Year 2003 Paper two: Questions supplied by Tricia

Question 21
A 25-year-old woman complains of tiredness. She has no significant past medical history and denies any medications. Apart from being thin, there are no abnormalfindings on examination. Her blood pressure is 105/70 mmHg

Results of investigations are listed below

Serum biochemistry
- Sodium: 138 mmol/L [135-145]
- Potassium: 2.3 mmol/L [3.4-5.0]
- Chloride: 85 mmol/L [103 – 109]
- Creatinine: 0.10 mmol/L [0.06-0.12]

Arterial blood gases:
- PH: 7.50 [7.34-7.45]
- P02: 95 mmHg [80-100]
- PCO2: 42 mmHg [35-45]
- Bicarbonate: 39 mmol/L [22-28]

Urinary biochemistry:
- Sodium: 30 mmol/L
- Potassium: 42 mmol/L
- Chloride: 13 mmol/L

The most likely explanation for these results is:
A. Occult diuretic use
B. Occult laxative use
C. Self-induced vomiting
D. Primary hyperaldosteronism
E. Bartter's syndrome

C

Refs Hypokalemi F. John Gennari review article 1998 NEJM Vol 339 No 7 pp451 - Hypokalemia with associated
- Alkalosis
- Raised bicarbonate

Clinical Spectrum
Normal range 3.4 – 5.0

Mild 3.0 – 3.5 mmol per liter often no symptoms

Less than 3.0 mmol per liter – non specific symptoms such as generalized weakness, lassitude and constipation
Less than 2.5mmol per liter – muscle necrosis can occur
Less than 2.0 mmol per liter – ascending paralysis can develop with eventual impairment of respiratory function

In patients without underlying heart disease, abnormalities in cardiac conduction are extremely unusual, even when the serum potassium concentration is below 3.0 mmol per liter. In patients with cardiac ischemia, heart failure, or left ventricular hypertrophy, however, even mild-to-moderate hypokalemia increased the likelihood of cardiac arrhythmias
- Hypokalemia increased the arrhythmogenic potential of digoxin
- Potassium depletion and hypokalemia increase both systolic and diastolic blood pressure when sodium intake is not restricted, presumable by promoting renal sodium retention

Causes
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Drugs – most common

Acute shift of potassium from extracellular compartment to cells

- Inadequate intake
- Abnormal losses
  - Via kidney induced by metabolic alkalosis
  - Loss in stool induced by diarrhea

