By
Chad J. DeFrain, M.D.
Department of Laboratory Medicine and Pathology
Memorial Medical Center
2-18-2010
Too Much of a Good Thing
A Woman with Hypertension and Hypokalemia
History

• 64 year old woman with a history of paranoid schizophrenia.

• Presented to outpatient clinic with no specific complaint.

• Additional history of hypertension, hyperlipidemia, and hypokalemia.

• Medications included an oral potassium supplement and Olanzapine (Zyprexa) 10 mg daily.
Exam

- Patient appeared well
- Blood pressure 188/105 mm Hg
Labs

- Na: 142 mmol/L
- BUN: 8 mg/dL
- Creatinine: 0.6 mg/dL
- Mg: 2.4 mg/dL
- Glucose: 94 mg/dL
- CO₂: 43 mmol/L (ref int 22-32 mmol/L)
- K: 1.9 mmol/L (critically low)
Hypokalemia

- Decreased intake
- Increased loss
- Redistribution
Decreased Intake

- Starvation
- Clay ingestion
Increased Loss

- Renal
  - Diuretics
  - Osmotic diuresis (hy erglycemia)
  - Hyperaldosteronism
  - Apparent hyperaldosteronism
  - Congenital adrenal hyperplasia
  - Cushing syndrome
  - Bartter syndrome
  - Vomiting
  - Hypomagnesemia
  - Liddle syndrome

- Non-renal
  - GI loss (diarrhea)
  - Integumentary (sweat)
Redistribution into cells

- Metabolic alkalosis
- Insulin
- \(B_2\) adrenergic agonists
Patient Course

- In the ED, the patient was persistently hypertensive.
- Review of prior records showed prior hypokalemia (2.1 and 3.3 mmol/L).
- Her ECG was normal.
- Upon further interview, the patient denied diuretic use, laxative abuse, prolonged fasting, diarrhea, or vomiting.
- Repeat serum potassium was 2.1 mmol/L and calculated serum osmolality was 301 mOsm/kg.
Hypokalaemia

? Redistribution into cells

? ↓ K intake

Excessive K losses

Urine K > 20–30 mmol/day

RENAL

With hypertension
- Hyperaldosteronism
  1° (incl. Conn’s syndrome)
  2° (with renal ischaemia)
- Other forms of mineralocorticoid receptor activation
  Cushing’s syndrome/ectopic ACTH
  Corticosteroid therapy
  Apparent mineralocorticoid excess
  Liquorice/carbenoxolone
- Liddle’s syndrome

With normal–low blood pressure
- With alkalosis
  Diuretic therapy (loop and thiazide)
  Bartter’s and Gitelman’s syndromes
- With acidosis
  Renal tubular acidosis (types 1 and 2)
  Carbonic anhydrase inhibitor therapy
- With variable pH
  Post-obstructive diuresis
  Recovery after acute tubular necrosis
  Mg depletion

GASTROINTESTINAL

With alkalosis
- Vomiting
- Nasogastric aspiration

With acidosis
- Diarrhoea
- Laxative abuse
- Villous adenoma of rectum
- Bowel obstruction/fistula
- Ureterosigmoidostomy

Urine K < 20–30 mmol/day
Clinical approach

FIGURE 49-3  Algorithm depicting clinical approach to hypokalemia. RTA, renal tubular acidosis; TTKG, transtubular K⁺ concentration gradient.
Urine

- Untimed urine collection
  - Urine creatinine: 10 mg/dL
  - Urine sodium: 73 mmol/L
  - Urine potassium: 21 mmol/L
  - Urine osmolality: 226 mOsm/kg.
- Patient was placed on continuous cardiac monitoring and given IV and oral potassium supplementation.
- Morning aldosterone and renin were low.
Increased Loss

- Renal
  - Diuretics
  - Osmotic diuresis (hyperglycemia)
  - Hyperaldosteronism
  - Apparent hyperaldosteronism
  - Congenital adrenal hyperplasia
  - Cushing syndrome
  - Bartter syndrome
  - Vomiting
  - Hypomagnesemia
  - Liddle syndrome

- Non-renal
  - GI loss (diarrhea)
  - Integumentary (sweat)
Cushing syndrome
Hypothalamic-Pituitary-Adrenal Axis

Episodic cortisol secretion in Cushing’s syndrome
What is Cushing’s?

