Drug Management in CRRT

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Overview

✓ Pharmacokinetics

✓ Extracorporeal drug removal

✓ Pharmacodynamics

✓ Practical guidelines
Serum antibiotic levels over a dosing interval
Pharmacokinetics = what the body does to the drug.

It describes the fundamental processes of ADME

Absorption
Distribution
Metabolism
Elimination
Pharmacokinetic Terms

- Volume of distribution (Vd)
- Protein binding (PB)
- Clearance (Cl)
- Half-life ($t_{1/2}$)
Pharmacokinetics

Volume of distribution (Vd)

- plasma protein binding, tissue binding, total body water
- a conceptual volume referring to the volume the drug would occupy if the body were a single homogeneous compartment with drug concentration equal to the plasma concentration

\[ Vd = \frac{\text{Amount in the body}}{\text{plasma concentration}} \]

- used to calculate the loading dose required to reach a target concentration

\[ \text{Loading dose} = Vd \times \text{target concentration} \]
Pharmacokinetics in the critically ill

Changes in Vd due to

Changes of extracellular volume
- blood loss
- fluid resuscitation
- fluid shifts (third spacing)
- capillary leak, edema
- ascites
- vomiting, diarrhea

Changes in PB

Circulatory failure (decreased tissue perfusion)
### Volume of distribution in the critically ill

<table>
<thead>
<tr>
<th>Drug</th>
<th>Critically ill</th>
<th>Healthy volunteers</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>0.41 L/kg</td>
<td>0.25 L/kg</td>
<td>Marik 93</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>20 L</td>
<td>10.1 L</td>
<td>Joynt 01</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>0.32 L/kg</td>
<td>0.21 L/kg</td>
<td>Hanes 00</td>
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<tr>
<td>Ceftazidime</td>
<td>56.9 L</td>
<td>13.6 L</td>
<td>Gomez 99</td>
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<tr>
<td>Vancomycin</td>
<td>1.69 L/kg</td>
<td>0.72 L/kg</td>
<td>Del Mar Fernandez 07</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>0.38 L/kg</td>
<td>0.08 L/kg</td>
<td>Brink 09</td>
</tr>
</tbody>
</table>
Practical application of Vd in critical illness

Gentamicin: target level 10-15mg/L - 70kg patient - 240mg

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters in hypo- and hyperdynamic septic patients and a control group. Values are given as mean±SD. From Tang et al. (17).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>Hyperdynamic patients (n=52)</td>
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<tr>
<td>Hypodynamic patients (n=25)</td>
</tr>
<tr>
<td>Control group (n=27)</td>
</tr>
</tbody>
</table>

7.1mg/L
10.7mg/L
11.8mg/L


<table>
<thead>
<tr>
<th>Pharmacokinetic parameters (17)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>$V_d$ (l/kg)</td>
</tr>
<tr>
<td>$T_{1/2}$ (h)</td>
</tr>
<tr>
<td>$Cl$ (l/kg/h)</td>
</tr>
</tbody>
</table>

7.9 - 11.8mg/L

Volume Overload

• Must increase loading dose for selected drugs
• As volume overload is corrected, doses must change again

CRRT is best RRT choice for fluid overload as volume is removed continually
Multicompartment pharmacokinetic model

Mueller, Artificial Organs 2003; 27: 808-814
Pharmacokinetics

Protein binding (PB)

• determines the free fraction of a drug and hence the amount that is distributed, pharmacologically active at the tissue receptor sites, metabolised and excreted

• acidic drugs bind to albumin
• basic drugs bind to α1-acid glycoprotein
Pharmacokinetics in the critically ill

Changes in PB due to

- acidosis
- elevated FFA
- hypoalbuminemia = negative acute phase reactant
- increased a1-acid glycoprotein = acute phase reactant
- fever
- displacing substances (uremia with increased organic acids, bilirubin, other drugs)

Misinterpretation of drug monitoring results
Changes only important for drugs with high PB
Pharmacokinetics

