ACID BASE Conference

Hasan Fattah
9/4/2012
75y/o F w/ complex PMH of OSA on home O2, T2DM, HTN, diastolic HF, and pulm HTN presented in respiratory distress, Patient reported lost consciousness per daghuter.

ROS: Patient denied any recent fever, chills, weight loss, change in cough or sputum production, chest pain, diarrhea, or constipation.

Meds -- Bosentan 62.5mg BID, Carvedilol 25mg BID, lisinopril 20mg qd, nifedipidine XL 60mg qd, lasix 40mg qd, doxazosin 4mg BID, lantus 10 units qhs, novolin, glipizide 10mg qd, Nexium 40mg qd, Docusate 100mg qd, Polyethylene glycol 1 pack/d, warfarin 5mg qd
• Upon presentation to ED:
  V/S: afebrile, Pulse 99, RR18, BP179/84.
• notable labs:
  Hgb 9.1. LeWBC: 12.1, Cr: 0.9, Co2: 38, K: 4.2, Cl:99, Na:143, AG: 5
  VBG: ph 7.119, pCO2 121, bicarb 38
• was subsequently intubated and admitted to ICU
<table>
<thead>
<tr>
<th>Date</th>
<th>PH</th>
<th>PCO₂</th>
<th>PO₂</th>
<th>HCO₃</th>
<th>Na</th>
<th>K</th>
<th>Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>31/7 V</td>
<td>7.1</td>
<td>121</td>
<td></td>
<td>38</td>
<td></td>
<td></td>
<td>4.6</td>
</tr>
<tr>
<td>31/7</td>
<td>7.3</td>
<td>69</td>
<td>378</td>
<td>34</td>
<td>141</td>
<td>4.7</td>
<td>98</td>
</tr>
<tr>
<td>31/7</td>
<td>7.53</td>
<td>41</td>
<td>96</td>
<td>34</td>
<td>141</td>
<td>4.1</td>
<td>100</td>
</tr>
<tr>
<td>1/8</td>
<td>7.44</td>
<td>49</td>
<td>167</td>
<td>33</td>
<td>142</td>
<td>4.6</td>
<td>102</td>
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</table>
retention of excess alkali and is manifested by an increase in venous \([\text{total CO}_2]\) to greater than 30 mmol/l or in arterial \([\text{HCO}_3^-]\) to greater than 28 mmol/l

Metabolic alkalosis is a unique acid-base disorder because it can be induced and sustained by functional alterations in renal ion transport.
In some instances, the pathophysiologic process is not completely understood. As a result, the causes often have been categorized based on response to treatment rather than on the specific pathophysiologic process.
General Considerations

Persistent alkalosis occurs only when tubule ion transport is altered in a way that limits or prevents bicarbonate excretion.
Causes of Impaired Renal Bicarbonate Excretion in Metabolic Alkalosis

1. Kidney failure

2. Secondary stimulation of collecting duct ion transport
   - Extrarenal Cl\(^-\) losses with secondary renal K\(^+\) losses
   - Renal Cl\(^-\) losses with secondary K\(^+\) losses
     ◊ Pharmacologic (diuretics)
     ◊ Inactivating genetic mutations of Cl\(^-\)-linked Na\(^+\) cotransporters

3. Primary stimulation of collecting duct ion transport
   - Mineralocorticoid induced
   - Activating genetic mutations of ENaC or its signal pathway
Key Apical Membrane Ion Transporters Along the Nephron
PT Hydrogen Ion Secretion:

- 2 apical membrane transporters: sodium/hydrogen exchanger (NHE3), H\(^+\)-ATPase, removes \(\sim 70\%\) of filtered bicarbonate from the tubule lumen.
- Potassium depletion: upregulating transport proteins involved in bicarbonate movement from cells to the peritubular interstitium.
- Endogenous endothelins: NHE3\(^*\)

• **Na⁺/K⁺/Cl⁻ Cotransporter:**
  • Impairment of its function leads to increasing sodium delivery to the CD, and hydrogen ion and potassium excretion.

• **Potassium/Cl depletion:**
  • decreases activity of the Na⁺/K⁺/2Cl⁻ cotransporter and mRNA levels for its synthesis.
  • promotes increased ammonium uptake through this cotransporter because ammonium competes with potassium for entry.
- **Na⁺/Cl⁻ Cotransporter:**
  - Potassium/Cl depletion: activity of this transporter and the messenger RNA for its synthesis also are downregulated by potassium depletion.
  - In chloride depletion states, it is proposed, but unproved, that a decrease in chloride delivery to this cotransporter impairs sodium uptake.
Pendrin (Cl⁻/HCO₃⁻) exchanger, Slc26a4:
- stimulated in metabolic alkalosis.
- In pendrin-null homozygous mice*, no secretion of bicarbonate occurs; however, metabolic alkalosis does not develop unless they also are placed on a chloride-restricted diet, In the absence of chloride restriction, these mutant animals downregulate hydrogen ion-secreting transport proteins in the collecting duct, compensating for the lack of bicarbonate secretion.
- Recent evidence suggests that the mechanism for this downregulation is a decrease in (ENaC) activity induced by a decrease in bicarbonate delivery to the principal cells containing this ion channel.

