Drug Prescribing in Kidney Disease: Initiative for Improved Dosing

Calculating Drug Doses in AKI

Section Leaders: Brian Decker and Deborah Pasko
Overview of AKI

• Mostly affects critically ill patients
• High mortality despite great advances
• Still controversy over clearance equations
AKI and Pharmacokinetics

- Absorption, Distribution, Metabolism, Excretion (Elimination)
- **Absorption**: GI changes, drugs, nutrition, bacterial overgrowth
- **Distribution** – most complicated but needs the most attention
- **Metabolism** – Discussed later
- **Elimination** – what to do?
Distribution

• Numerous fluid overload studies (adults and peds)
• Need to balance hydration for kidney perfusion vs. total body fluid overload
• Fluid restriction, diuretics, RRT
• Drugs most impacted are small Vd (AG’s, vanco, Pb, most atb)
Fluid and AG example

- 8.5kg child receives a gent dose of 21mg (2.5mg/kg)
- What peak concentration (mg/L) can be expected?
- Volume of distribution of gent is 0.2-0.4L/kg
- 0.25L/kg is normal, but in fluid overloaded patients, expect higher values. If 0.3L/kg =
  - 2.55 Liters = Vd
  - 21mg/2.55L = 8.2 mg/L assuming no drug removal (and constant kel)
AG example

30 min after the 21mg dose is done a peak is done = 4.0mg/L
What is the patients actual volume of distribution?
5.1 Liters = 0.6L/kg
(compare to normal values!!!!)
More distribution

• Critical care considerations
  – Acid base status – pH dependent drugs (nicardipine, atracurium)
  – Acute phase responses – A1G (lidocaine)
  – Uremia (phenytoin)
  – Albumin replacements
  – Advanced technology: CRRT, ECMO, MARS
    • Binding of proteins on membranes
    • Binding of proteins on tubing
Elimination

- Cockcroft-Gault
- MDRD
- Schwartz equation
- Which one in AKI?
## Elimination: RIFLE and pRIFLE

<table>
<thead>
<tr>
<th>Stage</th>
<th>Adult AKIN</th>
<th>Adult AKIN/RIFLE</th>
<th>RIFLE</th>
<th>Pediatric pRIFLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>a SCr &gt;0.3 mg/dl or a SCr &gt;150.200% from baseline</td>
<td>&lt;0.5 ml/kg per hour~6 h</td>
<td>Risk aSCr by 150% or GFR decrease by 25%</td>
<td>eCCl decrease by 25% &lt;0.5 ml/kg per hour~8 h</td>
</tr>
<tr>
<td>II</td>
<td>a SCr to &gt;200-300% from baseline</td>
<td>&lt;0.5 ml/kg per hour~12 h</td>
<td>Injury aSCr by 200% or GFR decrease by 50%</td>
<td>eCCl decrease by 50% &lt;0.5 ml/kg per hour~16 h</td>
</tr>
<tr>
<td>III</td>
<td>a SCr of &gt;300% from baseline or SCr &gt; 4.0 mg/dl</td>
<td>&lt;0.3 ml/kg per hour~24 h</td>
<td>Fail aSCr by 300% or SCr &gt; 4.0 mg/dl with acute rise or &lt;35 ml/min per hour for 24 h or anuric</td>
<td>eCCl decrease by 75% &lt;0.3 ml/kg per hour for 12 h</td>
</tr>
<tr>
<td></td>
<td>with an acute rise of at least 0.5 mg/dl anuria for &gt;12 h</td>
<td></td>
<td></td>
<td>1.73 m2 body surface area</td>
</tr>
<tr>
<td></td>
<td>Loss Failure &gt; 4 weeks</td>
<td>Loss Failure &gt; 4 weeks</td>
<td>ESRD Failure &gt;3 months</td>
<td>ESRD Failure &gt;3 months</td>
</tr>
</tbody>
</table>


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Drug Dosing and AKI: how to approach

Understand natural history of AKI

Identify children at high risk of AKI
- Underlying chronic kidney disease
- Undergoing coronary bypass surgery
- Those requiring contrast for imaging