Clearance (Cl)

- measures the intrinsic ability of the body to eliminate the drug from the blood or plasma
- only applies to drugs with first order kinetics (most drugs)
- defined as the volume completely cleared of the drug in unit time
- important for the calculation of the maintenance dose at steady state

**Maintenance dose** = **Cl** × **Cp** × **t**

**Cp** = desired plasma concentration

**t** = dosing interval
Pharmacokinetics

Clearance (Cl)

• total body Cl = sum of regional clearances
  (renal, metabolic and biliary)

• renal excretion = glomerular filtration + tubular secretion +
  tubular reabsorption

• hepatic clearance depends on hepatic blood flow, protein
  binding and enzymatic activity (intrinsic clearance)
Pharmacokinetics in the critically ill

Changes in extrarenal Cl

- decreased hepatic blood flow
- altered hepatic enzyme activity (hypoxemia, inflammatory mediators, hepatocellular damage, other drugs, hormones, stress, fever, age)
- renal failure alters metabolic transformation in both liver and kidney

Changes in metabolic clearance cannot be quantified by a single parameter such as creatinine clearance
Pharmacokinetics in the critically ill

Summary
often increased Vd
changes in PB
organ dysfunction resulting in decreased clearance
clearance may be increased in early hyperdynamic sepsis
Pharmacokinetics in the critically ill

Considerable intersubject variation already in healthy subjects
Important and dynamic changes in critical illness resulting in
still greater inter- and intrapatient variability
Extracorporeal drug removal
Extracorporeal drug removal

1. Drug-membrane interactions

Gibbs-Donnan effect depending on drug charge

Drug binding to the membrane
   eg. binding of aminoglycosides to AN69 (Kronfol 87)

saturation after 30-60 min
effect of membrane surface area
effect of timing of drug administration relative to filter change?
Extracorporeal drug removal

✓ Transfer through the membrane

✓ Adsorption
  - Depends on drug and membrane characteristics (charge) e.g. AN69 has high adsorptive capacity and aminoglycosides are readily adsorbed
  - Clinical significance?
Drug removal with adsorption

Tian et al, Antimicrob Agent Chemother 2008; 52: 1009-1013
Drug removal with adsorption

PAN membrane

Higher dose

lower dose

Drug removal with adsorption

Tian et al, Artificial Organs 2008; 32: 81-84
Drug removal with adsorption

Tian et al, Antimicrob Agent Chemother 2008; 52: 1009-1013
Extracorporeal drug removal

Transfer through the membrane: diffusion versus convection

Hemofiltration = convection

- drugs are smaller than the membrane cut-off, convective removal is independent of molecular weight
- the capacity of a drug to pass the membrane by convection is mathematically expressed in the sieving coefficient $SC$

\[
SC = \frac{C_f}{C_p}
\]

- the main determinant of $SC$ is drug $PB$

$SC \approx (1 - PB)$

$C_f$ = drug concentration in filtrate
$C_p$ = drug concentration in plasma
<table>
<thead>
<tr>
<th>Drug</th>
<th>Observed SC</th>
<th>Expected SC</th>
<th>Observed SC</th>
<th>Expected SC</th>
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<tbody>
<tr>
<td>amikacin</td>
<td>0.88-0.95</td>
<td>0.95</td>
<td>ganciclovir</td>
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<td>amphotericin B</td>
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<td>0.10</td>
<td>gentamicin</td>
<td>0.81-0.85</td>
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<td>anpho (liposom)</td>
<td>0.1</td>
<td>0.1</td>
<td>imipenem</td>
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<td>ampicillin</td>
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<td>meropenem</td>
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<td>cefepime</td>
<td>0.72</td>
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<td>flucytosine</td>
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<td>0.9</td>
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<td>0.90</td>
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</tbody>
</table>

Adapted from Golper, Contrib Nephrol 2001;132:349-353
Extracorporeal drug removal