Upregulated:
- chloride depletion.
- mineralocorticoid administration.
balance between bicarbonate secretion through pendrin and hydrogen ion secretion in the collecting duct has a key role in determining the steady-state serum bicarbonate level.
ENaC:
- regulated by: flow rate (and thus sodium delivery) and aldosterone, alkalemia.

Pendrin modulates ENaC function by changing luminal HCO₃⁻. An increase in bicarbonate delivery to ENaC, bicarbonate levels in tubule fluid and the peritubular interstitium may have an important role in stimulating this transporter in metabolic alkalosis, but sufficient sodium delivery also is a necessary factor*

Epithelial Potassium Channels:

- The ROMK (renal outer medullary potassium)
- The maxi-K channel not open under normal conditions, but opens when flow is increased at either site and facilitates potassium secretion with higher conductance than ROMK.
H\(^+\)-ATPase and H\(^+\)/K\(^+\)-ATPase:

- increase in sodium delivery to the collecting duct and reabsorption through ENaC.
- luminal bicarbonate.
Etiology

based on pathophysiology.

1. chloride depletion, due to abnormal losses from the gut or the kidney.
2. excess adrenal corticosteroids, or CD transport abnormalities that mimic excess mineralocorticoid activity.
3. alkali administration or ingestion.
## Causes of Chloride-Depletion Metabolic Alkalosis

<table>
<thead>
<tr>
<th>Cause</th>
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</thead>
<tbody>
<tr>
<td>Chloride loss from the stomach (common)</td>
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<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Nasogastric suction</td>
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<tr>
<td>Diuretic administration (common)</td>
</tr>
<tr>
<td>Thiazides</td>
</tr>
<tr>
<td>Metolazone</td>
</tr>
<tr>
<td>Loop diuretics: furosemide, bumetanide, torsemide, ethacrynic acid</td>
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<tr>
<td>Chloride-depleting diarrheas (rare)</td>
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<tr>
<td>Congenital chloridorrhea</td>
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<tr>
<td>Some villous adenomas of the colon</td>
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<tr>
<td>High-volume ileostomy losses</td>
</tr>
<tr>
<td>Impaired chloride-linked sodium transport (rare)</td>
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<tr>
<td>Bartter syndrome</td>
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<tr>
<td>Gitelman’s syndrome</td>
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<tr>
<td>Recovery from chronic hypercapnia (rare)</td>
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<tr>
<td>Gastrocystoplasty (rare)</td>
</tr>
<tr>
<td>Cystic fibrosis (rare)</td>
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<tr>
<td>Severe potassium deficiency (rare)</td>
</tr>
</tbody>
</table>
The Enigma of Chloride-Depletion Metabolic Alkalosis

- Renal, and extra-renal Cl losses induce metabolic alkalosis.
- the disorder is sustained by dietary chloride restriction despite cessation of the initiating cause.
- In all models of metabolic alkalosis sustained by chloride depletion, both hydrogen ion and potassium secretion into the collecting duct are increased abnormally, but the mechanisms are incompletely understood.
Proposals:

alkalemia-induced stimulation of ENaC coupled with just sufficient sodium delivery to the collecting duct may be the combination of events necessary to recapture all the filtered and secreted bicarbonate and sustain the metabolic alkalosis induced by chloride depletion.
Effects of Gastric Drainage with NaCl-Restricted Diet

Gastric drainage

- Plasma \( \text{HCO}_3^- \) (mmol/l)
- Plasma \( \text{Cl}^- \) (mmol/l)
- Cumulative \( \text{Cl}^- \) balance (mmol)
- Net acid excretion (mmol)
- Cumulative \( K^+ \) balance (mmol)

Time (days)
supplemental K without chloride does not correct the disorder.

In addition, induction and maintenance of the disorder is independent of either extracellular fluid (ECF) volume depletion or potassium losses and is not mediated by increased aldosterone levels.

However, in the absence of K repletion, much larger amounts of chloride are required to correct the alkalosis.
Data from Hernandez et al
Diuretic-Induced Metabolic Alkalosis
In other words..

