Diagnostic Challenge: Electrolyte Disorders

Princeton, NJ

September 5, 2008
12:30 PM – 1:45 PM
Session 9: Diagnostic Challenge: Electrolyte Disorders

Learning Objectives

- Identify 2 common causes of hyponatremia and their respective treatments
- Describe management options for treating hyperkalemia associated with ACEIs and ARBs

Faculty

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Dr Palmer received his medical degree from UT Southwestern Medical School and completed his residency in internal medicine at Walter Reed Army Medical Center, Washington, DC. He completed a research fellowship in the Department of Nephrology at the Walter Reed Army Institute of Research and a clinical fellowship in the Division of Nephrology at UT Southwestern Medical Center-Parkland Memorial Hospital.

Dr Palmer has been published in The New England Journal of Medicine, Transplantation, the American Journal of Medicine, the American Journal of Medical Science, and Advances in Internal Medicine. He is a fellow of the American College of Physicians and is a member of the Texas Medical Association, the International Society of Nephrology, the American Society of Nephrology, and the Southern Society for Clinical Investigation.

Faculty Financial Disclosure Statement

The presenting faculty reported the following:
Dr Palmer has no financial relationships to disclose.

Drug List

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<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
<th>Generic</th>
<th>Trade</th>
</tr>
</thead>
<tbody>
<tr>
<td>amiloride</td>
<td>various</td>
<td>naproxen</td>
<td>Aleve, Naprosyn</td>
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<tr>
<td>cyclosporin</td>
<td>Neoral, Gengraf, Sandimmune</td>
<td>pentamidine</td>
<td>Pentam</td>
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<td>eplerenone</td>
<td>Inspra</td>
<td>rosiglitazone</td>
<td>Avandia</td>
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<tr>
<td>fludrocortisone</td>
<td>Florinef</td>
<td>spironolactone</td>
<td>Aldactone</td>
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<tr>
<td>fluoxetine</td>
<td>Prozac</td>
<td>tacrolimus</td>
<td>Prograf</td>
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<td>furosemide</td>
<td>Lasix</td>
<td>ticarclillin + clavulanate</td>
<td>Timentin</td>
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<tr>
<td>hydrochlorothiazide (HCTZ)</td>
<td>HydroDIURIL</td>
<td>topiramate</td>
<td>various</td>
</tr>
<tr>
<td>indomethacin</td>
<td>Indocin</td>
<td>triamterene</td>
<td>various</td>
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<tr>
<td>linezolid</td>
<td>Zyvox</td>
<td>trimethoprim</td>
<td>Vancocin</td>
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<tr>
<td>methicillin</td>
<td>various</td>
<td>vancomycin</td>
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Investigational

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
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</thead>
<tbody>
<tr>
<td>methylenedioxymethamphetamine</td>
<td>Ecstasy (street name)</td>
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Suggested Reading List


Session 9
Case 1

A 21 yo woman is referred for chronic weakness. Her c/o weakness began over the last several months. She states that she has been gaining some weight over the past few years and wonders whether there is a medical reason for this. She denies vomiting, diarrhea, or ingestion of medicines.

BP of 90/60 lying and 80/60 on standing. PE is otherwise normal.

Labs: Na 133, K 2.8, Cl 83, total CO₂ 34. Arterial blood gases: pH of 7.46, pCO₂ 43 mm Hg. Urine electrolytes Na 74, K 35, Cl < 15. Urine pH 8.0

Which of the following is the most likely diagnosis?

1. Occult use of loop diuretics
2. Surreptitious use of laxatives
3. Vomiting
4. Bartter syndrome
5. Primary hyperaldosteronism
Case 1

- Labs: Na 133, K 2.8, Cl 83, total CO₂ 34
- Arterial blood gases: pH of 7.46, pCO₂ 43 mmHg
- Urine electrolytes: Na 70, K 35, Cl<15. Urine pH 8.0

Case 2

- A 65 yo man presents to the ER with shortness of breath and fever for 3 days. His PO intake has decreased during this period of time.
- PE: T 38.5 C°, RR 24, BP 110/70 supine, 90/60 standing, the remainder of the exam is significant for rales in the RUL.
- Lab: Na 140, Cl 102, K 4.3, HCO₃ 22, BUN 28, Creatinine 1.2, Chest X-ray RUL infiltrate
- He is treated with IV ticarcillin/clavulanate
- Two days later: Na 138, K 2.6, Cl 90, HCO₃ 34, Urine: Na 35, K 40, Cl < 10, pH 5.5

What is the cause of the hypokalemic metabolic alkalosis?