Drugs

**TABLE 1. DRUG-INDUCED HYPOKALEMIA.**

<table>
<thead>
<tr>
<th>Hypokalemia Due to Transcellular Potassium Shift</th>
<th>Hypokalemia Due to Increased Renal Potassium Loss</th>
<th>Hypokalemia Due to Excess Potassium Loss in Stool</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β2 Adrenergic agonists</strong></td>
<td><strong>Diuretics</strong></td>
<td><strong>Phenolphthalein</strong></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Acetazolamide</td>
<td>Sodium polystyrene sultionate</td>
</tr>
<tr>
<td>Decongestants</td>
<td>Thiazides</td>
<td></td>
</tr>
<tr>
<td>Pseudoephedrine</td>
<td>Chlorothalidone</td>
<td></td>
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<tr>
<td>Phenylpropanolamine</td>
<td>Indapamide</td>
<td></td>
</tr>
<tr>
<td>Bronchodilators</td>
<td>Metolazone</td>
<td></td>
</tr>
<tr>
<td>Albuterol</td>
<td>Quinethazone</td>
<td></td>
</tr>
<tr>
<td>Terbutaline</td>
<td>Bumetamide</td>
<td></td>
</tr>
<tr>
<td>Pindolol</td>
<td>Ethacrynic acid</td>
<td></td>
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<tr>
<td>Isoprotanol</td>
<td>Furosemide</td>
<td></td>
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<tr>
<td>Fenoterol</td>
<td>Torsemide</td>
<td></td>
</tr>
<tr>
<td>Ephedrine</td>
<td>Mineralocorticoids</td>
<td></td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>Fludrocortisone</td>
<td></td>
</tr>
<tr>
<td>Metaproterenol</td>
<td>Substances with mineralocorticoids</td>
<td></td>
</tr>
<tr>
<td>Toxicologic agents</td>
<td>Effects</td>
<td></td>
</tr>
<tr>
<td>Rhododrine</td>
<td>Licorice</td>
<td></td>
</tr>
<tr>
<td>Nicardia</td>
<td>Carbamazepine</td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td>Gossypol</td>
<td></td>
</tr>
<tr>
<td>Caffeine</td>
<td>High-dose glucocorticoids</td>
<td></td>
</tr>
<tr>
<td>Verapamil intoxication</td>
<td>High-dose antibiotics</td>
<td></td>
</tr>
<tr>
<td>Chloroquine intoxication</td>
<td>Penicillin</td>
<td></td>
</tr>
<tr>
<td>Insulin overdose</td>
<td>NaClIn</td>
<td></td>
</tr>
<tr>
<td>Drug associated with magnesium depletion</td>
<td>Ampicillin</td>
<td></td>
</tr>
<tr>
<td>Xanthisines</td>
<td>Cisplatin</td>
<td></td>
</tr>
<tr>
<td>Drugs associated with magnesium depletion</td>
<td>Foscarnet</td>
<td></td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Amphotericin B</td>
<td></td>
</tr>
</tbody>
</table>

Drug induced causes due to transcellular shifts

Beta 2 sympathomimetic drugs

- decongestants, bronchodilators and inhibitors of uterine contraction
- eg a standard dose of nebulized albuterol reduces serum potassium by 0.2 – 0.4 mmol per liter, and a second dose taken within one hour reduces it by almost 1 mmol per liter
- intential ingestion of excess amount so psuedoephedrine

Xanthisines

- theophylline and caffeine stimulate the release of sympathetic amines and may also increase sodium/potassium ATPase activity by inhibiting cellular phosphodiesterase
- severe hypok feature of theophylline toxicity
other drugs
- ingestion/administration large amounts of verapamil, chloroquine, insulin

Drug induced causes due to abnormal losses of potassium

Diuretics
- the most common cause of hypokalemia
- both thiazide and loop diuretics block chloride-associated sodium reabsorption (with each inhibiting a different membrane-transport protein) and, as a result, increase delivery of sodium to the collecting tubules, where its reabsorption creates a favorable electrochemical gradient for potassium secretion
- degree related to dose of thiazide diuretic and greater when dietary sodium intake is higher
- usually but not always associated with a mild-to-moderate metabolic alkalosis (bicarbonate concentration 28-36 mmol per liter)

Drugs with mineralocorticoid or glucocorticoid effects
- fludrocortison (oral mineralocorticoid) promotes renal potassium excretion
- glucocorticoids (pred hydrocort) no direct effect on renal potassium secretion but the increase potassium excretion nonspecifically through their effect on the filtration rate and distal sodium delivery

other drugs
- IV penicillin (and derivatives) in large doses promote renal potassium excretion by increasing sodium delivery to the distal nephron
- Amnoglycoside antibiotics, antitumor drug cisplatin and antiviral drug foscarnet all cause renal potassium wasting by including depletion of magnesium
- Amphotericin B – inhibition of the secretion of hydrogen ions by collecting-duct cells as well as by causing magnesium depletion
- Laxatives and enemas – promote excessive loss in stool

Nondrug causes due to transcellular shifts
- Rarely with hyperthyroidism
- Ramilial hypokalemic periodic paralysis rare autosomal dominant disease
- Delirium tremens
- Accidental ingestion of barium compounds
- Treatment of severe pernicious anaemia with Vit b12 – due to rapid uptake of K by the new cells that are formed

Nondrug causes due to inadequate dietary intake

**Non drug causes due to abnormal losses of potassium**

Losses in stool
Losses from the lower GI tract (due most commonly to diarrhea) are usually associated with concurrent bicarbonate loss and metabolic acidosis. However, some patients with factitious diarrhea or surreptitious laxative abuse develop hypokalemia due to loss through the kidney.

