Drug dosing & CRRT

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An Apology!
Drug dosing in critically ill – what is the problem?

• Critically ill patients
• Drug dosing extrapolated from ‘ward patients’
• Critically ill with AKI!
• Drug dosing extrapolated from CRF patients
• Poor understanding of pathophysiology
• Poor understanding of PD and/or PK
• ‘Not very efficient systems of RRT’!
Back to the basics!

- Under normal physiological conditions & normal hydration

- Normal glomerular filtrate – 180 l/day
- Or – 7500 ml/hr
- Or – 125 ml/min
- The normal creatinine clearance!
## CC of CRRT systems

<table>
<thead>
<tr>
<th>Modality</th>
<th>Filtrate ml/hr</th>
<th>Filtrate ml/min</th>
<th>CC – ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAVH</td>
<td>500-600</td>
<td>8-10</td>
<td>≈ 10</td>
</tr>
<tr>
<td>CVVH*</td>
<td>2000</td>
<td>33.3</td>
<td>35</td>
</tr>
<tr>
<td>CVVH**</td>
<td>1250</td>
<td>20.3</td>
<td>22</td>
</tr>
<tr>
<td>CVVH (35 ml/kg/hr)</td>
<td>2800 (for 80 kg patient)</td>
<td>46</td>
<td>≈ 48-50</td>
</tr>
</tbody>
</table>

*Brocklehurst, Thomas, Kishen et al 1996; Anaesthesia 51:551

** Dorval et al 2003 Intensive Care Med 29:1186
Dose → Drug concentration in blood → Drug concentration at target site → Pharmacodynamics: Concentration/effect relationship → Effect.
PK and PD in the critically ill

- Altered pathophysiology
- Affects pharmacokinetics
- Which affects pharmacodynamics
- Drug efficacy at target site
- Poor understanding of these principles
- Paucity of literature to date
- Opinions, opinions, opinions!!!!!!!
PK – points to remember

- **Volume of distribution –** $V_d$
  
  Total amount of drug in the body

- **$V_d = \frac{\text{Concentration of drug in plasma}}{\text{Concentration of drug in plasma}}**

- $V_d$ – determines the loading dose

- **Clearance –** $C_l$ – renal & non-renal

- Determines half life – $t_{1/2}$

- **Protein binding**

- Critically ill – altered $V_d$ & $C_l$ & protein binding
Drug dosing in critically ill – Basic principles
Drugs in critically ill

- Most drugs given IV - infusions
- Sedatives, narcotics, inotropes
- Little literature
- Effect easily monitored
- Most studies – antibiotics
- Still - inappropriate recommendations
- ‘Nomograms’!
Drug dosing in critically ill

- Hyperdynamic circulation
- Volume of distribution
- Hypoalbuminaemia
- Increased renal elimination
- Renal & hepatic dysfunction
- Increased acute phase proteins
# Implications!

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Usual dose</th>
<th>Recommended dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>400 mg bd</td>
<td>400 mg tds</td>
<td>As MIC o.5 mg/l</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1 g bd</td>
<td>1 g tds</td>
<td>Continuous infusions better</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>5 mg od</td>
<td>7 mg od initial dose</td>
<td>Irrespective of CC</td>
</tr>
<tr>
<td>Colistin</td>
<td></td>
<td>↑ dose to tds</td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td></td>
<td>Continuous infusion: 300 mg loading &amp; 900 mg infusion - day 1, then 1200 mg/day continuous infusion</td>
<td></td>
</tr>
</tbody>
</table>

Varghese et al 2010; *Curr Opin Anaesthesiol* 23:472-78
Drug dosing in renal dysfunction

- Can be a difficult area
- Stable chronic renal failure patients
- BNF nomograms for these patients
- The ‘RENAL’ book!
- Extrapolated to critically ill with AKI!
- Critically ill (±AKI; ±CRRT) – different
- No relation to chronic ward patients
Drug dosing in patients with AKI and receiving CRRT
# Chronic stable renal failure VS AKI

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Chronic stable patient</th>
<th>Critically ill, Septic, AKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body water</td>
<td>Contracted</td>
<td>Expanded</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>Normal (may be low)</td>
<td>Low</td>
</tr>
<tr>
<td>$V_D$</td>
<td>Contracted</td>
<td>Expanded</td>
</tr>
<tr>
<td>Biochemistry</td>
<td>↑ Urea, Creatinine, $PO_4$</td>
<td>Near normal biochemistry</td>
</tr>
<tr>
<td>RRT mode</td>
<td>IHD</td>
<td>CRRT</td>
</tr>
<tr>
<td>Cardiac Output</td>
<td>Low (may be normal)</td>
<td>Usually high (normal – low)</td>
</tr>
<tr>
<td>Frequency</td>
<td>Dialysis every 2-3 days</td>
<td>Continuous</td>
</tr>
<tr>
<td>Medications</td>
<td>Concomitant long term drugs</td>
<td>Usually none</td>
</tr>
<tr>
<td>Cumulative CC</td>
<td>35 – 45 ml/min (intermittent)</td>
<td>&gt;45-50 ml/min (continuous)</td>
</tr>
</tbody>
</table>
AKI & drug metabolism

- Anuric AKI – No renal elimination
- Changes in non-renal elimination
- ‘Hidden’ clearance
- Liver most important
- Different in AKI, may be increased
- Paucity of studies
- Poor literature evidence
Non-renal clearance & AKI

• Altered hepatic elimination
  • Altered hepatic blood flow
  • Altered protein binding
  • Effect on CY P- super family

• Effect on transporters
  • Depression of P-glycoprotein activity (Pgp)
  • Organic anion transporters (OAT1, OAT3)

• Effect of uraemic toxins – possibly through effect on CYP3A4
Fluconazol story!