1. Vomiting
2. Antibiotic induced diarrhea
3. Antibiotic-induced tubulointerstitial disease
4. Non-reabsorbable anion effect of ticarcillin
5. Loop diuretic use
Which one of the following would be the most effective way to have prevented the electrolyte abnormalities?

1. Administer a loop diuretic
2. Administer fludrocortisone
3. Replete extracellular fluid volume
4. Prescribe spironolactone

Thiazolidinedione-Induced Edema

- Dose dependent weight gains of up to 4 kg can occur with these drugs
- When used with insulin the incidence of edema 15-16%
- Can lead to CHF in patients at risk

Body Weight Gain in Untreated and RGZ-Treated Control and Collecting Duct PPARγ KO Mice

Diuretic Treatment on Rosiglitazone-Induced Fluid Retention

Type II Diabetic patients
N=381
RSG 4 mg bid x 12 wks
Patients with 0.5% ↓ Hct
N=260
Randomize for 7 d to:
- RSG
- Withdraw RSG
- RSG + 40 mg/d furosemide
- RSG + 25 mg/d HCTZ
- RSG + 50 mg/d spironolactone

Topiramate-Induced Metabolic Acidosis

- An antiepileptic approved for treatment of partial seizures, primary generalized tonic-clonic seizures, and other conditions
- Carbonic anhydrase inhibitory effects can give rise to normal gap metabolic acidosis
- In 54 treated adult patients, 26 had mean HCO₃ of 18.8 (13-21)
Increased Stone Risk with Topiramate

- 32 topiramate treated subjects vs 50 ctrl
- ↑ Urine pH, U\(_{\text{HCO}_3^{-}}\)V, and FE\(_{\text{HCO}_3^{-}}\)
- ↓ Urine citrate
- Changes increase the risk for calcium phosphate stones


Linezolid-Induced Lactic Acidosis

- Oxazolidinone antibacterial agent effective against methicillin and vancomycin resistant gm positive organisms
- Lactic acidosis reported to spontaneously develop in patients after several weeks of therapy (40-58 d)
- Resolution occurs 3-4 days after discontinuation of drug
- Related to mitochondrial toxicity


Case 3

A young woman comes for her routine physical exam and was found to be hypokalemic (2.7 mEq/l). Upon more detailed investigation, she denied vomiting and the use of diuretics or laxatives. Her BP was 90/55 mm Hg, pulse 90 lying and 80/55 pulse 120 standing. The patient works as a fashion model and as such she has always been concerned about her body weight. She admitted use of diuretic in the past but denies recent use of diuretic, laxatives, or induced vomiting.

<table>
<thead>
<tr>
<th>Plasma:</th>
<th>Na(^+)</th>
<th>K(^+)</th>
<th>Cl(^-)</th>
<th>HCO(_3^{-})</th>
<th>Mg(_{2+})</th>
<th>Creat</th>
<th>Osmolality</th>
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<tbody>
<tr>
<td>138</td>
<td>2.7</td>
<td>95</td>
<td>32</td>
<td>1.0</td>
<td>1.0</td>
<td>287</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Urine:</th>
<th>Na(^+)</th>
<th>K(^+)</th>
<th>Cl(^-)</th>
<th>UpH</th>
<th>Mg(_{2+})</th>
<th>Ca(^{2+})</th>
<th>Osmolality</th>
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</thead>
<tbody>
<tr>
<td>56</td>
<td>61</td>
<td>67</td>
<td>6.5</td>
<td>100 mg</td>
<td>300 mg</td>
<td>275</td>
<td></td>
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</tbody>
</table>

What is the most likely diagnosis?
1. Vomiting
2. Surreptitious laxative abuse
3. Occult use of thiazide diuretics
4. Bartter syndrome
5. Hypokalemic periodic paralysis

Loop Diuretic or Bartter Syndrome

TAL

TAL=thick ascending limb; CD=collecting duct

What is the most likely diagnosis?
Case 3 continued

The patient is admitted to the hospital for further evaluation. Her BP was 100/65 mm Hg, pulse 90 lying and 90/60 pulse 105 standing. Laboratory examination 24 hours later show the following:

<table>
<thead>
<tr>
<th>Plasma</th>
<th>Na⁺</th>
<th>K⁺</th>
<th>Cl⁻</th>
<th>HCO₃⁻</th>
<th>Mg²⁺</th>
<th>Creat</th>
<th>Osmolality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>138</td>
<td>2.8</td>
<td>95</td>
<td>32</td>
<td>1.0</td>
<td>1.0</td>
<td>287</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Urine</th>
<th>Na⁺</th>
<th>K⁺</th>
<th>Cl⁻</th>
<th>UₚH</th>
<th>Mg²⁺</th>
<th>Ca²⁺</th>
<th>Osmolality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
<td>10</td>
<td>&lt;10</td>
<td>6.0</td>
<td>25</td>
<td>100</td>
<td>580</td>
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</tbody>
</table>

