)

- **Concentration** dependent
- **Time dependent**

- $C_{\text{max}}$ (Peak)/MIC
- $T \geq \text{MIC}$
- $AUC$/$\text{MIC}$
- $C_{\text{min}}$ (Trough)
Simplified Classification

<table>
<thead>
<tr>
<th>Type A</th>
<th>Type B</th>
<th>Type C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>Cephalosporins</td>
<td>Levofloxacin</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Carbapenems</td>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td></td>
<td>Penecillins</td>
<td>Vancomycinin</td>
</tr>
</tbody>
</table>

- Peak/MIC > 10
- T > MIC > 70%
- 24h AUC/MIC > 13-125
Susceptibility in ICU

- Higher MICs in ICU patients
- International variability in sensitivity patterns
  - *Measure MIC whenever possible*
  - European Committee on Antimicrobial Susceptibility and Testing (available at http://www.eucast.org)

Achieving [Blood] in an individual ICU patient

• Blood antibiotic concentration
  – Altered blood pharmacokinetics that occur with critical illness (changes in Vd)
  – Elimination by CRRT
  – Non-CRRT clearance (hepatic and residual renal)

• Satisfy MIC + blood profile to meet the optimal pharmacodynamics of chosen antibiotic
Individualized dosing

- 70kg man in ICU D8
- VAP and septic shock, anuria
- *Post dilution* CRRT 35mL/kg/h effluent flow rate
- Meropenem MIC 4mg/L

Loading dose = Desired concentration x Vd

Calculate CRRT clearance based on mode of CRRT, formulae & published values

Total clearance (Cl_{tot}) = calculated CRRT clearance + non-CRRT clearance

Pharmacokinetic target?

Time above threshold concentration

C_{max}:MIC & AUC_{24}:MIC

C_{max}:MIC ratio

Calculate elimination rate = concentration x Cl_{tot}

Calculate half-life = 0.693 x Vd / Cl_{tot}

Calculate time to reach target trough concentration

Repeat loading dose at calculated time

Calculate target mean concentration = target AUC_{24}/24

Calculate dosing interval = Dose / (Cp x Cl_{tot})

Repeat loading dose at calculated dosing interval

Maintenance infusion rate = elimination rate
**Loading dose=Desired concentration x Vd (28 l)**

Desired concentration = 5 x MIC = 20 mg/l

Loading dose = 20 x 28 ≈ 500 mg
Calculate CRRT clearance based on mode of CRRT & published Sc or Sd values

\[
Cl_{\text{CVVH (post)}} = Qf \times Sc = 2450 \times 0.95 = 2327 \text{ ml/h} = 39 \text{ ml/min}
\]

**Pharmacokinetic target?**

- **Time above threshold concentration**
- **C\textsubscript{max}/MIC & AUC\textsubscript{24}/MIC**
- **C\textsubscript{max}/MIC ratio**

**Calculate elimination rate**

\[= \text{concentration} \times Cl_{\text{tot}}\]

**Calculate half-life**

\[= 0.693 \times Vd / Cl_{\text{tot}}\]

**Calculate target mean concentration**

\[= \text{target } AUC_{24}/24\]

**Calculate dosing interval**

\[= \frac{\text{Dose}}{(Cp \times Cl_{\text{tot}})}\]

**Calculate time to reach target trough concentration**

**Repeat loading dose at calculated time**

**Repeat loading dose at calculated dosing interval**

**Loading dose = Desired concentration} \times Vd**
Loading dose = Desired concentration x Vd

Calculate CRRT clearance based on mode of CRRT, formulae & published values

Total clearance \( (C_{\text{tot}}) \) = calculated CRRT clearance + non-CRRT clearance
\[ = 39 + 60 \approx 100 \text{ ml/min} = 0.1 \text{ l/min} \]

Pharmacokinetic target?

