Nephrotoxicity and Electrolyte Complications of Common Drugs
Leah A. Haseley, MD

Case
- A 59 year old woman with stage 3 CKD presents to your office c/o dysuria and bladder spasms. UA is loaded with WBCs. Prior urine cultures showed *ecoli* resistant only to ampicillin. You elect to treat with TMP-SMX.

Possible lab abnormalities that you might expect to see include:
- Hypocalcemia
- Hypernatremia
- Hyperkalemia and a small increase in creatinine
- None - you are just trying to scare me

Drug-induced hyperkalemia
- Most common cause of hyperkalemia in every day practice
- Highest risk:
  - CKD
  - Elderly
  - Multiple offending meds

Drug-Induced hyperkalemia

Blockade of ENAC
- Amiloride
- Triamterine
- Trimethoprim

Decreased Aldo
- ACEI
- ARB
- Spironolactone
- Heparin
- NSAIDs

Block intracellular shift
- Beta-blockers
- Digoxin Toxicity

Hyperkalemia from TMP-SMX

- First described in 1983 (treatment for PCP pneumonia) NEJM 1990, 1993
- 76-100% of pts have a rise in potassium ranging 0.36-1.21 meq/liter
- Average onset: 4-5 days after treatment
- 10-20% develop K > 5.5

Hyperkalemia from TMP-SMX: Risk factors

- Creatinine > 1.2mg/dl
- High dose TMP
- Elderly
- Other meds
- ACE
- ARB
- NSAIDs
- Aldactone
TMP-SMX treatment results in....

- 2.46x Increased risk of sudden death among older pts on spironolactone (n= 328 on antibiotics)
- 3x Increased risk of hospitalization for high K among elderly woman treated for UTI (n = 393,039)
- 6x Increased risk of hospitalization for hyperkalemia among pt on ACE/ARB
- 1.33x Increased risk of sudden death among older pts on ACE/ARB

Trimethoprim causes a “false” rise creatinine

- Creatinine in healthy state
  Filtered 85% = glomerulus
  Secreted 15% = tubules through organic cation transporters (OCTs)
- Trimethoprim also secreted via OCTs

**TMP-SMIX: What is a PCP to do?**

- Do I need it?...
- Avoid in elderly on RAAS inhibitors
- Check potassium after 3-4 days
- Accept a small rise in creatinine (< 0.5mg/dl), but if higher, need to consider interstitial nephritis
Case

- A 67 year old woman with a long history of GERD has been lost to f/u for 6 years. She presents for routine care. GFR is normal. Medications include:
  - Trazadone 50mg qHS
  - Omeprazole 20mg BID
  - Vitamin D 1000iu daily
- Which of the following would be the most likely medication-induced electrolyte disturbance:
  a) Hyperphosphatemia
  b) Hypocalcemia
  c) Hypomagnesemia
  d) Hypoglycemia

PPIs and hypomagnesemia

- 2006: First cases reported of omeprazole in NEJM (Tetany with mg < 0.5mmol/liter)
- 2009: All PPIs have potential
- 2013: First meta-analysis
- Not the kidney’s fault

Drug causes of ↓ Mg

Renal loss
- Cisplatinum
- Diuretics
- Ampho B
- Cyclosporine
- ETOH
- EGF receptor inhibitors

GI loss
- PPI

PPIs and hypomagnesemia

- Transient receptor potential melastatin subtype 6
Hypomagnesemia

Tetany

Arrhythmia

Hypocalcemia (PTH resistance)

Hypokalemia (renal wasting of K)

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<table>
<thead>
<tr>
<th>First Author</th>
<th>Design</th>
<th>Population</th>
<th>Patient #</th>
<th>Result</th>
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<td>Gau</td>
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<td>487</td>
<td>+</td>
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PPIs and Hypomagnesemia

- Most pts on PPI > 1 year
- Majority asymptomatic, but tetany, seizure, arrhythmias described
- Relapse after re-challenge with another PPI
- Refractory to magnesium repletion
- Got better quickly after stopping PPI
PPIs and Hypomagnesemia

- N = 11,490 ADMITTED TO ICU at single center
- Nested case control
- In pts taking diuretics on admission, use of PPIs was associated with a 0.028 mg/dl lower adjusted magnesium level
- In pts not on diuretics, PPI use did not associate with hypomagnesemia.
- Among pts taking diuretics:
  - Diuretics + PPI = 15.6% hypomagnesemia
  - Diuretics no PPI = 11% hypomagnesemia

From the FDA...

- Consider obtaining serum magnesium levels prior to initiation of prescription PPI treatment and checking levels periodically thereafter for patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics).
- Advise patients to seek immediate care from a healthcare professional if they experience arrhythmia, tetany, tremors, or seizures while taking PPIs. These may be signs of hypomagnesemia.
- Consider PPIs as a possible cause of hypomagnesemia, particularly in patients who are clinically symptomatic.
- Be aware that consumers either on their own, or based on a healthcare professional’s recommendation, may take OTC PPIs for periods of time that exceed the directions on the OTC label. This is considered an off-label (unapproved) use. Healthcare professionals should communicate the risk of hypomagnesemia to patients if they are recommending prolonged use of an OTC PPIs.