**metabolic alkalosis**

Either metabolic or respiratory alkalosis can promote potassium entry into cells. In these settings, hydrogen ions leave the cells to minimize the change in extracellular pH; the necessity to maintain electroneutrality requires the entry of some potassium (and sodium) into the cells. In general the direct effect is relatively small.

Urinary potassium loss with removal of gastric acid – associated metabolic alkalosis raised the plasma bicarbonate concentration and therefore the filtered bicarbonate load above its reabsorptive threshold. As a result, more sodium bicarbonate and water are delivered to the distal potassium secretory site in combination with a hypovolemia-induced increase in aldosterone release. The net effect is increased potassium secretion and potentially large urinary potassium losses. There is also inappropriate sodium wasting at this time; thus, only the demonstration of a low urine chloride concentration points to the presence of volume depletion.

The urinary potassium wasting seen with loss of gastric secretions is typically most prominent in the first few days; thereafter, bicarbonate reabsorptive capacity increases, leading to a marked reduction in urinary sodium, bicarbonate, and potassium losses. At this time, the urine pH falls from above 7.0 (due to bicarbonate wasting) to acid (below 6.0).

- **Most commonly Induced by selective chloride depletion due to vomiting or nasogastric drainage**
- More rarely metabolic alkalosis occurs independently of chloride depletion as a result of systemic or intrarenal abnormalities that augment sodium reabsorption in the distal nephron – list in table.

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**Table 2. Causes of Potassium Loss in Stool.**

<table>
<thead>
<tr>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious diarrhea</td>
</tr>
<tr>
<td>Cholera</td>
</tr>
<tr>
<td>Salmonella</td>
</tr>
<tr>
<td>Strongyloides</td>
</tr>
<tr>
<td>Yersinia</td>
</tr>
<tr>
<td>Diarrhea associated with AIDS*</td>
</tr>
<tr>
<td>Tumor</td>
</tr>
<tr>
<td>Vipoma</td>
</tr>
<tr>
<td>Villous adenoma of the colon</td>
</tr>
<tr>
<td>Zollinger–Ellison syndrome</td>
</tr>
<tr>
<td>Jejunuleal bypass</td>
</tr>
<tr>
<td>Enteric fistula</td>
</tr>
<tr>
<td>Malabsorption</td>
</tr>
<tr>
<td>Intestinal ion-transport defects</td>
</tr>
<tr>
<td>Congenital chloride diarrhea</td>
</tr>
<tr>
<td>Cancer therapy</td>
</tr>
<tr>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Radiation enteropathy</td>
</tr>
<tr>
<td>Geophagia</td>
</tr>
</tbody>
</table>

*AIDS denotes the acquired immunodeficiency syndrome.*
Most common or these rare presentations primary hyperaldosteronism usually severe hypoK

Cushings but usually milder than hyperaldosteronism

Genetic abnormalities that influence the activity of renal ion transporters are rare causes of metabolic alkalosis and hypokalemia

- Liddle’s syndrome
- 11beta-hydroxysteroid dehydrogenase deficiency
- Bartter’s syndrome

- Rare disorder with a characteristic set of metabolic abnormalities
- HypoK, metabolic alkalosis, hyperreninaemia, hyperaldosteronism, hyperplasia of the juxtaglomerular apparatus
- The renal release of vasodilator prostaglandins (prostaglandin E2 and prostacyclin) is also increased in this condition and may partially e
- Gitelman’s syndrome

Metabolic acidosis
Increased urinary potassium losses can occur in several forms of metabolic acidosis – distal renal tubular acidosis

- diabetic ketoacidosis,
- increased distal sodium and water delivery

Other disorders

- Mag depletion
- Renal K wasting occurs in patients with acute mylogenous, mnomyeloblastic or lymphoblastic leukaemia
- Uncontrolled diabetes mellitus – renal glucose loss causes osmotic diuresis, increasing sodium delivery to the distal nephron and promoting potassium excretion