Understand association between AKI and poor outcome
- Improve severity of illness scoring in pediatric ICU
- Identify risk factors leading to poor outcome in those with AKI
- Identify factors that influence renal recovery

Strategies to improve pediatric AKI outcomes

Strategies to prevent AKI in those at risk for AKI
- NaHCO3
- Fluid resuscitation
- Pharmacy
- Avoid Nephrotic medications
- NSAIDs
- aminoglycosides

Strategies to alter the natural course of AKI
- Early identification of AKI
  - IL-1β
  - NGAL
  - KIM-1
- Blood pressure support
  - Drugs to provide adequate renal perfusion
  - Methods to assess intravascular volume and perfusion
  - Pharmacologic interventions
- Goal-oriented strategies to support children with AKI
  - Fluid management strategies
  - Blood pressure support
  - Ventilator support
  - Renal replacement therapies

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Research Recommendations

• AKI dosing based on RIFLE criteria
• Proactive approach using RIFLE/pRIFLE, and biomarkers
• More research on non-renal clearance in AKI: $\text{CL(body)} = \text{CL(renal)} + \text{CL(hepatic)} + \text{CL(pulmonary)} + \text{CL(etc)}$
Drug Prescribing in Kidney Disease: Initiative for Improved Dosing

Calculating Drug Doses in AKI: Impact of non-renal clearance

Section Leaders:
Brian Decker and Deborah Pasko

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Calculating drug doses in AKI: impact of non-renal clearance

Objectives
• Background
• AKI and CYP450-mediated metabolism
• AKI and drug transport
• Renal replacement therapy and non-renal clearance
• Drug dosing recommendations
• Future research directions
Calculating drug doses in AKI: impact of non-renal clearance

**Background**

- Animal and human studies have shown that CYP450-mediated drug metabolism and drug transport is reduced in CKD and ESRD
- Postulated to be secondary to accumulation of inhibitory uremic solutes
- Inhibition of these metabolic processes may affect drug disposition leading to increased risk of drug toxicity
- Current AKI literature is conflicted with a majority of animal studies showing no effect on CYP450-mediated metabolism and human AKI studies showing decrements in nonrenal clearance

## AKI and CYP450-mediated metabolism

<table>
<thead>
<tr>
<th>Drug</th>
<th>Animal</th>
<th>AKI model</th>
<th>Effect of AKI on hepatic metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin</td>
<td>rat</td>
<td>Uranyl nitrate</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>rat</td>
<td>Gentamicin</td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td>rat</td>
<td>Uranyl nitrate</td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td>rabbit</td>
<td>Folate</td>
<td></td>
</tr>
<tr>
<td>Etoposide</td>
<td>rat</td>
<td>Uranyl nitrate</td>
<td></td>
</tr>
<tr>
<td>Losartan</td>
<td>rat</td>
<td>Uranyl nitrate and bilateral ureter ligation</td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td>rat</td>
<td>Bilateral ureter ligation</td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td>rat</td>
<td>Glycerol</td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>rat</td>
<td>Cisplatin</td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>rat</td>
<td>Bilateral ureter ligation</td>
<td></td>
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<tr>
<td>Tacrolimus</td>
<td>rat</td>
<td>Cisplatin</td>
<td></td>
</tr>
<tr>
<td>Telithromycin</td>
<td>rat</td>
<td>Uranyl nitrate</td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td>rat</td>
<td>Uranyl nitrate</td>
<td></td>
</tr>
<tr>
<td>Ajmaline</td>
<td>rat</td>
<td>Uranyl nitrate</td>
<td></td>
</tr>
</tbody>
</table>

- Unlike CKD, most studies showed no effect from AKI on hepatic metabolism
- Others demonstrated increase or decrease in hepatic metabolism
- Interspecies differences also observed

*Adapted from Vilay AM et al. Critical Care, 2008.*

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AKI and CYP450-mediated metabolism