Convective drug clearance $\text{Cl}_f$

$$\text{Cl}_f = Q_f \times SC \approx Q_f \times (1 - \text{PB})$$

$Q_f$ = filtration rate

$SC$ = sieving coefficient

$PB$ = protein binding
Extracorporeal drug removal

Predilution hemofiltration

\[ Cl_f = Q_f \times (1 - PB) \times \frac{Q_b}{Q_b + Q_s} \]

- \( Q_b \) = blood flow
- \( Q_s \) = prefilter substitution rate
<table>
<thead>
<tr>
<th></th>
<th>Qb</th>
<th>Hct</th>
<th>Predicted decrease in Cl (4.5L predilution)</th>
<th>Observed decrease in Cl</th>
<th>Urea</th>
<th>Creat</th>
<th>Urate</th>
<th>Beta2-M</th>
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<td>31%</td>
<td>38%</td>
<td>35%</td>
<td>40%</td>
<td></td>
</tr>
</tbody>
</table>

Troyanov, Nephrol Dial Transplant 2003
Extracorporeal drug removal

3. Transfer through the membrane: diffusion versus convection

Hemodialysis = diffusion

- diffusion is a molecular weight-dependent process
- the capacity of a drug to pass the membrane by diffusion is mathematically expressed in the dialysate saturation $S_a$

$$S_a = \frac{C_d}{C_p}$$

$C_d =$ drug concentration in dialysate
$C_p =$ drug concentration in plasma
Extracorporeal drug removal

3. Transfer through the membrane: diffusion versus convection

Hemodialysis = diffusion

- SA is determined by PB
  - drug-membrane interactions
  - drug molecular weight
  - membrane pore-size, thickness (flux)
  - membrane surface area
  - dialysate flow (Qd) / blood flow (Qb)

- in continuous hemodialysis: Qd << Qb
  - complete equilibration of small drugs or

  \[ SA \approx (1-PB) \]
Reetze-Bonorden, Clin Pharmacokinet 1993; 24: 362-379
3. Transfer through the membrane: diffusion versus convection

Hemodialysis = diffusion

\[ K_{d_{\text{rel}}} = \frac{K_d}{K_{d_{\text{creat}}}} = \left(\frac{\text{MW}}{113}\right)^{-0.42} \]

- \( K_d \) = drug diffusive mass transfer coefficient
- \( K_{d_{\text{creat}}} \) = creatinine diffusive mass transfer coefficient
- \( \text{MW} \) = drug molecular weight
- 113 = molecular weight of creatinine

Vincent and Vos, 1993
Extracorporeal drug removal

CVVHD - Diffusive small drug clearance $Cl_d$

$$Cl_d = Q_d \times S_d \approx Q_d \times (1 - PB)$$
Extracorporeal drug removal

3. transfer through the membrane: diffusion versus convection

hemodiafiltration = diffusion + convection

clearance in continuous hemodiafiltration = Cl_{df}

\[ Cl_{df} = Q_f \times S + Q_d \times S_d \]
\[ \approx (Q_f + Q_d) \times (1-PB) \]

interaction between diffusion and convection resulting in overestimation of the combined clearance
Extracorporeal drug clearance

Summary

\[
\begin{align*}
\text{CVVH Cl} &= Q_f \times S & \approx & Q_f \times (1-PB) \\
\text{CVVHD Cl} &= Q_d \times S_d & \approx & Q_d \times (1-PB) \\
\text{CVVHDF Cl} &= Q_f \times S + Q_d \times S_d & \approx & (Q_f + Q_d) \times (1-PB)
\end{align*}
\]

Assumptions:
- protein binding is normal
- no drug-membrane interactions
- dialysate saturation independent of molecular weight
- dialysate saturation independent of dialysate flow
- no interaction between diffusion and convection
### Calculated (Clc) versus measured (Clm) clearance