- Fluconazol cleared at first pass in kidneys
- 85% clearance by kidneys; no hepatic clearance
- Reabsorbed in renal tubules
- Thus a long half life
- Twice daily dosing sufficient
- Usual dose – 200 mg bd
- Patients on IHD – 100-200 mg after dialysis
- Till next dialysis
Fluconazol story!

- Now consider a patient on CVVH
- Drug filtered like normal nephron
- But filter is a ‘stupid’ nephron
- No reabsorption
- Fluconazol cleared but not reabsorbed
- Need higher doses – i.e., 400 mg bd
- New recommendation – 800 mg bd!
Factors affecting drug kinetics in CRRT

- Patient related factors
- Drug related factors
- CRRT related factors
Patient Related Factors

- **Dose**
- **Absorption** – most drugs in ICU are IV
- **Protein binding**
  - Low albumin
  - Acidosis
  - Uraemic toxins, bilirubin, free fatty acids
- **Vd**
  - \(\uparrow\) Vd in sepsis
  - Water retention in AKI
- **Clearance** (renal & non-renal); residual renal function
Drug related factors

• Molecular weight
  • Most antibiotics <1kD
  • Convective transport ↑ as MW ↑

• Protein binding
  • Most antibiotics minimally protein bound
  • ↓ Alb, ↓ pH, uraemia, acute phase proteins

• Tubular secretion & tubular reabsorption

• CRRT clearance VS total clearance
CRRT related factors

- Sieving coefficient
  - Ability to pass through filter membrane (0-1)
  - From 0.02 (oxacillin) – 0.9 (ceftazidime)
- Volume of ultrafiltrate produced
- Membrane factors
  - Concentration polarisation
  - Porosity
  - Membrane material
  - Adsorption
- Pre or post-dilution
CUT THE CRAP AND SHOW US YOUR WILLY!
What suggestions for drug dosing in AKI and RRT?
Suggestions?

- Problematic
- Variability in RRT/CRRT
- Variable Qf
- Down times etc
- Local MIC, AUC & AUC$_{24}^*$:MIC
- AKI is not a homogeneous entity!
- Paucity of literature
- CAVH, CVVH, CVVHD, CVVHDF????????
**Some guidance re antibiotics**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Loading Dose</th>
<th>Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pip-Tazo</td>
<td>4,500 mg</td>
<td>4,500 mg q 8 h – Tazobactam may accumulate</td>
</tr>
<tr>
<td>Meropenum</td>
<td>1,000 mg</td>
<td>1,000 mg q 12 h – q 8 h</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>15 mg/kg</td>
<td>1,000 – 1,500 mg daily – Monitor levels (15 – 25 mg trough)</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Once daily dose regimens – monitor drug levels</td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td>No dose adjustment required</td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td>No dose adjustment required</td>
<td></td>
</tr>
<tr>
<td>Cefpriome</td>
<td>2,000 mg</td>
<td>1,000 mg q 12 h</td>
</tr>
</tbody>
</table>
Basic principles of drug dosing in CRRT

- Forget BNF, Renal book, data from CKD patients
- AKI & RRT ≠ reduction in antibiotic dosing
- Antibiotics in RRT require adjustments based on mode of RRT & Qf (in CRRT)
- $\uparrow$ protein binding & low $V_d = \downarrow$ elimination by CRRT
- Water solubility = $\uparrow$ elimination by CRRT
- Drugs with narrow therapeutic index = monitor levels
- Broad therapeutic index = err on higher dose
- Use basic principles and common sense!!!
- Ethambutol
More suggestions

• AKI is a dynamic process
• AKI may affect non-renal clearance
• Metabolites may accumulate
• RTT/CRRT affect drug elimination
• Depends upon mode of RRT
• CRRT is not same as IRRT
• RRT may modify non-renal elimination
Drugs in CRRT

- Avoid a drug if it is not needed!
- Avoid nephrotoxins if you can
- Drug dosing – extrapolated from ESRD patients on IHD
- Inappropriate for patients on CRRT
- Monitor drug levels
- Watch out under-dosing!
- Be wary of ‘books’ on renal drug doses!
Some important references

  http://journal.ics.ac.uk/pdf/0902160.pdf

• Vilay AM et al *Crit Care* 2008; 12:235

• Choi G et al *Crit Care Med* 2009; 37:2268
Be careful with drug dosing in AKI and in patients on CRRT
For those who were listening, Questions?