Urinary response
A normal subject can, in the presence of potassium depletion, lower urinary potassium excretion below 25-30 meq per day; values above this level reflect at least a contribution from urinary potassium wasting
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- Metabolic acidosis with a low rate of potassium excretion is, in an asymptomatic patient, suggestive of lower gastrointestinal losses due to laxative abuse or a villous adenoma.
- Metabolic acidosis with potassium wasting is most often due to diabetic ketoacidosis or to type 1 (distal) or type 2 (proximal) renal tubular acidosis.
- Metabolic alkalosis with a low rate of potassium excretion is due to surreptitious vomiting (often in bulimia in an attempt to lose weight) or diuretic use (in which the urinary collection is obtained after the diuretic effect has worn off).
- Metabolic alkalosis with potassium wasting and a normal blood pressure is most often due to surreptitious vomiting or diuretic use or to Bartter’s syndrome. In this setting, measurement of the urine chloride concentration is often helpful, being low in vomiting at a time when urinary sodium and potassium excretion may be relatively high due to the need to maintain electroneutrality as some of the excess bicarbonate is being excreted.
- Metabolic alkalosis with potassium wasting and hypertension is suggestive of surreptitious diuretic therapy in a patient with underlying hypertension, renovascular disease, or one of the causes of primary mineralocorticoid excess.

Sodium concentration is not necessarily an accurate reflection of the patient’s volume status in metabolic alkalosis. This possibility should be suspected if sodium excretion is relatively high and the urine pH is above 7.0, suggesting a high rate of bicarbonate excretion. The presence of underlying hypovolemia can be detected more accurately by finding a urine chloride concentration below 25 meq/L equiv 25 mmol/L.

### Urine chloride concentration in the diagnosis of metabolic alkalosis

<table>
<thead>
<tr>
<th>Less than 25 meq/L equiv 25 mmol/L</th>
<th>Greater than 40 meq/L equiv 40 mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting or nasogastric suction</td>
<td>Primary mineralocorticoid excess</td>
</tr>
<tr>
<td>Diuretics (late)</td>
<td>Diuretics (early)</td>
</tr>
<tr>
<td>Factitious diarrhea</td>
<td>Alkali load (bicarbonate or other organic anion)</td>
</tr>
<tr>
<td>Posthypercapnia</td>
<td>Bartter’s or Gitelman’s syndrome</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Severe hypokalemia (plasma K &lt; 2.0 mmol/L)</td>
</tr>
<tr>
<td>Low chloride intake</td>
<td></td>
</tr>
</tbody>
</table>

This patient has

- Significant hypokalemia and low chloride
- Metabolic alkalosis with raised bicarbonate
- Normal blood pressure
- Hypovolemic as evidenced by low urinary chloride

The most likely explanation for these results is:

#### Occult diuretic use

- Denies medication use
- Significant hypokalemia and low chloride
- Metabolic alkalosis with raised bicarbonate
- Normal blood pressure
- Hypovolemic
- Early in presentation would expect urinary chloride to be high so this is incorrect

#### Occult laxative use

- Incorrect – lower gastrointestinal losses usually result in metabolic acidosis

**Self-induced vomiting fulfils all criteria of presentation**

- Denies medication use
- Significant hypokalemia and low chloride
- Metabolic alkalosis with raised bicarbonate
- Normal blood pressure
- Hypovolemic
- Urinary chloride low
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Primary hyperaldosteronism
- Significant hypokaleamia and low chloride
- Metabolic alkalosis with raised bicarbonate
- Normal blood pressure
- Usually effective volume expansion due to the stimulatory effect of aldosterone on sodium reabsorption

Bartter’s syndrome
- Significant hypokaleamia and low chloride
- Metabolic alkalosis with raised bicarbonate
- Normal blood pressure
- Rare disorder – not the most likely