<table>
<thead>
<tr>
<th></th>
<th>Qd 1l/h</th>
<th></th>
<th>Qd 2l/h</th>
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<tbody>
<tr>
<td></td>
<td>Clmeas</td>
<td>Clcalc</td>
<td>Clmeas</td>
<td>Clcalc</td>
</tr>
<tr>
<td>urea</td>
<td>22,02</td>
<td>23,30</td>
<td>33,46</td>
<td>40</td>
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<tr>
<td>cefuroxime</td>
<td>13,97</td>
<td>15,37</td>
<td>16,22</td>
<td>26,4</td>
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<tr>
<td>ceftazidime</td>
<td>13,11</td>
<td>19,30</td>
<td>15,24</td>
<td>33,2</td>
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<tr>
<td>ciprofloxacin</td>
<td>16,31</td>
<td>16,31</td>
<td>19,93</td>
<td>28</td>
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<tr>
<td>vancomycin</td>
<td>11,70</td>
<td>16,31</td>
<td>14,85</td>
<td>28</td>
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<td>tobramycin</td>
<td>11,10</td>
<td>22,10</td>
<td>14,85</td>
<td>38</td>
</tr>
<tr>
<td>gentamicin</td>
<td>20,51</td>
<td>22,10</td>
<td>25,94</td>
<td>38</td>
</tr>
</tbody>
</table>

Clm from Davies, Contrib Nephrol 1991; 93 : 117-119
Fractional extracorporeal clearance

\[ Fr_{EC} = \frac{Cl_{EC}}{Cl_{EC} + Cl_{NR} + C_R} \]

A regional clearance is only clinically important if its contribution to total body clearance exceeds 25%
Extracorporeal drug elimination should not be taken into account if

low extracorporeal clearance because of
  • high protein binding
  • low Qf or Qd

high non-extracorporeal clearance because of
  • high extrarenal clearance
  • high residual renal clearance
Can Pharmacokinetics (ADME) explain all differences in drug response?

• Absorption
  – Critical illness likely affects GI absorption

• Distribution
  – Volume status & protein binding

• Metabolism
  – Drug interactions, genetic differences in metabolism

• Elimination
  – Differences in CRRT clearances
Pharmacokinetics vs. Pharmacodynamics

- Pharmacokinetics
- "How the body processes a drug" resulting in a drug concentration in the body.
- ADME
- Removal by RRT = Pharmacokinetics

Figure from MJ Rybak.
CID 2006;42:S35-S39
Have You Observed Pharmacodynamic Alterations in Patients with AKI?

- Tolerance documented for selected agents: dobutamine, loop diuretics; fentanyl, alfentanil in burn patients, barbiturates in TBI patients.
  - Wagner BKJ, O’Hara DA. Clin Pharmacokinet 1997;33:426-63
- Seemingly poor response to “appropriately” dosed antibiotics
- Higher doses of EPO used in AKI vs. CKD
Why might pharmacodynamic response differ between typical CRRT patients?

• Pharmacokinetics!
  – Does 100 mg given to patient A yield the same serum concentration as 100 mg given to patient B?
  – More importantly, does it achieve the same concentration at the “effect site”?

• Differences in ADME
  – Absorption
  – Distribution
  – Metabolism
  – Elimination
Serum antibiotic levels over a dosing interval

Not shown here

- $t_{1/2}$
- Vd
- Cl
- Protein binding

Concentration (mg/L)

AUC

Cmax (Peak)

Cmin (Trough)

Time (hours)
Pharmacodynamics correlates the concentration of the antibiotic with its ability to kill or inhibit the target pathogen.
PK-PD Relationship

PK

Dose $\rightarrow$ concentration

PD

Concentration $\rightarrow$ effect

PK-PD

Dose $\rightarrow$ concentration $\rightarrow$ effect

PK-PD Relationship
PK-PD Relationship

PK → Dose → concentration → effect → PD

PK-PD Relationship
Pharmacokinetic/Pharmacodynamic Parameters: Rationale for Antibacterial Dosing of Mice and Men

William A. Craig

From the Department of Medicine, William S. Middleton Memorial Veterans Hospital, Madison, Wisconsin

