

## ACID-BASE AND ELECTROLYTE TEACHING CASE

### A Physiologic-Based Approach to the Evaluation of a Patient With Hyperkalemia

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Hyperkalemia generally is attributable to cell shifts or abnormal renal potassium excretion. Cell shifts account for transient increases in serum potassium levels, whereas sustained hyperkalemia generally is caused by decreased renal potassium excretion. Impaired renal potassium excretion can be caused by a primary decrease in distal sodium delivery, a primary decrease in mineralocorticoid level or activity, or abnormal cortical collecting duct function. Excessive potassium intake is an infrequent cause of hyperkalemia by itself, but can worsen the severity of hyperkalemia when renal excretion is impaired. Before concluding that a cell shift or renal defect in potassium excretion is present, pseudohyperkalemia should be excluded.

*Am J Kidney Dis* 56:387-393. © 2010 by the National Kidney Foundation, Inc.

**INDEX WORDS:** Hyperkalemia; cell shift; abnormal collecting duct; pseudohyperkalemia; impaired renal potassium excretion.

Note from Feature Editor Jeffrey A. Kraut, MD: This article is part of a series of invited case discussions highlighting either the diagnosis or treatment of acid-base and electrolyte disorders. The present case discussion is the first of 2 articles describing a physiologic-based approach to the diagnosis or treatment of acute hyperkalemia. In this article, Dr Palmer presents his approach to the evaluation of acute hyperkalemia, and in a future teaching case, Drs Shingarev and Allon will describe their approach to the treatment of acute hyperkalemia.<sup>1</sup>

#### INTRODUCTION

A high serum potassium level can occur in the setting of normal or altered body stores of potassium. The body has a marked ability to protect against hyperkalemia. This includes regulatory mechanisms that will excrete excess potassium quickly and mechanisms that will redistribute excess potassium into cells until it is excreted. The development of hyperkalemia in patients with diabetes is illustrative of abnormalities in both these mechanisms.

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*Received November 27, 2009. Accepted in revised form January 4, 2010. Originally published online as doi:10.1053/j.ajkd.2010.01.020 on May 21, 2010.*

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#### CASE REPORT

##### Clinical History and Initial Laboratory Data

A 30-year-old man with known insulin-dependent diabetes mellitus is admitted with diabetic ketoacidosis precipitated by the development of cellulitis on the right lower extremity. Admission and subsequent laboratory data are listed in Table 1. The patient is treated with intravenous fluids and insulin, and serum potassium level decreases from 6.2 to 2.0 mEq/L (6.2 to 2.0 mmol/L, respectively) during the first 48 hours after admission. Supplemental potassium is given and the patient is discharged after successful treatment of the cellulitis.

Two weeks later, the patient is noted to have much improved glycemic control on split-dose insulin therapy. Physical examination findings are significant for blood pressure of 142/90 mm Hg and mild background diabetic retinopathy. The physician wants to initiate therapy with an angiotensin receptor blocker to treat the patient's hypertension and provide renal protection, but is concerned about the potential for worsening the degree of hyperkalemia.

##### Additional Investigations

Upon further questioning, the patient admits to use of over-the-counter ibuprofen for occasional joint pain. He also drinks noni juice each day after reading an article suggesting that noni has a beneficial effect in helping to control blood glucose levels.

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0272-6386/10/5602-0019\$36.00/0  
doi:10.1053/j.ajkd.2010.01.020

Table 1. Laboratory Data

	Admission	48 h After Admission	2 wk After Admission
Sodium (mEq/L)	120	137	140
Potassium (mEq/L)	6.2	2.0	5.2
Chloride (mEq/L)	80	110	106
Bicarbonate (mEq/L)	10	16	22
Glucose (mg/dL)	850	180	145
Creatinine (mg/dL)	2.4	1.8	1.8 <sup>a</sup>
Other	pH 7.2; Pco <sub>2</sub> , 25 mm Hg	–	Random UPCR, 1.7 mg/mg

Note: Conversion factors for units: serum creatinine in mg/dL to  $\mu\text{mol/L}$ ,  $\times 88.4$ ; glucose in mg/dL to mmol/L,  $\times 0.05551$ ; eGFR in mL/min/1.73 m<sup>2</sup> to mL/s/1.73 m<sup>2</sup>,  $\times 0.01667$ . No conversion necessary for serum potassium, sodium, chloride, and bicarbonate in mEq/L and mmol/L.

