Causes of hypokalemia in adults

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INTRODUCTION

Hypokalemia is a common clinical problem. Potassium enters the body via oral intake or intravenous infusion, is largely stored in the cells, and then excreted in the urine. Thus, decreased intake, increased translocation into the cells, or, most often, increased losses in the urine, gastrointestinal tract, or sweat can lead to a reduction in the serum potassium concentration (table 1).

This topic will review the major causes of hypokalemia. The evaluation and treatment of hypokalemia are discussed separately. (See "Evaluation of the adult patient with hypokalemia" and "Clinical manifestations and treatment of hypokalemia in adults".)

DECREASED POTASSIUM INTAKE

Potassium intake is normally 40 to 120 mEq per day, most of which is then excreted in the urine. The kidney is able to lower potassium excretion to a minimum of 5 to 25 mEq per day in the presence of potassium depletion [1]. Thus, decreased intake alone rarely causes significant hypokalemia. This was demonstrated in a study of normal individuals in whom lowering potassium intake to 20 mEq per day was associated with a reduction in serum potassium from 4.1 mEq/L at baseline to 3.5 mEq/L [2].

However, a low potassium intake can contribute to the severity of potassium depletion when another cause of hypokalemia is superimposed, such as diuretic therapy.

INCREASED ENTRY INTO CELLS

More than 98 percent of total body potassium is intracellular, chiefly in muscle [3,4]. The normal distribution of potassium between cells and the extracellular fluid is primarily maintained by the Na-K-ATPase pump in the cell membrane [3,4]. Increased activity of the Na-K-ATPase pump and/or alterations in other potassium transport pathways can result in transient hypokalemia due to increased potassium entry into cells.

Increased availability of insulin — Insulin promotes the entry of potassium into skeletal muscle and hepatic cells, predominantly by increasing the activity of the Na-K-ATPase pump [3]. This effect is most prominent after the administration of exogenous insulin to patients with diabetic ketoacidosis or severe nonketotic hyperglycemia who are often normokalemic or hyperkalemic at presentation, even though they have lost potassium [5]. Hypokalemia can rarely result from an insulin overdose [6]. (See "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Treatment", section on 'Potassium replacement'.)

Endogenous insulin released in response to a carbohydrate load may also contribute to hypokalemia. This has been described in patients with refeeding syndrome [7] and after the administration of intravenous potassium in a dextrose in water solution. Thus, initial intravenous potassium therapy for hypokalemia should be given in a saline rather than dextrose solution. This issue is discussed in detail elsewhere. (See "Clinical manifestations and treatment of hypokalemia in adults", section on 'Intravenous potassium repletion'.)

Elevated beta-adrenergic activity — Endogenous catecholamines, acting via beta-2 adrenergic receptors [4,8], can promote potassium entry into cells by increasing the activities of the Na-K-ATPase pump [9] and the Na-K-2Cl (NKCC1) cotransporter [10] and possibly by increasing the release of insulin [11]. A proposed physiologic role for this effect of increased beta-2 adrenergic activity is to moderate the acute hyperkalemia of exercise [12].

As a result of potassium flux into cells, transient hypokalemia can develop in any setting in which there is stress-induced release of epinephrine, including alcohol withdrawal [3,13], acute myocardial infarction [3,14], head injury [15], or theophylline intoxication [16,17].

Similar effects, in which the serum potassium concentration can fall acutely by more than 0.5 to 1 mEq/L, have been observed in the following settings:

- After the administration of exogenous beta-adrenergic agonists (such as albuterol, terbutaline, or dobutamine) to treat asthma or heart failure or to prevent premature labor [3,18-21]

- Ingestion of over-the-counter sympathomimetics found in decongestants or dieting agents, such as pseudoephedrine and ephedrine [3,22]

- Exposure to heroin or meats contaminated with the beta-adrenergic agonist, clenbuterol [4]

Regardless of the cause of increased beta-adrenergic activity, the degree of hypokalemia will be greater in patients with preexisting hypokalemia due, for example, to diuretic therapy (figure 1) [23]. (See 'Diuretics' below.)