Clinical Infectious Diseases 1998;26:1-10
Figure 1. Overview of pharmacokinetics and pharmacodynamics in antimicrobial chemotherapy.
PK-PD Relationship

Pharmacokinetic/Pharmacodynamic Parameters: Rationale for Antibacterial Dosing of Mice and Men

William A. Craig
PK-PD Relationship

Cefotaxime vs Klebsiella pn

Pharmacokinetic/Pharmacodynamic Parameters: Rationale for Antibacterial Dosing of Mice and Men

Clinical Infectious Diseases 1998;26:1-10
Kill Characteristics

**TIME DEPENDENT**

- β-lactams: Time > MIC
- Aminoglycosides: Dose dependent
- Vancomycin: ?Time > MIC
- Fluoroquinolones: Peak/MIC, AUC/MIC

**CONC. DEPENDENT**
<table>
<thead>
<tr>
<th>Concentration (mg/L)</th>
<th>Time (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmin (Trough)</td>
<td></td>
</tr>
<tr>
<td>Cmax (Peak)</td>
<td></td>
</tr>
</tbody>
</table>

**Serum antibiotic levels over a dosing interval**

- **MIC**
- **AUC**
- **AUC/MIC** = AUIC
- **t>MIC**
- **Cmin (Trough)**
Serum antibiotic levels over a dosing interval

Concentration (mg/L)

Time (hours)

Cmin (Trough)

Cmax (Peak)

AUC/MIC = AUIC

AUC

t>MIC

MIC

Cmin (Trough)

Time dependent

Concentration dependent

AUC/MIC
CIPROFLOXACIN

**Figure 2.** Bacterial kinetics of *Klebsiella pneumoniae* during exposure to concentrations of ciprofloxacin simulating serum pharmacokinetics of various dosing regimens. △ = control; ▲ = 2 × 200 mg iv; ● = 2 × 400 mg iv; ■ = 2 × 600 mg iv; ○ = 3 × 400 mg iv.

**Figure 5.** Percent probability of a microbiological cure vs. area under the concentration-time curve/MIC (AUIC) ratio fit to a modified Hill equation. The curve is the fitted relationship; each point represents three or four patients.

Lode et al *CID* 1998;27:33-9

Forrest et al *AAC* 1993;37:1073-81
WHAT THIS SHOWS
IS THE HIGHER THE
AUIC THE BETTER
THE BACTERIAL KILL

NEED AUIC AT LEAST 125

Forrest et al AAC 1993;37:1073-81
PK parameters of 400mg q8h ciprofloxacin in severe sepsis.

<table>
<thead>
<tr>
<th></th>
<th>Day 0 (n=18)</th>
<th>Day 2 (n=17)</th>
<th>Day 6-8 (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (mg/l)</td>
<td>5.9 (1.33)</td>
<td>6.6 (1.31)</td>
<td>6.7 (1.24)</td>
</tr>
<tr>
<td>Cmin (mg/l)</td>
<td>0.0 (0.00)</td>
<td>0.61 (1.93)</td>
<td>0.54 (2.18)</td>
</tr>
<tr>
<td>t 1/2 (hours)</td>
<td>3.6 (1.5)</td>
<td>3.1 (1.31)</td>
<td>3.1 (1.49)</td>
</tr>
<tr>
<td>CL (l/h/kg)</td>
<td>0.36 (1.58)</td>
<td>0.36 (1.49)</td>
<td>0.39 (1.45)</td>
</tr>
<tr>
<td>Vd (l/kg)</td>
<td>1.4 (0.3)</td>
<td>1.21 (0.3)</td>
<td>1.2 (0.5)</td>
</tr>
<tr>
<td>AUC (0-8)(mg.h/l)</td>
<td>12.8 (1.32)</td>
<td>16.0 (1.39)</td>
<td>15.0 (1.32)</td>
</tr>
</tbody>
</table>

Antibiotic resistance—What’s dosing got to do with it?

