Too Much of a Good Thing: A Woman with Hypertension and Hypokalemia
Sean C. Murphy, Sean Agger, and Petrie M. Rainey*

CASE
A 64-year-old woman with a history of paranoid schizophrenia, hypertension, hyperlipidemia, and unexplained chronic hypokalemia presented in the outpatient psychiatric clinic for a routine follow-up visit with no specific complaints. Her history and review of systems revealed no remarkable findings. Her medications included an over-the-counter oral potassium supplement (equivalent to 2.5 mmol 3 times daily) and olanzapine (10 mg daily). She appeared well, and her physical exam was notable only for hypertension (188/105 mm Hg). A blood sample was obtained and blood chemistry tests were performed for routine monitoring.

Laboratory evaluation showed concentrations within reference intervals for the patient’s serum sodium (142 mmol/L), urea nitrogen [2.9 mmol/L (8 mg/dL)], creatinine [53 µmol/L (0.6 mg/dL)], magnesium [1.0 mmol/L (2.4 mg/dL)], and glucose [5.2 mmol/L (94 mg/dL)]. Her total carbon dioxide was high at 43 mmol/L (reference interval 22–32 mmol/L), and her serum potassium was critically low at 1.9 mmol/L (reference interval 3.7–5.2 mmol/L). The critical potassium result was reported to the ordering physician, who arranged patient transport to the emergency department.

In the emergency department, the patient was persistently hypertensive (170–180/95–110 mmHg). Review of the patient’s earlier records showed prior hypokalemia (2.1 and 3.3 mmol/L). Her electrocardiogram was normal. The patient reported no prescription diuretic use, laxative abuse, prolonged fasting, diarrhea, or vomiting. A repeat serum potassium measurement was 2.1 mmol/L, and at that time the patient’s serum osmolality was calculated to be 301 mOsm/kg. No arterial or venous blood gas measurements were performed. An untimed urine collection showed urine creatinine of 884 µmol/L (10 mg/dL), urine sodium 73 mmol/L, urine potassium 21 mmol/L, and urine osmolality 226 mOsm/kg. The primary abnormal findings were hypertension with concurrent hypokalemia and metabolic alkalosis.

The patient was placed on continuous cardiac monitoring and given intravenous and oral potassium. Morning aldosterone [<0.06 nmol/L (<2.0 ng/dL)] and renin (<14.2 pmol/L per h) were low. The medical team wondered why this patient had developed such severe hypokalemia. Subsequent interviews with the patient identified the likely cause of her hypertension and severe hypokalemia.

DISCUSSION

DIFFERENTIAL DIAGNOSIS
Hypokalemia with metabolic alkalosis presents a broad differential diagnosis that can be systematically approached by first measuring urine potassium to rule out skin and/or gastrointestinal losses (1). The patient’s random urine potassium concentration of 21 mmol/L in the setting of hypokalemia suggested renal potassium loss. Measurement of 24-h urinary potassium excretion would establish excessive loss most definitively, but this procedure was not done owing to rapid initiation of potassium supplementation, which could confound the result. The transtubular potassium gradient [(Osm\textsubscript{plasma} × K\textsuperscript+\textsubscript{urine})/(K\textsuperscript+\textsubscript{plasma} × Osm\textsubscript{urine})], although more commonly used to evaluate hyperkalemia, can be rapidly calculated and in this patient was found to be 13.3, which was inappropriately high (2) and confirmed excessive renal potassium loss.

