Diuretics in Acute Kidney Injury: When and How?

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Disclosures

• Research Support
  – Baxter

• Consulting
  – DURECT
  – Sanofi
Diuretics and AKI: A complex relationship

• Brief overview of diuretics in AKI
• Therapeutic role of diuretics in AKI
  – Volume management
  – Prevention of AKI
  – Treatment of established AKI
• Diuretics for AKI prognostication
• Tips for effective diuretic dosing in the setting of AKI
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Brief overview of diuretics

Nephron sites of action of diuretics

Site of diuretic action
- Carbonic anhydrase inhibitors
- Osmotic diuretics
- Loop diuretics
- Thiazide diuretics
- K⁺-sparing diuretics

© Elsevier 2015, Minneman & Wecker: Brady’s Human Pharmacology 4e www.studentconsult.com
Focus on furosemide

- Na-K-2-Cl transporter also found on surface of macula densa cells
- Inhibition of Na, Cl entry into macula densa cells
- Furosemide impairs tubuloglomerular feedback
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The toxicity of volume expansion in AKI

- PICARD cohort, multicentre cohort of 610 patients with AKI in the ICU
- Fluid overload was defined as > 10% total fluid excess in relation to admission body weight

Bouchard et al Kid Int 2009
Fluid overload at AKI diagnosis was strongly associated with 60-day mortality.
Cumulative fluid accumulation was also associated with mortality

Bouchard et al *Kid Int* 2009
If fluid overload is toxic, are diuretics beneficial?

- multicentre cohort of 552 critically ill patients with AKI
- 326 (59%) received diuretics at the time of nephrology consultation
The danger of diuretics in AKI?

<table>
<thead>
<tr>
<th>Variable</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
<th>Propensity-Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-Hospital Mortality</td>
<td>1.37 (0.97-1.92)</td>
<td>1.65 (1.05-2.58)</td>
<td>1.68 (1.06-2.64)</td>
</tr>
<tr>
<td>Non-Recovery</td>
<td>1.53 (1.08-2.15)</td>
<td>1.70 (1.14-2.53)</td>
<td>1.79 (1.19-2.68)</td>
</tr>
<tr>
<td>Composite</td>
<td>1.48 (1.02-2.12)</td>
<td>1.74 (1.12-2.68)</td>
<td>1.77 (1.14-2.76)</td>
</tr>
<tr>
<td>Composite (Ever/Never, n=416)</td>
<td>2.01 (1.26-3.20)</td>
<td>3.15 (1.74-5.62)</td>
<td>3.12 (1.73-5.62)</td>
</tr>
</tbody>
</table>
Are diuretics toxic or is it the poor response to diuretic?

Mehta et al, JAMA 2002
Slide courtesy of S. Bagshaw

Day 1 Status
- No Diuretics
- Total Daily Furosemide Equivalent/Total Urine Output <1.0
- Total Daily Furosemide Equivalent/Total Urine Output ≥1.0

Log Rank $\chi^2$, $P<.001$
Diuretics in AKI: Friend or foe?

• Conceivable benefits
  – control of volume overload
  – oliguric → non-oliguric AKI
  – reduction in renal energy expenditure
  – Improve GFR by inhibiting TGF
  – “renal flushing”

• Limitations
  – Precipitation of intravascular volume depletion
  – Non-oliguric AKI may reflect underlying severity of illness, delay RRT
  – Nephroprotective mechanisms unproven
Inferences from observational studies limited

• difficulty dissecting “effect” of diuretics from fluid overload (confounding by indication)
• patients more likely to get diuretics may have a variety of traits predisposing them to worse outcomes
• timing of diuretic administration in AKI course variable
Diuretics for AKI prevention

- theoretically relevant in select “high-risk AKI” settings, typically angiography, elective nephrotoxic drug administration, cardiac surgery
- classic studies for prevention of radiocontrast nephropathy showed no benefit of diuretics
PROTECT TAVI

• PROphylactic effecT of furosEmide-induCed diuresis with matched isotonic intravenous hydraTion in Transcatheter Aortic Valve Implantation

• Concept of forced diuresis with close matching of volume:urine in patients with PCI

• RenalGuard™ device is central to this intervention
PREVENT-TAVI Overview

**Control Group**

- Start treatment
- i.v. saline
- Continuous infusion of isotonic saline solution matched with urine output
- TAVI
- 12h
- 6h