This potassium-lowering effect of beta agonists may be particularly likely to induce arrhythmias in the following settings:

- When administered concurrently with diuretic therapy in patients with hypertension [18]. (See "Treatment of hypertension in asthma and COPD".)

- In women with preterm labor. One study, for example, found that 3 of 14 patients treated with either ritodrine or terbutaline for the prevention of preterm labor developed a symptomatic arrhythmia, such as supraventricular tachycardia or premature atrial complex (PAC; also referred to a premature atrial beat, premature supraventricular complex, or premature supraventricular beat) and premature ventricular beats [21].

In addition, beta agonists can be given acutely to treat severe hyperkalemia. On the other hand, nonselective beta blockers can raise the serum potassium, particularly if given with a potassium load (figure 2). (See "Treatment and prevention of hyperkalemia in adults", section on 'Beta-2-adrenergic agonists' and "Causes and evaluation of hyperkalemia in adults", section on 'Beta blockers' and "Causes and evaluation of hyperkalemia in adults", section on 'Exercise'.)

Elevated extracellular pH — Either metabolic or respiratory alkalosis can promote potassium entry into cells. In the presence of alkalemia, hydrogen ions leave the cells to minimize the increase in extracellular pH; the necessity to maintain electroneutrality then requires the entry of some potassium (and sodium) into the cells. The serum potassium concentration falls by less than 0.4 mEq/L for every 0.1 unit rise in pH [24].

In addition to alkalemia leading to cellular potassium uptake, metabolic alkalosis is a common finding in hypokalemia, primarily because the major causes of hypokalemia (such as diuretics, vomiting, and hyperaldosteronism, described below) also lead to losses of hydrogen ions.

Hypokalemia is an important cofactor in the **maintenance** of metabolic alkalosis since it promotes bicarbonate reabsorption, thereby impairing correction of the alkalemia by excretion of the excess bicarbonate (figure 3). (See "Pathogenesis of metabolic alkalosis", section on 'Hypokalemia' and "Treatment of metabolic alkalosis".)

Hypokalemic periodic paralysis — Hypokalemic periodic paralysis is a rare neuromuscular disorder characterized by potentially fatal episodes of muscle weakness or paralysis that can affect the respiratory muscles. It may be hereditary, with an autosomal dominant mode of inheritance, or acquired in patients with hyperthyroidism. Acute attacks, in which the sudden movement of potassium into the cells can reduce the serum potassium to as low as 1.5 to 2.5 mEq/L, are often precipitated by rest after exercise, stress, or a carbohydrate meal. The serum potassium is normal during periods between the recurrent attacks of paralysis, a characteristic which can help distinguish periodic paralysis from other forms of hypokalemic paralysis. Patients with hypokalemic periodic paralysis will also have a low urinary excretion of potassium; this finding can help distinguish these patients from those who have hypokalemic paralysis due to renal loss of potassium [25]. (See "Hypokalemic periodic paralysis" and "Thyrotoxic periodic paralysis".)

Paradoxical hypokalemia after repletion — Some patients with either periodic or nonperiodic hypokalemia can develop worsening, "paradoxical" hypokalemia after potassium repletion. In a cohort of 78 patients with thyrotoxic periodic paralysis, for example, the serum potassium decreased (rather than increased) by a mean of 0.4 mEq/L in 20 patients [26]. These patients with paradoxical hypokalemia had higher thyroxine concentrations, required more potassium chloride supplementation to reverse symptoms of hypokalemia, and had more pronounced rebound hyperkalemia posttreatment. High thyroxine levels may produce a more exaggerated potassium uptake in these patients, resulting in paradoxical hypokalemia.

The mechanism of paradoxical hypokalemia is likely different in patients with nonperiodic hypokalemia. In a cohort of 58 such patients, paradoxical hypokalemia developed in 30 [27]. Correlates of paradoxical hypokalemia included higher urinary potassium excretion rates, higher renin levels, and higher volumes of saline resuscitation.

Increased blood cell production — An acute increase in hematopoietic cell production is associated with potassium uptake by the new cells and this may lead to hypokalemia. Administration of vitamin B12 or folic acid to treat a megaloblastic anemia or use of granulocyte-macrophage colony-stimulating factor (GM-CSF) to treat neutropenia are the most common scenarios in which this occurs [28-30].