Jason A. Roberts, B Pharm (Hons); Peter Kruger, MBBS, FJFICM; David L. Paterson, MBBS, FRACP, PhD; Jeffrey Lipman, MBBCh, FJFICM, MD

Critical Care Medicine 2008;36:2433-40
β-lactams have no Post Antibiotic Effect and no dose dependent kill characteristics

β-lactam bactericidal activity
• Correlates with the time above MIC
• Optimal time above MIC unknown
  • ≈100% of the dosing interval ≈4-5 times MIC
• Serum conc < MIC for 61% of the dosing interval → resistance
• No resistance when serum conc > MIC for longer than 61% of dosing interval
Meropenem

Relationship between time > MIC and efficacy

Change in log$_{10}$ CFU/thigh over 24 h

Thigh

Lung

Time above MIC (% of 24 h)

Drusano
Meropenem
Relationship between time > MIC and efficacy

Change in log_{10} CFU/thigh over 24 h

E. coli

P. aeruginosa

Time above MIC (% of 24 h)

Drusano
Cephalosporins (cepha-whatever) 60%
Penicillins 50%
Carbapenems 40%
Cidal vs static is still an unresolved issue
This doesn’t address resistance issues
You may need 100% T>MIC for prevention
Patients with $T>MIC$ of 100% had significantly greater clinical cure (82% vs. 33%; $P = 0.002$) and bacteriological eradication (97% vs. 44%; $P < 0.001$) than patients with $T>MIC$ of <100%.
**β-lactams - eg. ceftriaxone 2g/daily**

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>mg/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>150</td>
</tr>
<tr>
<td>8</td>
<td>14hrs</td>
</tr>
<tr>
<td>24</td>
<td>0</td>
</tr>
</tbody>
</table>

**Bolus Dosing**

- 14hrs after administration

**Continuous Infusion**

- Constant concentration
Kill Characteristics

\[ \beta\text{-lactams:} \quad \text{Time} > \text{MIC} \]

\[ \text{Vancomycin:} \quad \text{Time} > \text{MIC} \]

\[ \text{Aminoglycosides:} \quad \text{Dose dependent} \]

\[ \text{Fluoroquinolones:} \quad \text{Peak/MIC} \quad \text{AUC/MIC} \]
Ideal antibiotic dosing

Extended interval Dosing

High Troughs

Large AUIC

Pinder et al Anaesth Intens Care 2002
Sepsis pathophysiology and antibiotic pharmacology

- Increased Cardiac Output
- Leaky Capillaries &/or altered protein binding
- Normal Organ Function
- End Organ Dysfunction (e.g., renal or hepatic)

- Increased CL
- Increased Vd
- Unchanged Vd
- Decreased CL

- Low Plasma Concentrations
- Normal Plasma Concentrations
- High Plasma Concentrations
Antibiotic resistance—What’s dosing got to do with it?

Jason A. Roberts, B Pharm (Hons); Peter Kruger, MBBS, FJFICM; David L. Paterson, MBBS, FRACP, PhD; Jeffrey Lipman, MBBCh, FJFICM, MD

Critical Care Medicine 2008;36:2433-40
AUGMENTED RENAL CLEARANCE

Editorial
Anaesth Intensive Care 2009; 37: 11-13
You only find what you look for: the importance of high creatinine clearance in the critically ill
Udy A, et al

Review Article
Augmented Renal Clearance
Implications for Antibacterial Dosing in the Critically Ill
Andrew A. Udy, Jason A. Roberts, Robert J. Boots, David L. Paterson and Jeffrey Lipman

Short communication
Augmented renal clearance in the Intensive Care Unit: an illustrative case series
Andrew A. Udy, Michael T. Putt, Sulochana Shanmugathasan, Jason A. Roberts, Jeffrey Lipman