**RenalGuard Group**

- Start treatment
- i.v. saline
- RenalGuard
- Time necessary to achieve an optimal urine flow of ≥300 ml/h
- 10h
- 4h
- Continuous infusion of isotonic saline solution matched with urine output
- TAVI

Forced diuresis using RenalGuard reduced AKI risk

**FIGURE 4 Study Primary Endpoint**

**AKI Incidence**

- Control Group: 1.8%
- Renalguard Group: 5.4%

p=0.014
RR 0.21 [95% CI 0.06-0.71]

Incidence of acute kidney injury (AKI) stages 1 and 3 in the study population. CI = confidence interval; RR = relative risk.
Do diuretics have a role in treating *established* AKI?

The effect of low-dose furosemide in critically ill patients with early acute kidney injury: A pilot randomized blinded controlled trial (the SPARK study)

Sean M. Bagshaw, MD, MSc\textsuperscript{a,*}, R.T. Noel Gibney, MD\textsuperscript{a}, Peter Kruger, MD, PhD\textsuperscript{b}, Imran Hassan, MSc\textsuperscript{c}, Finlay A. McAlister, MD, MSc\textsuperscript{d}, Rinaldo Bellomo, MD, PhD\textsuperscript{e}
SPARK: Overview

• Multicentre double-blind placebo-controlled trial of 73 critically ill patients with AKI
  – Early AKI (RIFLE-R)
  – ≥ 2 SIRS criteria
  – Rescusitated
  – Key exclusions: clinical need for furosemide, kidney recovery, recent RRT, advanced CKD
SPARK: Interventions and outcome

• Furosemide 0.4 mg/kg bolus then 0.05 mg/kg/hr vs saline control
  – titrated to urine output of 1-2 mL/kg/hr
  – Maximum dose: 0.4 mg/kg/hr

• Primary outcome: progression of AKI
### SPARK: Outcomes

#### Summary of study outcomes.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Furosemide (n = 37)</th>
<th>Placebo (n = 36)</th>
<th>OR/difference (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsened AKI (n, %)</td>
<td>16 (43.2)</td>
<td>13 (37.1)</td>
<td>–</td>
<td>0.6</td>
</tr>
<tr>
<td>Cumulative fluid balance (mL) (med [IQR])</td>
<td>877 (−515 to 2920)</td>
<td>2407 (−522 to 4383)</td>
<td>−1081 (−2697 to 467)</td>
<td>0.2</td>
</tr>
<tr>
<td>Kidney recovery (n, %)</td>
<td>11 (29.7)</td>
<td>15 (42.9)</td>
<td>–</td>
<td>0.3</td>
</tr>
<tr>
<td>Time to recovery (h) (median, IQR)</td>
<td>48.6 (42.9–82.4)</td>
<td>54.6 (43.5–82.7)</td>
<td>4 (−33.5 to 19.4)</td>
<td>0.7</td>
</tr>
<tr>
<td>Received RRT (n, %)</td>
<td>10 (27.0)</td>
<td>10 (28.6)</td>
<td>–</td>
<td>0.9</td>
</tr>
<tr>
<td>ICU death (n, %)</td>
<td>3 (8.1)</td>
<td>6 (17.1)</td>
<td>–</td>
<td>0.3</td>
</tr>
<tr>
<td>Hospital death (n, %)</td>
<td>3 (8.1)</td>
<td>5 (14.3)</td>
<td>–</td>
<td>0.5</td>
</tr>
<tr>
<td>Mortality at 90-days (n, %)</td>
<td>8 (21.6)</td>
<td>11 (30.5)</td>
<td>–</td>
<td>0.4</td>
</tr>
<tr>
<td>Received RRT or death at 90-days (n, %)</td>
<td>17 (46.0)</td>
<td>19 (54.3)</td>
<td>–</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Electrolyte abnormalities more frequent in furosemide arm

Bagshaw et al *J Crit Care* 2017
Leading Science. Leading Practice.
What is the effect of diuretics as part of a broader volume management strategy?