A similar mechanism may lead to spurious hypokalemia in blood samples drawn from patients with many metabolically active blood cells, such as patients with acute myeloid leukemia and a high white blood cell count [31]. If the blood is allowed to stand at room temperature prior to measurement of the potassium concentration, the measured value may be below 1 mEq/L even though the patient is without symptoms, signs, or sequelae of hypokalemia. This spurious hypokalemia can be prevented by either rapid separation of the plasma from the cells following venipuncture, or storage of the blood at 4°C before assay. (See "Acute myeloid leukemia: Overview of complications", section on 'Hypokalemia'.)

Hypothermia — Accidental or induced hypothermia can drive potassium into the cells and lower the serum potassium concentration to 3.0 to 3.5 mEq/L or less [32,33]. By contrast, hypothermic patients who are unresponsive to resuscitation may have marked preterminal hyperkalemia, due to irreversible tissue necrosis [33].

Barium intoxication — Barium intoxication, which usually results from the ingestion of contaminated food or from a suicide attempt [34], can cause hypokalemia by blocking the potassium channels in the cell membrane that normally allow cellular potassium to diffuse into the extracellular fluid [35]. Treatment of barium poisoning with potassium replacement serves to both increase the serum potassium concentration and to displace barium from affected potassium channels [35]. Hemodialysis is also an effective treatment [36].

Patients undergoing radiographic procedures are not at risk for this complication since the barium sulfate used in these studies does not enter the systemic circulation.

Cesium intoxication — Cesium intoxication, usually due to the use of cesium chloride as an alternative therapy for cancer, can be associated with hypokalemia [37]. How this occurs is unclear, but may result from cesium blockade of membrane potassium channels [38].

Chloroquine intoxication — Hypokalemia, with the serum potassium concentration falling below 2.0 mEq/L in severe cases, is a common finding in acute chloroquine intoxication [6]. This effect is presumably mediated by potassium movement into the cells and can be exacerbated by the administration of epinephrine to help treat the intoxication.

Antipsychotic drugs — Hypokalemia is a rare complication of therapy with selected antipsychotic drugs, such as risperidone and quetiapine [39,40].

INCREASED GASTROINTESTINAL LOSSES

Loss of gastric or intestinal secretions from any cause (vomiting, diarrhea, laxatives, or tube drainage) is associated with potassium losses and, possibly, hypokalemia [28].

Upper gastrointestinal losses — The concentration of potassium in gastric secretions is only 5 to 10 mEq/L; thus, potassium depletion in this setting is primarily due to increased urinary losses [28].

The following sequence is responsible for the urinary potassium loss with removal of gastric acid. The associated metabolic alkalosis and rise in plasma bicarbonate concentration increases 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. Because of inappropriate sodium wasting with bicarbonate, a low urine chloride concentration is used to detect the presence of volume depletion. (See "Clinical manifestations and evaluation of metabolic alkalosis".)

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 [28]. At this time, the urine pH falls from above 7.0 (due to bicarbonate wasting) to below 6.0.

Lower gastrointestinal losses — In contrast to gastric secretions, the potassium concentration in lower intestinal losses is relatively high (20 to 50 mEq/L) in most cases. In addition, hypokalemia due to lower gastrointestinal tract losses (usually from diarrhea) are typically associated with bicarbonate wasting and hyperchloremic metabolic acidosis rather than the metabolic alkalosis observed with upper gastrointestinal losses. However, some patients with hypokalemia due to factitious diarrhea or surreptitious laxative abuse develop metabolic alkalosis via an uncertain mechanism. (See "Factitious diarrhea: Clinical manifestations, diagnosis, and management", section on 'Clinical manifestations'.)

Hypokalemia from lower gastrointestinal losses is most common when the losses occur over a prolonged period, as with a villous adenoma, a vasoactive intestinal peptide secreting tumor (VIPoma), or with persistent infectious diarrhea [41-43]. In many cases, increased fecal losses cannot explain the entire potassium deficit. Since most people ingest an average of 80 mEq of potassium per day and urinary potassium excretion should fall below 15 to 25 mEq/day in the presence of hypokalemia [44], fecal losses (which are normally approximately 10 mEq/day) must exceed 55 to 65 mEq/day to directly induce hypokalemia. However, many patients with diarrhea who become hypokalemic have fecal potassium excretion below this level, indicating that other

factors, such as decreased intake and volume depletion with increased aldosterone activity, must also play a contributory role [42]. (See 'Increased urinary losses' below.)

