Case Based Discussions of Electrolyte and Acid-Base Disorders

Timothy Yau, M.D.
Assistant Professor of Medicine

Department of Medicine
Division of Nephrology
Review of the Kidney’s Functions

- Salt and Water balance
- Acid-base balance
- Electrolyte balance
- Bone-Mineral Metabolism
- Erythropoietin production
## Complications of CKD in relation to GFR

<table>
<thead>
<tr>
<th>GFR ml/min</th>
<th>Stage 5</th>
<th>Stage 4</th>
<th>Stage 3</th>
<th>Stage 2</th>
<th>Stage 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>Hypertension/Edema</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>2º Hyperparathyroidism</td>
<td>Anemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>Hyperkalemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>Metabolic Acidosis</td>
<td>Uremic symptoms</td>
<td></td>
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</tbody>
</table>
HYPERKALEMIA
CASE 1

- 60 year old male with CKD IV secondary to DM, HTN (baseline SCr 3.6 mg/dL) is seen by his regular nephrologist for routine management. Blood pressure and sugars are well controlled.

- Meds include lisinopril 40 mg/day, amlodipine 10 mg/day, metoprolol 50 mg BID, ASA 81 mg/day, insulin

- Na 136  K 5.8  Bicarb 19  BUN 61  Cr 3.8
- Glucose 160  HbA1C 7.1
What would you do next in your office?

- Counsel him on a low potassium diet
- Stop/decrease the lisinopril
- Stop/decrease the metoprolol
- Start oral bicarbonate
- Start him on chronic kayexhelate therapy
- Monitor conservatively
- Start him on dialysis
HYPERKALEMIA IN CKD

- GFR < 30 ml/min
- Can occur earlier in
  - Diabetes mellitus
  - Type IV RTA
  - Sickle Cell Anemia
  - Obstruction
  - Tubulointerstitial disease

ETIOLOGY

- Dietary indiscretion
- Iatrogenic
  - ACE inhibitors & ARBs
  - Beta-blockers
  - K-sparing diuretics
  - Septra ®/Bactrim®
  - NSAID’s/COX II Inhibitors
  - Cyclosporine and Tacrolimus
  - Heparin
CONTROL OF POTASSIUM

Goal of K+ - 4.0-5.0 mEq/L
- Dietary Modifications
- Stop causative meds
- Correct acidosis
- Loop Diuretics
- AVOID NSAIDS and COX II Inhibitors

K+ level of 5-5.6 mEq/L is acceptable, provided the patient has regular follow-up.

Otherwise........
- ?Potassium Binding Resins
- Stop/Reduce ACE-I, ARB
QUESTION

How much potassium can be removed with a typical 30 gram dose of Kayexelate, assuming maximal exchange and excretion?

1) 10 mEq
2) 15 mEq
3) 30 mEq
4) 60 mEq
5) 90 mEq
Newer Agents – Zirconium Cyclosilicate

**ZS-9 Crystal Structure**

**ZS-9 PROPERTIES**
- Unique microporous zirconium silicate compound
- Designed to be selective for K⁺ trapping
- Insoluble and highly stable
- Non-systemically absorbed
- Builds on long history of Zr use in dialysis and other biomedical applications

Average Width of Micropore Opening 3Å
**Potassium, Calcium, and Magnesium Concentration Ratio (1:1:1)**

**ZS-9 Ion Binding**

- K+ binding: 96
- Ca2+ binding: 2**
- Mg2+ binding: 2**

**Selectivity Ratio**

- K+/Ca2+ selectivity: >25**
- K+/Mg2+ selectivity: 2**

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**Kayexalate Ion Binding**

- K+ binding: 18
- Ca2+ binding: 59
- Mg2+ binding: 24

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**KEY OBSERVATIONS**

- ZS-9 has 9.3 times more K+ binding capacity than Kayexalate® (SPS)
- ZS-9 is >125 times more selective for K+ than Kayexalate
- Kayexalate is more selective for Ca2+ than K+
A

Serum Potassium (mmol/liter)

0.0  0.4  0.8  1.2  1.6  2.0  2.4  2.8  3.2  3.6  4.0  4.4  4.8  5.2  5.4

Hour

Placebo (N=158)
ZS-9, 5 g (N=157)
ZS-9, 10 g (N=143)

Dose *P<0.05

NEJM – Packham, 2015
A Time to First Serum Potassium Level ≥5.5 mmol/liter

Patients with Recurrent Hyperkalemia (%)