Hypomagnesemia-induced hypokalemia was ruled out in this patient because her magnesium concentra-

QUESTIONS TO CONSIDER
1. What are common causes of hypokalemia in the setting of hypertension?
2. What are some medications or foods that can alter potassium handling?
3. What are possible mechanisms for this patient’s hypokalemia and hypertension?
tion was within the reference interval, and her increased carbon dioxide eliminated the possibility of diabetic ketoacidosis and renal tubular acidoses 1 and 2 as causes. Urinary potassium wasting can be caused by loop or thiazide diuretics. These diuretics lower blood pressure but may not be sufficient to normalize it in refractory hypertension. Our patient denied diuretic use. There are also genetic conditions that physiologically mimic diuretic use. Bartter syndrome is an autosomal recessive channelopathy of the Na-K-2Cl channel in the thick ascending limb of the loop of Henle. Patients with this condition present in childhood with metabolic alkalosis and increased urinary potassium, sodium, and chloride. Gitelman syndrome is an autosomal recessive channelopathy of the Na-Cl transporter in the distal collecting tubule that can mimic hyperaldosteronism and may present later in life. Patients with these genetic defects usually have low to normal blood pressure.

Among hypertensive patients with hypokalemia and metabolic alkalosis, Cushing syndrome or excess mineralocorticoids from primary or secondary hyperaldosteronism may cause hypokalemia. This patient, however, had low aldosterone and did not have physical findings consistent with Cushing syndrome.

Pseudohyperaldosteronism presents with low aldosterone and low renin and may result from genetic or acquired etiologies. Liddle syndrome (autosomal dominant channelopathy of the Na/K transporter in the renal collecting duct) would manifest at an earlier age. Genetic deficiency of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) leads to apparent mineralocorticoid excess and sometimes presents in adulthood. 11β-HSD2 is normally abundant in renal tubules and selectively converts cortisol to cortisone. In deficiency states, unmetabolized cortisol readily binds to aldosterone receptors and produces mineralocorticoid effects such as sodium retention and potassium wasting, leading to hypertension and hypokalemia (3). Metabolic alkalosis develops as a consequence of hypokalemia. 11β-HSD2 deficiency is rare and can be evaluated by DNA sequencing. Congenital adrenal hyperplasia presents with low aldosterone, but the late-onset form usually does not produce significant renal electrolyte losses. Ectopic adrenocorticotropic hormone syndrome or a deoxycorticosterone-secreting adrenocortical adenoma could also present with low aldosterone and renin.

During our investigation and interviews with the patient, she revealed that she was taking several herbal supplements, including an animal adrenal extract and black licorice oil. Adrenal extracts are manufactured from raw cow, pig, or sheep adrenal glands; whether or not such extracts provide exogenous mineralocorticoids is unclear. Black licorice oil was suspected to be responsible for this patient’s condition through its inhibition of 11β-HSD2.

**LICORICE-INDUCED HYPERTENSION AND HYPOKALEMIA**

Consumption of large amounts of black licorice candy has been associated with hypertension and hypokalemia. However, most currently available licorice-flavored candy is flavored with anise seed rather than the raw root of the licorice plant, *Glycyrrhiza glabra*. True licorice root contains biologically active glycyrrhizin (glycyrrhizic acid, glycyrrhizinic acid). Glycyrrhizin is a triterpenoid glycosidic saponin used as an intense sweetener in candies and for its purported beneficial effects against inflammation, viruses, ulcers, and gastrointestinal discomfort. However, glycyrrhizin inhibits metabolism of cortisol and can lead to acute and chronic cases of severe hypertension and hypokalemia. The medicinal uses of licorice have been reviewed elsewhere (4).

**MECHANISM OF GLYCYRRHIZIN**

Although many hormones exert tissue-specific effects through specific receptor interactions, the mineralocorticoid receptor in the renal collecting tubules binds cortisol and aldosterone with equally high nanomolar affinity in vitro. The in vivo primacy of aldosterone in the normal kidney is instead due to the activity of 11β-HSD2, which is abundant in renal tubules, where it
selectively converts cortisol to cortisone, thereby decreasing its affinity for mineralocorticoid receptors (3). Because aldosterone is not a substrate for 11β-HSD2, aldosterone serves as the major hormone in the kidney, regulating the exchange of potassium for sodium ions. However, when glycyrrhizin inhibits 11β-HSD2, unmetabolized cortisol stimulates aldosterone receptors, leading to a functional mineralocorticoid excess, with resulting hypertension, hypokalemia and metabolic alkalosis (Fig. 1).