Case 4

- A 60 yo woman with long standing degenerative joint disease and hypertension presents with complaint of dizziness. Current Meds: fluoxetine 20 mg/d, indomethacin 25 mg bid, HCTZ 25 mg (started 2 weeks ago for hypertension)
- PE: BP supine 148/86, P 88 standing 134/80, 104, rest of exam unremarkable
- Labs: Na 122, K 3.8, Cl 88, HCO₃ 27

Which one of the following is true regarding the serum Na?

1. The patient likely has primary polydipsia
2. Fluoxetine decreases the risk for hyponatremia
3. NSAIDs impair renal concentrating ability
4. Thiazide-induced hyponatremia is more common in summer months

Characteristics of Thiazide-Induced Hyponatremia

- Occurs in 13% of treated patients
- Thiazides implicated in 20-30% of hyponatremic subjects
- Thiazides used in 75% of hospitalized HTN patients
- Risk factors:
  - Increasing age
  - Female sex
  - Low body weight
  - Increased incidence in summer
- Typically occurs 2-12 days after initiation, but can develop at any point during use
Thiazides Impair Urinary Dilution

SSRIs are the most common cause of drug induced increases in ADH


Mechanisms of Thiazide-Induced Hyponatremia

• Decrease in free water formation due to increased proximal reabsorption resulting from contraction of EABV
• Impairs maximal urinary dilution at level of distal convoluted tubule
• Increased ADH due to unloading of low and high pressure baroreceptors
• Increased insertion of aquaporin-2 in collecting duct


A Recipe for Hyponatremia

• 60-year-old women with hypertension and degenerative joint disease
• Medications: hydrochlorothiazide 25 mg/d, indomethacin (NSAID) 25 mg bid and fluoxetine 20 mg/d (SSRI)


Treatment Considerations

• Hyponatremia will resolve upon discontinuation of thiazide
• Fluid restriction < 1.0 L/d
• Do not correct any faster than 12 mEq/L/d

Hyponatremia and “Ecstasy” (3,4 methylenedioxymethamphetamine) Ingestion

• Ecstasy ingestion is associated with acute development of hyponatremia
• Parent compound and metabolites have been shown to stimulate AVP in both humans and experimental models
• Ecstasy also stimulates thirst

Case 5

- A 54-year-old woman is referred for evaluation and treatment of chronic kidney disease stage 3 secondary to diabetic nephropathy, BP 146/88 mmHg
- Current medications include naproxen 500 mg twice daily prescribed by an ER physician secondary to a sprain two weeks earlier and HCTZ 25 mg/d
- Labs (mEq/l) Na 140, K 5.4, Cl 106, HCO3 19, creatinine 1.8 mg/dL, glucose 148 mg/dL, albumin/creatinine ratio 3800 mg/g

Management of Hyperkalemia in Patients Treated With ACEIs or ARBs

- Discontinue other meds that interfere in K⁺ excretion

Management of Hyperkalemia in Patients Treated With ACEIs or ARBs

- Discontinue other meds that interfere in K⁺ excretion
- Low K⁺ diet (70 mEq/d)
- Effective diuretic therapy: loop diuretics when estimated GFR < 30 ml/min (use furosemide twice daily)
- NaHCO₃ tablets (650-mg tablet, 8 mEq)
- Decrease dose of ACEI or ARB

Case 5 Continued

- An ARB is prescribed and on follow-up two weeks later the blood pressure has fallen from 146/88 mmHg to 134/78 mmHg
- Repeat labs show the creatinine has increased from 1.8 to 2.4 mg/dL

Which of the Following Would Be the Most Appropriate Next Step in Management of This Patient?

1. Note in the chart that an ARB or ACEI should not be used in this patient because of the risk of worsening hyperkalemia
2. Start high dose ARB therapy since these agents do not cause the serum potassium to increase
3. Discontinue the non-steroidal anti-inflammatory drug and recheck the potassium in 1 week
4. Discontinue the HCTZ and begin furosemide 20 mg once daily

Drug Interactions in the RAS

RAS=renin angiotensin system


Therapeutic Complications
Effect of BP Control on $P_{eg}$ in Setting of Impaired Renal Autoregulation


Therapeutic Complications

- Renal artery stenosis
- PCKD
- Arteriolar lesions

Functional
- ↓ EABV
- NSAIDs, CyA
- Sepsis