Normally, the pituitary gland, located at the base of the brain, releases ACTH (adrenocorticotropin hormone) that stimulates the adrenal gland (located above the kidney) to release the exact amount of cortisol needed by the body.

There are several situations that can cause over-production of cortisol by the body’s adrenal glands:

1. A pituitary tumor can secrete excess ACTH. The excess ACTH causes over-production of cortisol by the adrenal glands. Cushing’s due to a pituitary tumor is called Cushing’s Disease and all other causes are termed Cushing’s Syndrome.

2. A benign or malignant tumor on the lung or other organ can also secrete excessive amounts of ACTH, which again, stimulates over-production of cortisol by the adrenal glands.

3. Tumors of the adrenal gland can secrete too much cortisol by themselves.

Courtesy of www.CSRF.com
Signs and symptoms

- Emotional disturbance
- Enlarged sella turcica
- Moon facies
- Osteoporosis
- Cardiac hypertrophy (hypertension)
- Buffalo hump
- Obesity
- Adrenal tumor or hyperplasia
- Thin, wrinkled skin
- Abdominal striae
- Amenorrhea
- Muscle weakness
- Purpura
- Skin ulcers (poor wound healing)

HTN in ~80%
Etiology and Classification

Table 1. Classification of endogenous Cushing's syndrome and rate of occurrence. (1)

<table>
<thead>
<tr>
<th>Classification</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH-dependent</td>
<td>85</td>
</tr>
<tr>
<td>Pituitary (disease)</td>
<td>80</td>
</tr>
<tr>
<td>Ectopic ACTH</td>
<td>20</td>
</tr>
<tr>
<td>Ectopic CRH</td>
<td>Rare</td>
</tr>
<tr>
<td>ACTH-independent</td>
<td>15</td>
</tr>
<tr>
<td>Adrenal adenoma</td>
<td>30</td>
</tr>
<tr>
<td>Adrenal carcinoma</td>
<td>70</td>
</tr>
<tr>
<td>Micronodular adrenal disease</td>
<td>Rare</td>
</tr>
<tr>
<td>Massive micronodular adrenal disease</td>
<td>Rare</td>
</tr>
<tr>
<td>&quot;Transitional state&quot;</td>
<td>Rare</td>
</tr>
</tbody>
</table>

ACTH, adrenocorticotropic hormone (corticotrophin); CRH, corticotrophin releasing hormone.
Source: From Kamilaris & Chrousos(1), with permission.

~10-15 new cases per million per year

Magiakou-Smyrnaki_Hypertension in Cushing's syn_BestPract_2006
Diagnosis of Cushing’s

The first step in diagnosing Cushing’s is to determine whether the patient has high levels of cortisol.

Cortisol levels vary throughout the day, making testing more difficult. The normal “diurnal rhythm” for cortisol secretion is that cortisol and ACTH levels are the highest in the morning and the lowest at 11PM to midnight.

Mild or cyclical cases of Cushing’s can be very difficult to diagnose and repeated testing is very often required.

Cyclic Cushing’s will only show abnormal test results when the tumor is active.

The second step in the diagnosis of Cushing’s is to determine whether the cortisol production is dependent on ACTH (pituitary or ectopic sources) or ACTH independent (adrenal tumors). This is termed the “differential diagnosis”.