The effect of the associated potassium depletion to stimulate hydrogen ion secretion earlier in the nephron and cause a shift in sodium reabsorption from the loop and early distal tubule to the collecting duct, as well as alkali-induced stimulation of ENaC, may be the combination required for sustaining this common disorder.
Interplay of $K^+$, $Cl^-$, and $HCO_3^-$ Transport by the Kidney
Primary Abnormalities in Renal Ion Transport:

- less than 1% of all causes, mainly primary hyperaldosteronism.
- More rarely, genetic mutations in the regulation and function of specific transporters in the loop of Henle and distal nephron.
Renal Ion Transport Derangements and Metabolic Alkalosis

- Impaired activity in Gitelman’s syndrome
- Abnormal stimulation in:
  - Primary hyperaldosteronism
  - Glucocorticoid-remediable aldosteronism
  - Apparent mineralocorticoid excess
  - Liddle syndrome
  - 11β-Hydroxysteroid dehydrogenase deficiency
Recovery from Chronic Hypercapnia:

The renal response: serum $[\text{HCO}_3^-]$ increases and body Cl$^-\,$ stores are reduced. When $\text{PCO}_2$ is restored to normal, renal excretion of excess $\text{HCO}_3^-\,$ requires repletion of the Cl$^-\,$ losses incurred during adaptation. If these losses are not replaced, recovery from hypercapnia can result in a persistent metabolic alkalosis.
Severe K\(^+\) Deficiency:

- (serum [K\(^+\)] <2 mmol/l), metabolic alkalosis can be sustained despite Cl\(^-\) administration.
- Chloride resistance in this setting is due to impairment of renal Cl\(^-\) reabsorption. Even partial repletion of K\(^+\) stores rapidly reverses this problem and makes the alkalosis Cl\(^-\) responsive.
Corticosteroid and Apparent Corticosteroid-Induced Metabolic Alkalosis

<table>
<thead>
<tr>
<th>Causes of Corticosteroid and Apparent Corticosteroid-Induced Metabolic Alkalosis</th>
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<tbody>
<tr>
<td><strong>Mineralocorticoid excess</strong></td>
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<tr>
<td><strong>Apparent mineralocorticoid excess</strong></td>
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<tr>
<td><strong>Glucocorticoids (high dose)</strong></td>
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Exogenous Alkali

- If renal $\text{HCO}_3^-$ excretion is impaired as a result of kidney failure, alkali administration can cause a sustained metabolic alkalosis independent of $\text{Cl}^-$ intake.
<table>
<thead>
<tr>
<th>Renal Status</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal renal function (only in association with K⁺ depletion or low NaCl intake)</td>
<td>Alkali intake: NaHCO₃, citrate, lactate, acetate, amino acid anions</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Milk–alkali syndrome Alkali intake Aluminum hydroxide with K⁺ exchange resin</td>
</tr>
<tr>
<td>Alkali/Alkali Precursor</td>
<td>Source</td>
</tr>
<tr>
<td>------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>NaHCO₃: pills, intravenous solutions Proprietary brands, e.g., Alka–Seltzer Baking soda KHCO₃: pills, oral solutions</td>
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<tr>
<td>Lactate</td>
<td>Ringer’s solution, peritoneal dialysis solutions</td>
</tr>
<tr>
<td>Acetate Glutamate Propionate</td>
<td>Parenteral nutrition</td>
</tr>
<tr>
<td>Citrate</td>
<td>Blood products, plasma exchange, K⁺ supplements, alkalinizing agents</td>
</tr>
<tr>
<td>Calcium compounds (alkalinizing effect minimal when given orally)</td>
<td>Calcium supplements, phosphate binders</td>
</tr>
<tr>
<td>Acetate Citrate Carbonate</td>
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Clinical Manifestations

- Mild to moderate metabolic alkalosis is well tolerated, with few clinically important adverse effects.
- Hypokalemia/cardiac arrhythmias
- With more severe metabolic alkalosis (serum $[\text{HCO}_3^-]$ >45 mmol/l), arterial $\text{PO}_2$ often decreases to less than 50 mm Hg (<6.65 kP) secondary to hypoventilation, and ionized calcium decreases (due to alkalemia).
- Patients with serum $[\text{HCO}_3^-]$ greater than 50 mmol/l may develop seizures, tetany, delirium, or stupor.
Diagnosis:

(Total CO₂) > 30 mmol/l

(K⁺) < 3.5 mmol/l and/or (Total CO₂) < 40 mmol/l

Vomiting, NG suction, loop or thiazide diuretic use?

- Yes
  - Manage disorder

- No
  - Assess BP, ECF volume, urine (Cl⁻)
    - ↑ BP, ECF volume replete or expanded
      - Urine (Cl⁻) > 30 mmol/l
      - Consider mineralcorticoid excess or apparent excess syndromes

(K⁺) > 3.5 mmol/L and/or (total CO₂) > 40 mmol/l or ? about diagnosis

Measure arterial PCO₂ and pH to fully characterize disorder

Consider

- Not easily corrected
  - Consider hereditary Cl⁻ wasting disorders

- Easily corrected
  - Simple Cl⁻ depletion disorder