Licorice-induced hypertension and hypokalemia can be suspected on the basis of an increased cortisol-to-cortisone ratio in urine (reflecting the activity of renal 11β-HSD2 rather than more widely distributed 11β-HSD type 1) and confirmed by measuring plasma glycyrrhizin concentrations or by resolution of symptoms and laboratory abnormalities following withdrawal of the glycyrrhizin source. This case illustrates licorice-containing supplements as a potential cause of significant hypertension and hypokalemia. Such supplements should be considered as possible causative agents in any patient with signs and symptoms consistent with pseudo-hyperaldosteronism.

**Table 1. Laboratory results at admission, discharge, and follow-up.**

<table>
<thead>
<tr>
<th></th>
<th>Sodium, mmol/L</th>
<th>Serum potassium, mmol/L</th>
<th>Carbon dioxide, mmol/L</th>
<th>Blood pressure, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission</td>
<td>142</td>
<td>1.9</td>
<td>43</td>
<td>188/105</td>
</tr>
<tr>
<td>Discharge</td>
<td>144</td>
<td>2.3</td>
<td>34</td>
<td>144/72*</td>
</tr>
<tr>
<td>2-Week follow-up</td>
<td>141</td>
<td>4.4</td>
<td>31</td>
<td>140/78</td>
</tr>
<tr>
<td>4-Week follow-up</td>
<td>136</td>
<td>4.4</td>
<td>29</td>
<td>135/70</td>
</tr>
</tbody>
</table>

* The patient received 10 mg oral hydralazine before this measurement.

**POINTS TO REMEMBER**

- Glycyrrhizin is contained in licorice-based foods and supplements and inhibits renal metabolism of cortisol by 11β-HSD2. When cortisol is not metabolized, it can have mineralocorticoid effects on the kidney.
- Excessive consumption of glycyrrhizin can lead to hypertension and hypokalemia and should be considered in the differential of patients presenting with these findings.
- Licorice-induced hypertension and hypokalemia may be suspected on the basis of an increased cortisol-to-cortisone ratio in urine and can be confirmed by measuring plasma glycyrrhizin concentrations or by resolution of symptoms and laboratory abnormalities following withdrawal of the glycyrrhizin source.

**USE OF LICORICE AND GLYCYRRHIZIN IN FOODS AND SUPPLEMENTS**

Glycyrrhizin has been “generally recognized as safe” in the US for more than 20 years, and the glycyrrhizin content of foods and supplements is largely unregulated (5). In addition to licorice candy (3, 6), licorice-containing herbal supplements are an increasingly reported cause of hypertension and hypokalemia (7). Such supplements may be tablets or other formulations, including laxatives, licorice tea, and traditional Chinese medicines (4), and are sold under a variety of names (8).

Licorice-induced hypertension and hypokalemia may be suspected on the basis of an increased cortisol-to-cortisone ratio in urine and can be confirmed by measuring plasma glycyrrhizin concentrations or by resolution of symptoms and laboratory abnormalities following withdrawal of the glycyrrhizin source. This case illustrates licorice-containing supplements as a potential cause of significant hypertension and hypokalemia. Such supplements should be considered as possible causative agents in any patient with signs and symptoms consistent with pseudo-hyperaldosteronism.

**Author Contributions:** All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

**Authors’ Disclosures of Potential Conflicts of Interest:** No authors declared any potential conflicts of interest.
Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

References


Commentary

David Windus

This case illustrates the complex interplay of aldosterone action, sodium and potassium balance, and acid-base regulation. The 2 key diagnostic steps were demonstration of suppressed plasma aldosterone and renin, and an inappropriate increase in urine potassium. Persons with decreased total body potassium should excrete no more than approximately 15 mmol of potassium daily. A timed urine collection, although definitive, is often not practical. The urine potassium concentration of 21 mmol/L was borderline increased but does not take into account urine flow rate or concentration. In fact, the urine was relatively dilute with an osmolality of 226 mOsm/kg. Thus, indirect measures that can allow assessment of potassium excretion are needed to assess an untimed urine sample. The authors report the result of the transtubular potassium gradient. This calculation relates the osmolality of the urine to the potassium concentration in plasma and urine. A typical result is 8–9, but the value should drop to <2 if the kidney is appropriately conserving potassium. The ratio of the urine potassium concentration to the creatinine concentration has also been suggested to be useful (1).