- Time above threshold concentration
- \( C_{\text{max}} : \text{MIC} & \text{AUC}_{24} : \text{MIC} \)
- \( C_{\text{max}} : \text{MIC} \) ratio

Calculate elimination rate = concentration \( x \) \( C_{\text{tot}} \)

Calculate half-life = \( 0.693 \times \text{Vd} \) / \( C_{\text{tot}} \)

Calculate time to reach target trough concentration

Calculate target mean concentration = target \( \text{AUC}_{24}/24 \)

Calculate dosing interval = \( \text{Dose} / (C_p \times C_{\text{tot}}) \)

Maintenance infusion rate = elimination rate

Repeat loading dose at calculated time

Repeat loading dose at calculated dosing interval
**Loading dose** = Desired concentration $\times$ Vd

Calculate CRRT clearance based on mode of CRRT, formulae & published values

Total clearance ($C_l_{tot}$) = calculated CRRT clearance + non-CRRT clearance

**Pharmacokinetic target?**

- $C_{max}$:MIC & $AUC_{24}$:MIC
- $C_{max}$:MIC ratio

**Calculate elimination rate**

$= \text{concentration} \times C_l_{tot}$

$= 20 \times 0.1 = 2 \text{ mg/min}$

**Calculate half-life**

$= \frac{0.693 \times Vd}{C_l_{tot}}$

**Calculate target mean concentration**

$= \frac{\text{target } AUC_{24}}{24}$

**Calculate dosing interval**

$= \frac{\text{Dose}}{(C_p \times C_l_{tot})}$

**Calculate time to reach target trough concentration**

- Repeat loading dose at calculated time

**Calculate maintenance infusion rate**

- Elimination rate

**Repeat loading dose at calculated dosing interval**
Loading dose = Desired concentration x Vd

Calculate CRRT clearance based on mode of CRRT, formulae & published values

Total clearance (Cl\text{tot}) = calculated CRRT clearance + non-CRRT clearance

Pharmacokinetic target?

Time above threshold concentration

C\text{max}/MIC & AUC_{24}/MIC

C\text{max}/MIC ratio

Calculate elimination rate = concentration x Cl\text{tot}

Calculate half-life = 0.693 x Vd / Cl\text{tot}

Calculate target mean concentration = target AUC_{24}/24

Calculate dosing interval = Dose / (Cp x Cl\text{tot})

Calculate time to reach trough concentration

Repeat loading dose at calculated time

Repeat loading dose at calculated dosing interval

Maintenance infusion rate = elimination rate = 2 mg/min
Loading dose = Desired concentration x Vd

Calculate CRRT clearance based on mode of CRRT, formulae & published values

Total clearance ($C_{l_{tot}}$) = calculated CRRT clearance + non-CRRT clearance

Pharmacokinetic target?

- Time above threshold concentration
- $C_{max}$:MIC & $AUC_{24}$:MIC
- $C_{max}$:MIC ratio

Calculate elimination rate = concentration x $C_{l_{tot}}$

Calculate half-life = 0.693 x Vd / $C_{l_{tot}}$

Calculate time to reach target trough concentration

Maintenance infusion rate = elimination rate

Calculate target mean concentration = target $AUC_{24}$/24

Calculate dosing interval = Dose / (Cp x $C_{l_{tot}}$)

Repeat loading dose at calculated dosing interval

Repeat loading dose at calculated time
Advantages

• Individualized
  – CRRT actually in progress
  – Weight, etc.
• Adjusts for PKs in the critically ill
• Specifically targets PK/PD relationships

Problems

• Published data incomplete
• Not validated
  – But neither are current methods
• Cumbersome to use repeatedly for every patient (even with computerized apps)
  – MIC data
  – Renal CL
  – Non-renal CL

Therapeutic Drug Monitoring (TDM)

- Timely blood concentrations
- Dose adjustment
  - Empirical intuitive adjustments based on comparison of result and target
  - Nomograms (non-critically ill)
  - Software guided dosing
    - Estimation of antibiotic exposure with non-linear regression or Bayesian techniques

Software assisted dosing

• ICU population PK models
  – Software combines recorded patient data plus a population PK model to estimate the Bayesian posterior pharmacokinetic parameter values
  – The appropriate dose/interval that achieves the PK/PD is calculated

Summary

• Seems smart to individualize antibiotic drug dosing in CRRT
• Better outcomes
  – Cure or resistance?
• Future - real time TDM........integrated with PK based predictive software.... SMAART