Abbreviations: eGFR, estimated glomerular filtration rate; Pco<sub>2</sub>, partial pressure of carbon dioxide; UPCR, urine protein-creatinine ratio.

<sup>a</sup>Corresponding to eGFR of 38 mL/min/1.73 m<sup>2</sup>.

## Diagnosis

(1) Hyperkalemia on hospital admission caused by cell shift in the setting of total-body potassium depletion, and (2) hyperkalemia as an outpatient caused by impaired renal potassium excretion, likely due to underlying hyporeninemic hypoaldosteronism made worse with the use of nonsteroidal anti-inflammatory drugs and increased dietary potassium intake from ingestion of noni juice.

## Clinical Follow-up

The patient was placed on a low-potassium diet and use of ibuprofen and noni juice was discontinued. A repeated serum potassium test result 1 week later was 4.7 mEq/L (4.7 mmol/L). The patient was started on a low-dose angiotensin receptor blocker in combination with hydrochlorothiazide. A laboratory check 1 week later showed that serum potassium level was unchanged at 4.7 mEq/L (4.7 mmol/L).

### Box 1. Causes of Hyperkalemia Due to Cell Shift

- Hypertonicity
- Insulin deficiency
- Mineral acidosis
- $\beta$ -Blockade (impairs disposal)
- $\alpha$ -Stimulation
- Tissue injury
  - ◊ Rhabdomyolysis
  - ◊ Hemolysis
  - ◊ Tumor lysis
- Hyperkalemic periodic paralysis
- Drugs/toxins/herbal supplements
  - ◊ Digoxin (Chan su)
  - ◊  $\epsilon$ -Aminocaproic acid
  - ◊ Tetrodotoxin
  - ◊ Succinylcholine
- Rebound after insulin or thiopental infusion

## DISCUSSION

Does the patient have pseudohyperkalemia? Pseudohyperkalemia should be excluded before concluding that hyperkalemia is caused by cell shift or abnormal renal potassium excretion. Pseudohyperkalemia is an in vitro phenomenon caused by the mechanical release of potassium from cells during the phlebotomy procedure or specimen processing. This diagnosis is made when serum potassium concentration exceeds the plasma potassium concentration by  $>0.5$  mEq/L ( $>0.5$  mmol/L). Common causes include fist clenching during the phlebotomy procedure,

### Box 2. Approach to Patients at Risk of Hyperkalemia When Using Drugs That Interfere With the RAAS

- Accurately assess kidney function level to better define risk of hyperkalemia
- When possible, discontinue drugs that interfere with renal potassium secretion, inquire about herbal supplement preparations and over-the-counter use of nonsteroidal anti-inflammatory drugs
- Recommend a low-potassium diet, inquire about potassium-containing salt substitutes
- Prescribe effective diuretics therapy (use loop diuretics when estimated glomerular filtration rate  $<30$  mL/min/1.73 m<sup>2</sup>)
- Use sodium bicarbonate to correct metabolic acidosis in patients with chronic kidney disease
- Initiate therapy with low-dose RAAS blocker and monitor potassium closely

Abbreviation: RAAS, renin-angiotensin-aldosterone system.