- FACTT-AKI Sub-study
- Comparison of conservative vs liberalized volume control strategy in patients with acute lung injury
- 306 patients (out of 1000 in parent trial) who developed AKI within 2 days of randomization
- 60-day mortality ~40% in both groups

Grams et al CJASN 2011
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The prognostic value of furosemide: The furosemide stress test (FST)

- AKI, especially in early stages, may follow several courses
- the inability to forecast AKI progression has hampered the development of therapeutics
- response to a bolus of furosemide might help anticipate the course of an AKI episode
- diuretic response is a surrogate for renal tubular integrity
Validation of the FST

- 77 patients with Stage 1-2 AKI with evidence of acute tubular necrosis
- Furosemide 1 mg/kg (1.5 mg/kg if prior exposure) with 1:1 replacement with NS over 6 hours
- **Outcome**: Progression to stage 3 AKI (3x sCr from baseline, urine output < 0.3 mL/kg/hr x 24 hrs or receipt of RRT)
AKI Progression after FST

AUROC 0.87

Urine output cutoff < 200 mL @ 2hrs

Sn(AKI progression) 87%

Sp(AKI progression) 84%
The FST vs other AKI biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>AUC±SEM</th>
<th>P Value for Biomarker Alone</th>
<th>P Value Compared With FST alone</th>
<th>AUC of Biomarker and FST±SEM</th>
<th>P Value for Biomarker and FST Compared With FST Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>FST (2-hr UOP)</td>
<td>0.87±0.09</td>
<td>&lt;0.001</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Urine NGAL</td>
<td>0.65±0.06</td>
<td>0.04</td>
<td>0.002</td>
<td>0.84±0.05</td>
<td>0.10</td>
</tr>
<tr>
<td>Urine IL-18</td>
<td>0.65±0.07</td>
<td>0.04</td>
<td>0.009</td>
<td>0.85±0.05</td>
<td>0.89</td>
</tr>
<tr>
<td>Urine KIM-1</td>
<td>0.63±0.06</td>
<td>0.07</td>
<td>0.007</td>
<td>0.86±0.05</td>
<td>0.79</td>
</tr>
<tr>
<td>Uromodulin</td>
<td>0.54±0.07</td>
<td>0.54</td>
<td>0.002</td>
<td>0.85±0.05</td>
<td>0.94</td>
</tr>
<tr>
<td>Urine IGFBP-7</td>
<td>0.62±0.09</td>
<td>0.20</td>
<td>&lt;0.001</td>
<td>0.88±0.05</td>
<td>0.57</td>
</tr>
<tr>
<td>Urine TIMP-2</td>
<td>0.70±0.08</td>
<td>0.03</td>
<td>0.02</td>
<td>0.83±0.06</td>
<td>0.20</td>
</tr>
<tr>
<td>Urine IGFBP-7×TIMP-2</td>
<td>0.69±0.08</td>
<td>0.04</td>
<td>0.01</td>
<td>0.90±0.06</td>
<td>0.35</td>
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<tr>
<td>Urine Creatinine</td>
<td>0.48±0.08</td>
<td>0.77</td>
<td>&lt;0.001</td>
<td>0.84±0.06</td>
<td>0.85</td>
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<tr>
<td>Urine ACR</td>
<td>0.56±0.07</td>
<td>0.45</td>
<td>0.002</td>
<td>0.84±0.06</td>
<td>0.32</td>
</tr>
<tr>
<td>FeNa</td>
<td>0.51±0.07</td>
<td>0.92</td>
<td>&lt;0.001</td>
<td>0.83±0.06</td>
<td>0.47</td>
</tr>
<tr>
<td>Plasma NGAL</td>
<td>0.75±0.08</td>
<td>0.007</td>
<td>0.10</td>
<td>0.86±0.07</td>
<td>0.53</td>
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Practical usage of diuretics in AKI

• Will often need higher doses (especially in patients with prior lasix exposure) as GFR declines
• Furosemide 200 mg IV is a “ceiling” dose
• No clear evidence that infusion is superior to intermittent dosing
• Consider concomitant use of a diuretic that inhibits Na absorption in distal nephron
Final words

- Diuretics are a useful tool in the management of AKI-associated volume overload
- Unlikely to be inherently toxic when used appropriately
- But unlikely to have a therapeutic role in AKI as a “stand-alone” therapy
- Vital area of uncertainty in AKI: Does protocolized strategy of intensive volume control (diuretics +/- RRT) improve outcomes
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