Case

- A 62 year old woman presents with sx of GERD. She is normotensive and otherwise healthy. Creat = 0.7 mg/dl.
- Rx: omeprazole
- Two months later she presents with fatigue and poor appetite.
  - Creatinine 3.4mg/dl.
  - UA: 1+ protein, few WBCs, no eos

UA: WBC cast
PPIs and Interstitial nephritis

- First described in 1992
- 1990s: primarily omeprazole
- To date: Omeprazole, pantoprazole, lansoprazole, esomeprazole, rabeprazole
- Early studies: Eosinophilia, eos in biopsies
- Later studies: Renal failure >> hypersensitivity symptoms and signs

Biopsy –proven interstitial nephritis

n = 133, Mayo Clinic

<table>
<thead>
<tr>
<th>Cause</th>
<th>No. of Patients (%)</th>
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<td>Drug induced</td>
<td>95 (71%)</td>
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<td>Antibiotics</td>
<td>47</td>
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<tr>
<td>PPIs</td>
<td>13</td>
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<tr>
<td>NSAIDs</td>
<td>10</td>
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<tr>
<td>Other drugs</td>
<td>11</td>
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<td>Multiple drugs</td>
<td>14</td>
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<tr>
<td>Autoimmune</td>
<td>27 (20%)</td>
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<tr>
<td>Malignancy, fungal, etc</td>
<td>Remainder</td>
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PPIs: Interstitial nephritis

- 2014 series
- 25 biopsy-proven cases of omeprazole AIN in UK center
- Presented with renal failure, sterile pyuria, mild proteinuria
- No one with extra-renal sx
- Biopsies with macrophages, lymphocytes, PMNs
- 88% did not recover full renal function

Causes of Urinary Eos
(please don’t routinely send this test!)

- Acute interstitial nephritis
- Atheroembolic disease
- Glomerulonephritis
- UTI/prostatitis
- Transplant rejection
Different Flavors of AIN

<table>
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<th>Beta lactam</th>
<th>Rifampin/ PPI</th>
<th>NSAID</th>
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<tbody>
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<td>Kidney</td>
<td>Diarrhea</td>
<td>Fever</td>
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<td>Dermatologic</td>
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<td>Rash</td>
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<td>Gastrointestinal</td>
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<td>Eosinophilia</td>
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<tr>
<td>Pyuria</td>
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<td></td>
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<tr>
<td>Proteinuria</td>
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<td></td>
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<td>Extravascular symptoms</td>
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<tr>
<td>Eosinophilia</td>
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</tbody>
</table>

Fever + Rash + Eosinophilia < 10-15%

KI 2001

Case

37 year old man with HIV presents with a creatinine of 1.6mg/dl after starting HAART 5 months ago. His regimen: tenofovir, emtricitabine, efavirenz

The electrolyte complication you would be most likely to see is

a) Hypophosphatemia
b) Hypercalcemia
c) Hyponatremia
d) Hyperkalemia

Tenofovir: Most prescribed ARV

- Viread
- Truvada
- Atripla
- Complera
- Stribild

Drug-Induced Fanconi Syndrome

- Tenofovir
- Ifosfamide/Cisplatin
- Cidofovir/Adefovir
- Old tetracycline
- Suramin
- Alcohol
Fanconi Syndrome
Generalized proximal tubule dysfunction

- Aminoaciduria
- Glycosuria
- Phosphaturia
- Type II RTA

**Manifestation** | **Clinical Consequences**
--- | ---
Hypophosphatemia | Rickets, growth retardation
Type II RTA | Acidosis
Hypokalemia | Concentrating defects
Salt wasting | Dehydration
Osmotic diuresis | Polyuria/polydipsia
Aminoaciduria | Often none
Glycosuria | Probably none
**Tenofovir: Mitochondrial toxicity**

*Inhibits mitochondrial DNA synthesis*
*Upsets energy source of PCT*

**Vulnerability to tenofovir nephrotoxicity**

- Low body weight, advanced HIV
- Drug interactions: didanosine; ritonavir
- Pharmacogenetics- e.g. polymorphisms in genes coding for tubule transporters
- NOT traditional risk factors for CKD (diabetes, HTN)

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**Is tenofovir nephrotoxic?**

- Subclinical tubular defects- YES
- Fanconi Sydrome- YES
- ATN (reversible)- YES
- CKD-???

  **RCT- NO**
  **Industry sponsored- NO**
  **Observational :**
  **Yes- about 1% develop CKD**

**Department of Veteran Affairs**

**TDF study**

**Subjects**

- 10,842 HAART naïve veterans 1997-2007
- Exclude: advanced CKD
- 4303 exposed to TDF for mean of 1.3 years (max 6.3 years)

**Results**

- 11% increase risk of rapid decline in renal function
- 10% increased risk of creatinine doubling
- 33% increased risk of GFR < 60.
- **NO increased risk of GFR < 30**

Scherzer, AIDS 2012
Tenofovir: Monitoring

- For the first year, check every 3 months:
  - Creatinine
  - Urinary markers of Fanconi syndrome: glycosuria, fractional excretion of phosphate, proteinuria (tubular proteins if available)
- After the first year, check every 6 months
- Speak to a nephrologist if in doubt about whether to stop the drug