**Box 3. Key Teaching Points**

- Serum potassium measurement should be repeated to exclude pseudohyperkalemia in patients with a normal electrocardiogram and no risk factors for hyperkalemia
- The hyperkalemia typically observed in patients with diabetic ketoacidosis is caused by insulin deficiency and the hypertonic state and not the result of the underlying organic acidosis
- Hyperkalemia that is chronic is caused by impaired renal potassium excretion and not cell shift
- Impaired renal potassium excretion can be the result of conditions that severely limit distal sodium delivery, decreased mineralocorticoid levels or activity, or a distal tubular defect; in many instances, one or more mechanisms are present
- Withholding drugs that block the renin-angiotensin system only on the basis of impaired kidney function can potentially deprive many patients of the cardiovascular benefit they would otherwise receive because numerous steps can be taken to minimize the risk of hyperkalemia

application of tourniquets, and use of small-bore needles. Pathologic causes are seen mostly in the setting of hematologic disorders, such as thrombocytosis (platelets  $>500,000/\text{cm}^3$ ) and pronounced leukocytosis (leukocytes  $70,000/\text{cm}^3$ ). Contamination with potassium EDTA in certain sampling tubes can cause a spurious increase in plasma potassium concentration accompanied by a very low plasma calcium concentration.

Is there evidence of excess dietary intake? In the presence of normal renal and adrenal function, it is difficult to ingest enough potassium to become hyperkalemic. Dietary intake as a contributor to hyperkalemia usually is in the setting of impaired kidney function. Dietary sources particularly enriched with potassium include melons, citrus juice, and salt substitutes. Other hidden sources of potassium reported to cause life-threatening hyperkalemia include raw coconut juice (potassium concentration, 44.3 mEq/L [44.3 mmol/L]) and noni juice (potassium, 56 mEq/L [56 mmol/L]). Although clay ingestion can cause hypokalemia because of binding in the gastrointestinal tract, river bed clay is potassium enriched (100 mEq of potassium in 100 g of clay) and can cause life-threatening hyperkalemia in patients with chronic kidney disease. Ingestion of burnt match heads (cautopyreiophagia) also can be a hidden source of potassium.<sup>2</sup> This activity was found to add an additional 80 mEq of potassium to one dialysis patient's daily in-

take and produced a plasma potassium concentration of 8 mEq/L (8 mmol/L).

Is the hyperkalemia the result of a cellular shift? Cellular redistribution is a more important cause of hyperkalemia than hypokalemia (Box 1). One should realize that as little as a 2% shift in intracellular potassium to the extracellular fluid will result in a serum potassium level of 8 mEq/L (8 mmol/L).

The major physiologic regulators of potassium shift into cells are insulin and catecholamines. Metabolic acidosis promotes potassium exit from cells dependent on the type of acid present. Mineral acidosis ( $\text{NH}_4\text{Cl}$  or  $\text{HCl}$ ) by virtue of the relative impermeability of the chloride anion results in the greatest efflux of potassium from cells, whereas organic acidosis (ie, lactic,  $\beta$ -hydroxybutyric, or methylmalonic acid) results in no significant efflux of potassium. Hyperkalemia associated with lactic acidosis is the result of cell ischemia.

Cell shift is a potential complication of hypertonic states. Hyperglycemia leads to water movement from the intracellular to extracellular compartment. This water movement favors potassium efflux from the cell through the process of solvent drag. In addition, cell shrinkage causes the intracellular potassium concentration to increase, creating a more favorable concentration gradient for potassium efflux. This same phenomenon has been described in neurosurgical patients given large amounts of hypertonic mannitol.

The hyperkalemia on admission in the present patient most likely is caused by the effects of hypertonicity and insulin deficiency. Metabolic acidosis in diabetic ketoacidosis is not the cause of hyperkalemia because the acidosis is of the organic type. After treatment with intravenous fluids and insulin, serum potassium levels decreased rapidly to 2.0 mEq/L (2.0 mmol/L). Patients with diabetic ketoacidosis frequently are total-body potassium depleted because of renal potassium losses resulting from increased distal sodium delivery (osmotic diuretic effect of glucose and excretion of sodium-ketoacid salts) in the setting of high aldosterone levels (stimulated by volume depletion).