Courtesy of www.CSRF.com
Figure 1
Cushing’s Syndrome Suspected
Perform 1 or 2 of the following studies

11 pm Salivary Cortisol*  
(normal < 4.2 nmol/L)  
FDA cleared tests can be obtained at:  
ACL Labs: 800-877-7016  
Salimetrics: 800-790-2258

24 hour Urine Free Cortisol  
(normal < 40-50 ug/d)  
Upper limits of normal may be 90-100ug/d in some assays

Overnight 1 mg Dexamethasone Suppression  
(normal < 1.8 ug/dL)  
1 mg dexamethasone at 2300  
obtain serum cortisol before 0900 the following day

Normal  ➔  Abnormal

DX probably excluded. Repeat if high index of suspicion

Consult Endocrinologist

* Normal value above is for ACL Labs. Salimetrics normal range is slightly different. Salivary cortisol tests can also be obtained from Esoterix or Quest Diagnostics. Again, normal values are different than stated above.
Diagnosis

Determine ACTH-dependence

ACTH-dependent

ACTH-independent Cushing’s syndrome

CRH stimulation AND dexamethasone suppression tests

Adequate suppression (dex) and stimulation

Mixed or negative responses

IPSS

Cushing’s disease

Central step-up

No central step-up

Ectopic ACTH secretion

Adrenal tumor(s)

CRH test

No ACTH response

+ ACTH response

ACTH-dependent Cushing’s syndrome

Pituitary MRI

Tumor >6mm

No tumor or <6mm

OR

Adrenal CT/MR imaging

Suppressed ACTH <5 pg/mL

Intermediate ACTH 5 to 20 pg/mL

Normal to High ACTH >20 pg/mL

Measure ACTH
Inferior petrosal sinus sampling
Late Night Salivary

This is the latest diagnostic test for Cushing’s. Elevated cortisol levels between 11PM and midnight are the earliest indications of the disease. This is an easy test for patients to perform and provides 93-100% accuracy for the diagnosis of Cushing’s. Normal levels of cortisol at this time of day virtually eliminates a diagnosis of Cushing’s.

24-hour Urinary Free Cortisol

This test is considered the gold standard diagnostic test. However, additional testing is always needed. There are conditions not related to Cushing’s that provide the same results. Many Cushing’s patients will have a normal 24 hour urine free result from time to time, thus a normal result does not exclude the diagnosis of Cushing’s.

Dex-CRH Stimulation

In patients with equivocal results, combination of dexamethasone suppression with a stimulation test using the hypothalamic hormone CRH can be useful in making the diagnosis of Cushing’s syndrome. This study should only be performed in a setting by endocrinologists who have had experience with the test to ensure it is performed properly.

Courtesy of www.CSRF.com
Dexamethasone Suppression

This test has been used for 40 years. It is still widely used and useful when combined with other tests. Patients take 1 mg of dexamethasone, a synthetic steroid, at 11 pm and cortisol and ACTH are measured at 8 the next day. Normal persons will show low ACTH and low cortisol due to proper functioning of the feedback system. Cushing’s patients “do not suppress” thus the cortisol levels remain elevated. When performed accurately this test provides a 95-97% efficiency in the diagnosis of Cushing’s.

Petrosal Sinus Sampling

This test is useful in differentiating pituitary and ectopic sources of ACTH. PSS uses catheters inserted through the large veins in the groin to sample ACTH levels as they drain from the pituitary veins. This test is most useful when combined with CRH stimulation and can in some cases localize the pituitary tumor to one side of the pituitary gland.

This particular study needs to be performed by a skilled interventional radiologist with extensive experience. It has a diagnostic accuracy rate is between 95-98%.
If ACTH levels are increased, the next step in the diagnosis is to determine the location of the ACTH producing tumor. Hopefully direct visual imaging associated with MRI of the pituitary gland will show the tumor. If a tumor greater than 5mm is clearly identified, further testing may not be needed, however care needs to be exercised as approximately 10% of the population have small non-functioning pituitary tumors. In about 50% of cases, the pituitary tumor is so small that it can not be seen with conventional imaging techniques.

If ACTH is elevated, and the pituitary MRI is “normal”, further testing is required to differentiate between unseen pituitary sources and an ectopic tumor located elsewhere in the body.

If ACTH levels are low or not detectable, a CT or MRI of the adrenal glands almost always identifies the tumor or tumors.
Once it is established that cortisol levels are elevated, several tests are used to determine the cause of Cushing’s:

Measurement of serum ACTH – ACTH will be elevated in patients with pituitary tumors and ectopic tumors. ACTH will be low or not detectable in patients with adrenal tumors.