Week of Withdrawal Phase

No. at Risk
Placebo 52 46 38 31 29 25 25 23 15
Patiromer 55 53 49 48 45 43 42 42 32
## Adverse Events

**Table 2. Adverse Events during the Initial Treatment Phase and through the Safety Follow-up Period for That Phase.**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\geq 1$ Adverse event†</td>
<td>114 (47)</td>
</tr>
<tr>
<td>Constipation</td>
<td>26 (11)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Anemia</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>7 (3)</td>
</tr>
<tr>
<td>$\geq 1$ Serious adverse event†</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>

**Table 3. Adverse Events during the Randomized Withdrawal Phase and through the Safety Follow-up Period for That Phase.**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (N = 52) no. of patients (%)</th>
<th>Patiromer (N = 55) no. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\geq 1$ Adverse event</td>
<td>26 (50)†</td>
<td>26 (47)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (8)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Supraventricular extrasystoles</td>
<td>1 (2)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>2 (4)</td>
</tr>
<tr>
<td>$\geq 1$ Serious adverse event</td>
<td>1 (2)‡</td>
<td>0</td>
</tr>
</tbody>
</table>
METABOLIC ACIDOSIS
CASE 2

- A 30 year old African American female with FSGS since childhood has progressed to CKD IV-V, Cr is 4.0 mg/dL. She is listed for a pre-emptive transplant and is hoping to avoid dialysis.

- She denies nausea, vomiting, weight loss, poor appetite, fatigue, decreased urine output, or edema

- On exam her blood pressure is 125/82, she is very comfortable, has no edema, and her cardiovascular exam is normal

- Na 136  K 5.1  Bicarb 16  BUN 48  Cr 4.1
Is oral bicarbonate indicated in this patient?

• If so, what benefits would initiation of bicarbonate confer to this individual?

  • Delay in progression of her CKD
  • Improvement in serum potassium
  • Improved bone health
  • Reduce muscle wasting
METABOLIC ACIDOSIS

- Occurs in most CKD patients, usually at GFR < 30 ml/min

- Consequences:
  - Increased muscle catabolism with muscle wasting
  - Increased risk for bone loss and secondary hyperparathyroidism
  - ?CKD progression

- Treatment: Sodium Bicarbonate to maintain CO$_2$ levels > 22mEq/L
NH₄⁺ Production increases with intracellular acidosis
Covesdy, NDT 2012

- CKD stage 1: 7%
- CKD stage 2: 17%
- CKD stage 3B: 24%
NaHCO₃ therapy and CKD progression

Brito-Ashurst, JASN 2009
QUESTION

• How many mEq of bicarbonate is in a standard 650 mg tablet of NaHCO3?

1) 8 mEq
2) 15 mEq
3) 30 mEq
4) 65 mEq
- NaHCO₃ molecular weight = 84 g/mol
- 1 tablet = 650 mg
- 84,000 mg = 1 mol = 1000 mmol = 1000 mEq
- 84 mg = 1 mEq
- 650 mg = 7.8 mEq
# ALKALI REPLACEMENT OPTIONS

<table>
<thead>
<tr>
<th>sodium bicarbonate</th>
<th>potassium citrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>650 mg</td>
<td>10 mEq</td>
</tr>
</tbody>
</table>
ALTERNATIVELY, BUT STILL UNAPPEALING....

- 1/8 teaspoon = 600 mg NaHCO$_3$ = 7 mEq
BICARBONATE SUPPLEMENTATION

• Daily production of non-volatile acid is typically 50-100 mEq/day

• Supplementation typically not necessary until late stages of CKD

• A regimen of 2-3 650 mg tabs BID is enough to replace the buffered bicarbonate

• Once dialysis is initiated, bicarbonate supplementation not needed
DYSNATREMIA
CASE 3

• 40 year old female with CKD3 2/2 lupus nephritis, baseline Cr 1.8. Recently treated with high dose prednisone/Cyclophosphamide induction, recently tapered off steroids and maintained on Cellcept.