Does the patient have a disturbance in renal potassium excretion? Although redistribution of potassium can result in hyperkalemia, the in-

crease in potassium levels generally is mild and nonsustained. Prolonged and severe hyperkalemia implies the presence of concomitant decreases in renal potassium excretion. In most instances, the clinical setting will allow the clinician to determine whether there is a disturbance in renal potassium excretion. Nevertheless, determination of the transtubular potassium gradient (TTKG) is a popular tool among some clinicians to assess renal potassium handling.

$$\text{TTKG} = [K_{\text{urine}}^+ / (U_{\text{osmolality}} / S_{\text{osmolality}})] / K_{\text{serum}}^+$$

where  $K_{\text{urine}}^+$  is urine potassium concentration,  $U_{\text{osmolality}}$  is urine osmolality,  $S_{\text{osmolality}}$  is serum osmolality, and  $K_{\text{serum}}^+$  is serum potassium concentration. The TTKG is intended to estimate tubular fluid potassium concentration at the end of the cortical collecting duct by accounting for water reabsorption that takes place distal to where potassium secretion has ceased.

The TTKG may be most helpful in the evaluation of hyperkalemia when one is attempting to discriminate between low aldosterone levels and aldosterone resistance.<sup>3</sup> The best way to use the test is to compare a basal measurement with one obtained within 4 hours after administration of a physiologic dose (0.05 mg) of 9- $\alpha$ -fludrocortisone. An increase in TTKG to more than 6 within this time frame suggests aldosterone deficiency. Administration of a pharmacologic dose (0.2 mg) may elicit an increase in TTKG over 24 hours in the setting of aldosterone resistance.

Decreased renal potassium excretion can be caused by 1 or more of 3 abnormalities: decreased distal sodium delivery, mineralocorticoid deficiency, and abnormal cortical collecting tubule function.<sup>4</sup>

To understand the effect of decreased distal delivery of sodium, it is important to appreciate that potassium is freely filtered by the glomerulus. The bulk of filtered potassium is reabsorbed in the proximal tubule and loop of Henle such that only 10% of the filtered load reaches the distal nephron. Potassium is secreted in the distal nephron and the rate of secretion is regulated and varies according to physiologic needs.

Acute decreases in glomerular filtration rate (GFR), as occur in acute kidney injury, would not be expected to have a marked effect on potassium excretion. However, acute decreases

in GFR may lead to marked decreases in distal delivery of salt and water, which may secondarily decrease distal potassium secretion. Thus, when acute kidney injury is oliguric, hyperkalemia is a frequent problem; when nonoliguric, distal delivery usually is sufficient and hyperkalemia is unusual.

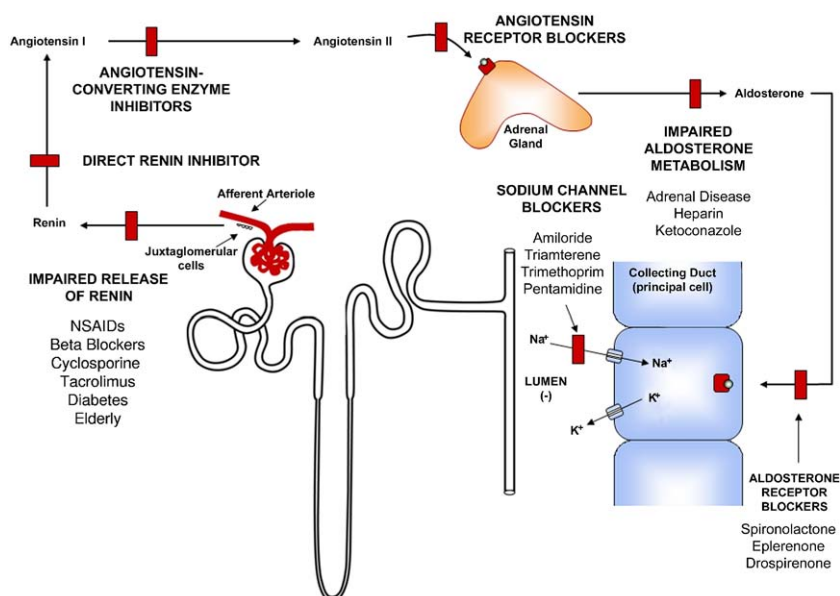
Chronic kidney disease is more complicated. In addition to the decreased GFR and secondary decrease in distal delivery, there is nephron dropout and less collecting tubule mass to secrete potassium. However, this is counterbalanced by a potassium adaptation in which the remaining nephrons develop increased ability to excrete potassium. Although patients with chronic kidney disease do not excrete a potassium load as fast as healthy persons, hyperkalemia is unusual until GFR has decreased to  $<10$  mL/min/1.73 m<sup>2</sup> ( $<0.2$  mL/s/1.73 m<sup>2</sup>). The occurrence of hyperkalemia with GFR  $>10$  mL/min/1.73 m<sup>2</sup> ( $>0.2$  mL/s/1.73 m<sup>2</sup>) should raise the question of decreased mineralocorticoid activity or a specific lesion of the cortical collecting tubule.