High Dose Dexamethasone Suppression Test

Endocrinologists may perform high-dose dexamethasone suppression testing to help distinguish a pituitary from a non-pituitary ACTH-secreting tumor.

Whole Body Imaging

If the source of ACTH secretion is thought to be ectopic, often whole body images are performed.

Some larger tumors may be identified using CT or MRI scans

PET scans can also be useful in identifying ectopic tumors

Ectopic tumors are successfully located in the majority of cases, however small tumors can remain unseen or “occult”.

Courtesy of www.CSRF.com
The truth comes out

• Additional interviews with the patient revealed that she was taking several herbal supplements, including an animal adrenal extract and black licorice oil.
Licorice-induced hypertension and hypokalemia

- Consumption of large amounts of black licorice candy has been associated with hypertension and hypokalemia.
- Most currently available licorice candy is flavored with anise seed rather than the root of the licorice plant (*Glycyrrhiza glabra*).
- True licorice root contains biologically active glycyrrhizin.
Glycyrrhizin

- Glycyrrhizin is a triterpenoid glycosidic saponin used as an intense sweetener in candies and for its purported beneficial effects against inflammation, viruses, ulcers, and GI discomfort.
- Inhibits metabolism of cortisol and can lead to acute and chronic cases of severe hypertension and hypokalemia.
Mechanism of Glycyrrhizin

- The mineralocorticoid receptor in the renal collecting tubules binds cortisol and aldosterone with equal affinity.
- Aldosterone is the primary mineralocorticoid in the normal kidney because 11B-HSD2 (abundant in renal tubules) converts cortisol to cortisone (which has a lower affinity for the mineralocorticoid receptor)
Excess cortisol overwhelms 11BHSD2

- Renal salt reabsorption = HTN

HTN

\[ \text{Renal salt reabsorption} \]
\[ \leftarrow \]
\[ \text{Renal salt reabsorption} \]
\[ \leftarrow \]
\[ \text{Intravascular volume} \]
\[ \leftarrow \]
\[ \text{Volume delivery to heart} \]
\[ \leftarrow \]
\[ \text{Cardiac output} \]
\[ \leftarrow \]
\[ \text{Systemic vascular resistance} \]
\[ \leftarrow \]
\[ \text{Blood pressure} \]
\[ \leftarrow \]
\[ \text{Cardiac output} \]
\[ \leftarrow \]
\[ \text{Blood pressure} \]
Detection of Licorice Use

- Licorice induced hypertension and hyperkalemia can be suspected on the basis of an increased cortisol-to-cortisone ratio in the urine (reflecting activity of renal 11B-HSD2).
- Can be confirmed by measuring plasma glycyrrhizin concentrations or resolution of symptoms following licorice withdrawal.
- Most reports of licorice-induced hypertension demonstrate low serum aldosterone and renin.
Use of licorice 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.
- Licorice containing herbal supplements are an increasingly reported cause of hypertension and hypokalemia.
- Such supplements may be tablets or other formulations including laxatives, licorice tea, and traditional Chinese medicines.
How much is too much?

- The EU recommends a 100 mg/day upper limit (approx 60-70 g of licorice).
- Licorice fluid extracts deliver 200-800 mg.
- Powdered licorice root contains 40-360 mg in a daily dose.
Follow up

- Patient was discharged home with a serum potassium of 2.3 mmol/L on the following day.
- With increased potassium supplementation and discontinuation of the black licorice oil, the patient’s serum potassium and total carbon dioxide concentrations normalized and hypertension decreased.
Points to remember

- Glycyrrhizin is contained in licorice-based foods and supplements and inhibits renal metabolism of cortisol by 11B-HSD2. When cortisol is not metabolized, it can act as a mineralocorticoid on the kidneys.
- 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 lab abnormalities following withdrawal of the glycyrrhizin source.
Summary

• This case illustrates licorice-containing supplements as a potential cause of significant hypertension and hypokalemia.
• Such supplements should be considered in the differential diagnosis in patients with signs and symptoms of pseudohyperaldosteronism.
Thank you!
References


• Harrison’s Textbook of Internal Medicine.

• Cushing’s Support and Research Foundation Website (CSRF.com).