• Na 128       K 5.8       HCO3 22       BUN 32       Cr 1.8

• Which tests should be considered?
  • Urine osmolality
  • Serum ADH level
  • Urine sodium
  • TSH
  • A.M. Cortisol
PHYSIOLOGY OF DYSNATREMIA

- Gradual development of isosthenururia

Normal urine osmolality

Serum Osm 300

Urine osmolality in advanced CKD

1200

500

50

150
WHAT CAUSES HYponATREMIA?

**Physiologic**
- Volume depletion
- Pain
- Nausea
- Hypothyroidism
- Adrenal insufficiency

**Pharmacologic**
- Thiazide diuretics
- SSRIs
- TCAs
- Opiates
- AEDs
• **Thiazides**
  - Enhances Na excretion
  - Impairs ability of kidney to maximally dilute

• **Loop Diuretics**
  - Enhances Na and water excretion
  - Washes out medullary concentration gradient
HYPERNATREMIA

• Excess water losses by the kidney (low urine osmolality). Hypernatremia develops only in the setting of impaired access to water or impaired thirst mechanism

• Kidney diseases that can predispose to hypernatremia include:
  • Lithium use
  • Loop diuretics
  • Medullary cystic kidney disease
  • Hypokalemia
  • Postobstructive diuresis
THE TAKEAWAY POINT

HYponatremia

• Too much water!

• Urine should be maximally dilute (low urine osm)

• Treat by restricting water and enhancing water excretion

HYPernatremia

• Not enough water!

• Urine should be maximally concentrated (high urine osm)

• Treat by giving water
BONE MINERAL DISEASE
CASE 4

- 65 year old woman with CKD4 2/2 DM (SCr 3.0 mg/dL) undergoes a DEXA scan which reveals osteopenia. She has been taking calcium carbonate supplements for the past year over the counter. She has never seen a nephrologist.

- What is the most appropriate next step?
  - Check parathyroid hormone (PTH)
  - Check 25-OH Vit D level
  - Check 1, 25-OH Vit D level
  - Start bisphosphonate
Let’s Meet the Players

• Parathyroid Hormone (PTH)
• Vitamin D / Active Vitamin D
• Fibroblast Growth Factor (FGF) -23
• Klotho Co-Factor
Parathyroid Hormone

- PTH is the primary defense against hypocalcemia, used in the minute-to-minute regulation of serum iCa$^{++}$

Riccardi et al, Archives of Med Res, 1999
Parathyroid Hormone

Ca++

CaSR
Parathyroid Hormone

At the bone, PTH promotes osteoclast differentiation and bone resorption, mobilizing calcium (and phosphorus)
Parathyroid Hormone

At the kidney, PTH stimulates calcium resorption in the distal nephron. . .

(AND, phosphorus excretion proximally...)

AND, vitamin D activation
Parathyroid Hormone

PTH promotes hydroxylation at the 1α-position “activating” vitamin D (calcitriol)
Parathyroid Hormone

This active vitamin D then facilitates calcium (and phosphorus) absorption in the GI tract
Calcium Homeostasis

As calcium drops...
Phosphorus Homeostasis
FGF23

• Fibroblast growth factor (FGF) 23 has been identified as a significant phosphaturic factor

• It is produced by osteocytes and osteoblasts primarily in response to elevated phosphorus levels
FGF23

“Oncogenic Osteomalacia”

FGF23 overproduction
Renal phosphorus wasting
Persistent hypophosphatemia
Calcitriol deficiency

PROXIMAL TUBULE

25-OH Vitamin D

1,25-(OH)₂ Vitamin D

Na⁺

Pi

P2T2a

NPT2a, NPT2c
Phosphorus Homeostasis

As phosphorus rises

PO₄

PTH

FGF23

Department of Medicine
Division of Nephrology
Parathyroid Hormone

FGF23

FGFR-1

KLOTHO

K
Mineral Homeostasis

• And so, that is what is supposed to happen when everything works. . .

• **Calcium** is primarily regulated by **PTH**
  • Active Vitamin D regulates PTH

• **Phosphorus** is regulated by **FGF23**
Phosphorus Homeostasis

1200 mg

400 mg

800 mg
Phosphorus Homeostasis

1200 mg

800 mg
Kidney Dysfunction

1,25 Vit D deficiency
Low Ca absorption
High phosphorus

Ca
PO₄

FGF23

PTH
Kidney Dysfunction

KLOTHO
Reduced in CKD
Kidney Dysfunction

SECONDARY HYPERPARATHYROIDISM!

- Low 1,25 Vit D
- Low Calcium
- High Phosphorus
- Low Klotho
- Loss of VDR/CaSR
CONCLUSION

• **HYPERKALEMIA** – New and safer binders are now available if you cannot control the potassium with medication adjustments or dietary restriction.

• **METABOLIC ACIDOSIS** – Bicarbonate should be considered in patients who cannot maintain a bicarbonate above 18-20 mEq/L and several options exist.

• **DYSNATREMIA** – Too much water or not enough water. Restrict water or give water.

• **BONE AND MINERAL METABOLISM** – It’s complicated...
THANK YOU!!!