The principal cell in the cortical collecting duct is the final site in the nephron for sodium reabsorption via electrogenic sodium channels at the apical membrane. Aldosterone stimulates electrogenic sodium channel insertion, leading to increased sodium reabsorption. This action produces a more electronegative lumen voltage caused by Na⁺ entry, which promotes potassium excretion via separate potassium-specific channels. The negative luminal voltage also enhances acid (H⁺) secretion by intercalated cells in the same segment. Aldosterone additionally stimulates the H⁺/ATPase in intercalated cells, causing further H⁺ excretion and systemic bicarbonate gain (2). As demonstrated in this case, the marked increased activation of the mineralocorticoid receptor thus caused sodium retention (hypertension), potassium loss (hypokalemia), and acid loss (metabolic alkalosis).

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures of Potential Conflicts of Interest: No authors declared any potential conflicts of interest.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

References

Commentary
Michael Stowasser

When hypokalemia occurs in conjunction with hypertension, plasma renin and aldosterone measurements help to determine underlying causes. Primary aldosteronism (PAL), a condition in which autonomous aldosterone overproduction leads to salt retention (causing hypertension and renin suppression) and potassium excretion, accounts for 5%–10% of hypertension, and if prolonged and severe enough, can lead to hypokalemia. Measurement of the aldosterone/renin ratio (increased in PAL) among hypertensive populations has shown that PAL is common, with most (>70%) of PAL patients being normokalemic. In these cases PAL masquerades as "essential" hypertension (1).

Renin and aldosterone are characteristically increased (but are sometimes normal), and the aldosterone/renin ratio is normal or low, in cases of secondary hyperaldosteronism that may occur in hypertensive patients who have been treated with thiazide diuretics and patients with renovascular hypertension or the rare reninoma. Conditions mimicking mineralocorticoid excess (with low-renin hypertension due to sodium retention, and hypokalemia) but with low aldosterone concentrations (unlike in PAL) include licorice overuse, which results in inhibition of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2); congenital 11β-HSD2 deficiency; Liddle syndrome (constitutive activation of the epithelial sodium channel); and conditions associated with adrenocorticotrophic hormone excess (causing high deoxycorticosterone concentrations), including ectopic adrenocorticotrophic hormone syndrome, congenital adrenal hyperplasia due to 11β-hydroxylase or 17α-hydroxylase deficiency, and glucocorticoid resistance syndrome (2). Hypokalemia due to gastroenterological potassium losses, such as in Bartter or Gitelman syndromes, is generally accompanied by low blood pressure due to loss of sodium/plasma volume, resulting in typically increased (but sometimes normal) plasma renin and aldosterone.

Unless properly controlled, variables such as medications, posture, dietary sodium, time of day, and hypokalemia itself can affect and confound interpretation of plasma aldosterone and renin, and their ratio (3). When possible, avoidance of confounding variables involves withdrawing diuretics for at least 4 weeks and withdrawing other interfering drugs (e.g., β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, dihydropyridine calcium antagonists, and nonsteroidal antiinflammatory agents) for at least 2 weeks and substituting these agents with others with lesser effects (including vera-pamil slow release, hydralazine, and prazosin); encouraging a liberalized sodium diet; correcting hypokalemia with potassium supplements; and collecting blood midmorning with patients seated. Proper blood collection (without stasis) minimizes the risk of factitious increases in plasma potassium that may mask hypokalemia (3).

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures of Potential Conflicts of Interest: No authors declared any potential conflicts of interest.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

References