Decreased mineralocorticoid activity, the second major reason for decreased renal potassium excretion, can result from disturbances that originate at any point along the renin-angiotensin-aldosterone system. Such disturbances can be the result of a disease state or effects of various drugs (Fig 1).

The syndrome of hyporeninemic hypoaldosteronism accounts for most unexplained hyperkalemia in patients in whom GFR and potassium intake would not be expected to result in hyperkalemia.<sup>5</sup> Diabetic nephropathy and interstitial renal disease are the most common clinical entities associated with this syndrome.

Hyperkalemia in the presence of mild decreases in GFR and normal aldosterone levels can arise from certain interstitial renal diseases that can affect the distal nephron specifically. Many of these diseases are the same associated with hyporeninemic hypoaldosteronism, and frequently, the impaired renin release and defect in tubular secretion coexist. Examples include patients with a kidney transplant, lupus erythematosus, amyloidosis, urinary obstruction, and sickle cell disease.

Potassium-sparing diuretics impair the ability of the cortical collecting tubule to secrete potassium. The non-testosterone-derived progestin



**Figure 1.** The renin-angiotensin-aldosterone system and regulation of renal potassium ( $K^+$ ) excretion. Aldosterone binds to a cytosolic receptor in the principal cell and stimulates sodium ( $Na^+$ ) reabsorption across the luminal membrane through a well-defined sodium channel. As sodium is reabsorbed, the electronegativity of the lumen increases, thereby providing a more favorable driving force for potassium secretion through an apically located potassium channel. The permeability of the anion that accompanies sodium also influences potassium secretion, with less permeable anions having a greater stimulatory effect on potassium secretion. Disease states or drugs that interfere at any point along this system can impair renal potassium secretion and increase the risk of hyperkalemia. In many patients, this risk is magnified because of disturbances at multiple sites along this system. Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

drosipirone contained in certain oral contraceptives possesses mineralocorticoid blocking effects similar to that seen with spironolactone (Fig 1). Serum potassium levels should be monitored when these drugs are prescribed in patients receiving potassium supplements, renin-angiotensin blockers, or nonsteroidal anti-inflammatory drugs.<sup>6</sup>

Pseudohypoaldosteronism type II (Gordon syndrome) is an autosomal dominant form of hypertension in which hyperkalemia and metabolic acidosis are key features. Plasma aldosterone concentrations are low despite the presence of hyperkalemia, which normally exerts a stimulatory effect on aldosterone released from the adrenal gland. The hypertension and hyperkalemia are particularly responsive to the administration of thiazide diuretics. Mutations in the WNK4 and WNK1 protein kinases are responsible for this disease.<sup>7</sup>

Pseudohypoaldosteronism type I is a disorder characterized by mineralocorticoid resistance that typically presents in newborns. Clinical findings include hyperkalemia, metabolic acidosis, and a

tendency toward volume depletion caused by renal salt wasting. In the autosomal recessive form of the disease, the defect has been localized to homozygous mutations in the 3 subunits of the epithelial sodium channel. The autosomal dominant form of the disease results from mutations in the mineralocorticoid receptor that, in turn, result in mineralocorticoid resistance.<sup>4</sup>

All clinically important manifestations of hyperkalemia occur in excitable tissue. Neuromuscular manifestations include paresthesias and fasciculations in the arms and legs. As serum potassium levels continue to increase, ascending paralysis with eventual flaccid quadriplegia supervenes. Classically, trunk, head, and respiratory muscles are spared; however, rarely, respiratory failure can occur.