See Wednesday’s lecture
**PK-PD Relationship**

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>β-lactams</th>
<th>Aminoglycosides</th>
<th>Fluoroquinolones</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Carbapenems</td>
<td>Metronidazole</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td>Fluoroquinolones</td>
<td>Azithromycin</td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
<td>Telithromycin</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td></td>
<td>Clarithromycin</td>
<td>Daptomycin</td>
<td>Glycopeptides</td>
</tr>
<tr>
<td></td>
<td>Lincosamides</td>
<td>Quinupristin/dalfopristin</td>
<td>Tigecycline</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Quinupristin/dalfopristin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Linezolid</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PD Kill characteristics</th>
<th>Time-Dependent</th>
<th>Concentration-Dependent</th>
<th>Concentration-Dependent with Time-Dependence</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Optimal PD parameter</th>
<th>$T &gt; \text{MIC}$</th>
<th>$C_{\text{max}} : \text{MIC}$</th>
<th>$\text{AUC}_{0-24} : \text{MIC}$</th>
</tr>
</thead>
</table>

Pharmacodynamic properties that correlate with efficacy of selected antibiotics.
Figure 1. Overview of pharmacokinetics and pharmacodynamics in antimicrobial chemotherapy.
MICRODIALYSIS
How does it work?
Tissue fluid sampling

- Concentric tube
- Fluid enters through inner tube
  - Flows to its distal end
  - Exits the tube
- Enters the space between inner tube and the outer membrane.
- Fluid moves toward the proximal end of the probe.
- “Dialysis” takes place
  i.e. the diffusion of molecules between the extracellular fluid and the perfusion fluid.
Pharmacokinetic cascade of antibiotics through (burnt) skin

- Serum level
  - Normal skin
  - Burnt skin
    - Punch biopsy
    - Discarded skin

That’s where previous data comes from

That’s where infection would occur
MICRODIALYSIS
MICRODIALYSIS

Burnt patients
Burnt and non-burnt skin
Healthy volunteers

Log Interstitial Cephalothin (mg/L)

Time (minutes)

Time > MIC in minutes

Antimicrobial Agents and Chemotherapy  in press
ARE OUR DOSAGES/REGIMENS RIGHT?

NO – THEY NEED MODIFICATION
I PROPOSE A NEW ALGORITHM

- INFECTION SITE, POSSIBLE ORGANISMS
- KILL CHARACTERISTICS for appropriate dosing
  - Concentration dependent vs non-concentration dependent (“time dependent”)
- PENETRATION
- HIGHEST DOSE WITHOUT SIDE-EFFECTS
ARE OUR DOSAGES/REGIMENS RIGHT?

NO – THEY NEED MODIFICATION
I PROPOSE A NEW ALGORITHM

• HIGHEST DOSE WITHOUT SIDE-EFFECTS

UNTIL ONE CAN USE PK/PD WITH TDM
(Therapeutic Drug Monitoring)

Watch this space
Practical guidelines
Drug dosing during CRRT

loading dose

= as usual... Or more?
Drug dosage adaptation during CRRT

maintenance dose adapted for renal failure =

cfr literature

Dependent on effluent rate
Drug Dosing Recommendations Based on Sieving Coefficient (SC)

• Drug clearance a function of
  – Rate of effluent flow
  – Ability of drug to cross membrane (sieving coefficient)

• For drugs <1500 Daltons:
  – Sieving Coefficient \( \approx \% \) Free Fraction
  – Protein binding important determinant of CRRT clearance
**CRRT Drug Removal**

- CRRT Clearance = SC X Effluent Rate
- Mg lost/time =
- (Serum Concentration)(SC)(effluent rate)
- Vancomycin example:
  - SC = 0.8,
  - CRRT Effluent rate= 2L/hr
  - Vancomycin Serum Concentration = 20mg/L
  - Amt lost= 20 mg/L (0.8) (2L/hr) = 32 mg/hr
**CRRT PK Challenges**

- Changing hepatic & renal function
- Drug therapy alters tissue blood flow
- Drug protein binding likely altered
- CRRT often interrupted
  - Clotted filter
  - Patient goes for a procedure
  - Infection Control mandates CRRT System change
- Patients often massively fluid overloaded