- Similarly, most studies did not show any effect from AKI on the metabolic activity of specific CYP450 enzymes
- Others showed an increase or decrease in CYP450 activity depending on AKI model used
  - CYP2C6 and CYP3A2 demonstrated no change or decreased metabolic activity
- The majority of the results of these animal studies of CYP450-mediated metabolism disagree with the findings from human studies of AKI

<table>
<thead>
<tr>
<th>Rat CYP450</th>
<th>AKI model</th>
<th>Effect of AKI on CYP450 metabolic activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2A1</td>
<td>Uranyl nitrate</td>
<td>![Arrow] ![Arrow]</td>
</tr>
<tr>
<td>2B1/2</td>
<td>Uranyl nitrate</td>
<td>![Arrow] ![Arrow]</td>
</tr>
<tr>
<td>2C6</td>
<td>Nephrectomy</td>
<td>![Arrow] ![Arrow]</td>
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<td></td>
<td>Bilateral ureter ligation</td>
<td>![Arrow]</td>
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<tr>
<td></td>
<td>Glycerol</td>
<td>![Arrow]</td>
</tr>
<tr>
<td></td>
<td>Cisplatin</td>
<td>![Arrow]</td>
</tr>
<tr>
<td>2C11</td>
<td>Uranyl nitrate</td>
<td>![Arrow]</td>
</tr>
<tr>
<td>2D2</td>
<td>Nephrectomy</td>
<td>![Arrow] ![Arrow]</td>
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<td></td>
<td>Bilateral ureter ligation</td>
<td>![Arrow]</td>
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<td></td>
<td>Cisplatin</td>
<td>![Arrow]</td>
</tr>
<tr>
<td>2E1</td>
<td>Uranyl nitrate</td>
<td>![Arrow]</td>
</tr>
<tr>
<td>3A1 (3A23)</td>
<td>Uranyl nitrate</td>
<td>![Arrow]</td>
</tr>
<tr>
<td>3A2</td>
<td>Nephrectomy</td>
<td>![Arrow] ![Arrow]</td>
</tr>
<tr>
<td></td>
<td>Bilateral ureter ligation</td>
<td>![Arrow]</td>
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Adapted from Vilay AM et al. Critical Care, 2008.
AKI and CYP450-mediated metabolism

Human studies

- Macias et al. evaluated the pharmacokinetics of vancomycin in AKI patients receiving continuous hemofiltration.
- Nonrenal clearance was initially preserved early in the course of AKI, but eventually approached the clearance of CKD patients.
- Mueller et al. and Vos et al. obtained similar results in studies of continuous hemofiltration and imipenem.
- Unknown what precisely constitutes nonrenal clearance in these studies.
  - Is this nonrenal clearance hepatic?
- Interestingly, nonrenal clearance was decreased despite concomitant uremic solute removal.

AKI and CYP450-mediated metabolism

• Heinemeyer et al. evaluated pharmacokinetics of metamizole and its primary metabolite monomethylaminoantipyrine (MMAAP) in critically-ill patients with AKI
  – Found reduced clearance of MMAAP in AKI patients
    • Researchers suggested this was secondary to decreased hepatic metabolism
  – However, there are several potential confounders
    • Clinical complexity of the critically-ill patient
      – Hypoxia, decreased protein synthesis, decreased hepatic perfusion, metabolic inhibition from other medications
      – Precise metabolic disposition of metamizole is currently unknown
        » Metamizole is an inducer of CYP2B6 and 3A4
        » 4-methylaminopyrine metabolite undergoes enzymatic metabolism with human liver microsomes
        » No specific CYP450 isoenzyme has been identified for metamizole
AKI and drug transport

- Drug transporters are found in liver, kidney, intestines, brain and pancreas
  - Two major classes
    - **Efflux**
      » Excrete drugs from within cells to extracellular space
      » P-gp (p-glycoprotein)
    - **Uptake**
      » Facilitate translocation of drugs into cells
      » OAT (organic anion transporter)
- Few studies of transporters in AKI