The depolarizing effect of hyperkalemia on the heart is manifest by changes observable in the electrocardiogram (ECG). The progressive changes of hyperkalemia are classically listed as peaking of T waves, ST-segment depression, widening of the PR interval, widening of the QRS interval, loss of the P wave, and develop-

ment of a sine-wave pattern. Appearance of a sine-wave pattern is ominous and a harbinger of impending ventricular fibrillation and asystole.

Less common patterns on the ECG include a right bundle branch block and right precordial ST-segment elevations reminiscent of Brugada syndrome. The tall, narrow, and symmetrical peaked T waves typical of hyperkalemia occasionally can be confused with the hyperacute T-wave change associated with ST-elevation myocardial infarction. A pseudoinfarct pattern also has been described, resembling both an anteroseptal and inferior wall myocardial infarction.

Correlation of ECG changes and serum potassium concentrations depends on the rapidity of hyperkalemia onset. Generally, with acute onset of hyperkalemia, ECG changes appear at a serum potassium level of 6-7 mEq/L (6-7 mmol/L). However, with chronic hyperkalemia, the ECG may remain normal up to a concentration of 8-9 mEq/L (8-9 mmol/L). Despite these generalities, clinical studies show poor correlation between serum potassium concentrations and cardiac manifestations.<sup>8</sup>

The initial approach to treatment of chronic hyperkalemia is to review the patient's medication profile and, when possible, discontinue drugs that can impair renal potassium excretion.<sup>9,10</sup> Patients should be questioned specifically about the use of over-the-counter nonsteroidal anti-inflammatory drugs and herbal remedies because herbs may be a hidden source of dietary potassium. Patients should be placed on a low-potassium diet with specific counseling against the use of potassium-containing salt substitutes. Diuretics are particularly effective in minimizing hyperkalemia. In patients with an estimated GFR  $>30$  mL/min/1.73 m<sup>2</sup> ( $>0.5$  mL/s/1.73 m<sup>2</sup>), thiazide diuretics can be used, but with more severely decreased kidney function, loop diuretics are required.

In patients with chronic kidney disease and metabolic acidosis, administration of sodium bicarbonate is an effective strategy to minimize increases in serum potassium concentration. Ensuring that the patient is first on effective diuretic therapy will lessen the likelihood of developing volume overload as a complication of sodium bicarbonate administration.

Development of hyperkalemia after the administration of renin-angiotensin blockers is of par-

ticular concern because patients at highest risk of this complication often are the same who derive the greatest cardiovascular benefit.<sup>11</sup> In addition to the steps mentioned, the risk of hyperkalemia with these drugs can be minimized by initiating therapy at low doses (Box 2). Serum potassium should be checked within 1 week of starting the drug. If potassium level is normal, the dose of the drug can be titrated upward. With each increase in dose, serum potassium should be measured again 1 week later. For increases in serum potassium concentration up to 5.5 mEq/L (5.5 mmol/L), one can try decreasing the dose, and in some cases, potassium concentration will improve, allowing the patient to remain on the renin-angiotensin blocker, albeit at a lower dose. Angiotensin receptor blockers and direct renin inhibitors should be used with the same caution as angiotensin-converting enzyme inhibitors in patients at risk of hyperkalemia.

Sodium polystyrene sulfonate commonly is used to treat hyperkalemia in the acute setting. However, ongoing use is poorly tolerated because the resin usually is given in a suspension with hypertonic sorbitol to promote osmotic diarrhea. In addition, ongoing use had been associated with mucosal injury in the lower and upper gastrointestinal tract.<sup>12</sup>

In summary, the development of hyperkalemia in diabetic patients can be the result of disturbances in factors that regulate both potassium distribution within the body and total-body potassium content. Key teaching points are listed in Box 3.

## ACKNOWLEDGEMENTS

*Support:* None.

*Financial Disclosure:* The author has received speaker honoraria from Novartis Pharmaceuticals and Boehringer Ingelheim.

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