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AKI and drug transport

- Studies of animal models of CKD have shown decreased expression and activity of drug transporters
- Studies of rat models of AKI have been similar
  - Increased P-gp expression in the kidney, but not in liver or intestines
    - Despite increased P-gp expression, renal clearance of P-gp substrate was reduced
    - Decreased clearance also observed in liver and intestines
    - Researchers concluded that AKI causes a systemic suppression of P-gp function
  - In studies of OAT transporters (rOAT1 and rOAT3)
    - rOAT1 and rOAT3 mRNA and expression were reduced
    - Resulted in decreased renal uptake and clearance of the rOAT substrate, p-aminohippurate
Renal replacement therapy and non-renal clearance

- Research by Nolin et al. demonstrated that 4 hours of hemodialysis increased the non-renal clearance of erythromycin in human subjects by 27%:
  - Results suggested that inhibitory uremic solutes affect CYP3A4 and transporters in combination or independently.
- Subsequent hemodialysis study by Nolin et al. implicated transporters (hOATP and/or intestinal P-gp) as the likely drug disposition bottle-neck in uremia rather than CYP3A4.
- Similar improvement in nonrenal clearance would be expected of AKI patients receiving hemodialysis:
  - Studies of vancomycin and imipenem and hemofiltration suggest that this may be more apparent later in AKI course when nonrenal clearance has attenuated.
  - May be a limit to magnitude of improvement in nonrenal clearance that can be expected from hemodialysis.
Drug dosing recommendations

- Majority of animal data demonstrated no effect on CYP450-mediated metabolism from AKI, however drug transport was attenuated.
- Human AKI studies appear congruent with CKD literature and support a negative effect on nonrenal clearance.
- Given uncertainty of current AKI and non-renal clearance literature, clinically meaningful conclusions are premature.
  - Various animal models of AKI may be affecting non-renal clearance differently.
  - Extrapolating findings with animal CYP450 enzymes to humans should be done with caution.
  - Cannot reliably extrapolate the effect of AKI on the metabolic activity of one metabolic organ such as the liver to another.
  - Human studies of the critically-ill introduce uncertainty.
    - Precise nature of nonrenal clearance of vancomycin and imipenem is unknown.
    - Metamizole metabolic pathway is incompletely characterized.
    - Clinical complexity and medical regimens of the critically-ill subjects may introduce confounding variables and influence drug disposition.
Drug dosing recommendations

- Recommendations for metabolized medications in AKI include more close monitoring than current clinical practice
  - Frequent monitoring of drug pharmacodynamics
  - Therapeutic drug monitoring/pharmacokinetic analysis
    - Limited by availability of laboratory testing in clinically relevant time-frame
- Duration of AKI may also be important
  - Using dosing recommendations for CKD and ESRD early in AKI for drugs with a significant nonrenal clearance component may lead to subtherapeutic levels
  - Higher dosing may be needed early in course with later reduction in dose and/or frequency as AKI persists and nonrenal clearance attenuates

Future research directions

- More accurate assessments of renal and hepatic function in the setting of AKI
- Human studies of AKI and nonrenal clearance
  - CYP450-mediated metabolism
  - Drug transport
- Elucidation of nonrenal clearance component of medications
- Studies of AKI, renal replacement therapies and nonrenal clearance are needed
- Development of rapid, clinically-relevant laboratory testing of the critical metabolized medications
Breakout Group 4: Discussion Questions/Objectives

• How does total body fluid overload change a drug's volume of distribution?
  – What drugs are more or less affected by changes in volume of distribution?
• How can drug therapies be managed in a proactive versus retroactive manner?
• What clearance equations are pertinent in patients with AKI?
Breakout Group 4: Discussion Questions/Objectives

• What are the methodological issues and limitations for research of AKI and nonrenal clearance?
  – Animal studies
  – Human studies
    • Renal replacement therapies

• What are the most important research studies to start now?
  – Focus on most critical metabolic pathways/medications?

• What clinically meaningful dosing recommendations can be made for metabolized medications in AKI?
Breakout Group 4: Clinical Recommendations

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Breakout Group 4: Research & Regulatory Recommendations
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