Other causes of hypokalemia due to lower gastrointestinal losses have been described. These include:

- Bowel cleansing for colonoscopy with both sodium phosphate (which is now infrequently used) and polyethylene-glycol (PEG)-based preparations, particularly among older adults [45,46]. (See "Acute phosphate nephropathy".)
- Acute colonic pseudo-obstruction (Ogilvie's syndrome), which is associated with a secretory diarrhea characterized by an abnormally high potassium content due to activation of colonic potassium secretion. (See "Acute colonic pseudo-obstruction (Ogilvie's syndrome)", section on 'Clinical manifestations'.)
- Ingestion of clay ("geophagia"), which binds potassium in the gastrointestinal tract [47-49].

INCREASED URINARY LOSSES

Urinary potassium excretion is derived mostly from the secretion of potassium in the distal nephron, particularly by the principal cells in the connecting tubule and cortical collecting tubule [3,50]. Hypokalemia due to increased urinary losses is primarily due to two factors [44,51]:

- Increased mineralocorticoid activity – Aldosterone acts mainly by stimulating sodium reabsorption via the epithelial sodium channel (ENaC). Reabsorption of cationic sodium makes the lumen relatively electronegative, thereby promoting passive potassium secretion from the tubular cell into the lumen through potassium channels (eg, ROMK) in the luminal membrane (figure 4).
- Increased distal delivery of sodium and water – Enhanced potassium secretion can result from increased delivery of sodium to the collecting tubule, particularly if accompanied by nonreabsorbable anions rather than chloride. (See 'Nonreabsorbable anions' below.)

  Potassium wasting can also result from polyuria as seen, for example, in primary polydipsia. In this setting, the urine potassium concentration is appropriately low (less than 15 mEq/L), but cumulative potassium excretion may be greater than intake due to the marked increase in urine volume. (See 'Polyuria' below.)

In most patients, increases in both mineralocorticoid activity and distal flow are present concurrently (eg, diuretic therapy, primary aldosteronism). **If only one parameter is increased, the other must be normal to permit excessive loss of potassium**. This important concept is illustrated by the absence of hypokalemia in patients who have a compensatory increase in aldosterone due to volume depletion. In such cases, angiotensin II stimulates sodium reabsorption in the proximal and distal tubules, which indirectly reduces distal sodium and water delivery. Angiotensin II also inhibits potassium secretory channels in the collecting tubule [50,52,53], thereby counterbalancing the stimulatory effect of aldosterone on potassium secretion.

In response to hypokalemia due to increased but stable urinary losses, urinary potassium excretion eventually falls to a value equivalent to potassium intake. At this point, the serum potassium is low but will not fall further unless potassium wasting forces increase due, for example, to an increase in diuretic dose or in aldosterone secretion in primary aldosteronism.

This adaptive response to hypokalemia results in part from reduction in the activity of the potassium secretory (eg, ROMK) channels in the luminal membrane of the cortical collecting tubule (figure 4), an effect that is potentially mediated by increased angiotensin II activity [50,54,55]. As an example, downregulation of luminal potassium channels will minimize the degree of hypokalemia seen in patients with primary aldosteronism and may explain why hypokalemia is an inconsistent finding in this disorder. (See "Pathophysiology and clinical features of primary aldosteronism", section on 'Hypokalemia: An inconsistent finding'.)

Major causes of urinary potassium wasting — The most common causes of hypokalemia due to urinary potassium losses include diuretic use, a primary increase in mineralocorticoid activity, increased distal delivery of nonreabsorbable anions, and loss of gastric secretions.

Diuretics — Any diuretic that acts proximal to the potassium secretory site – carbonic anhydrase inhibitors (eg, acetazolamide), loop diuretics, and thiazide-type diuretics – will both increase distal delivery and, via the induction of volume depletion, activate the renin-angiotensin-aldosterone system. As a result, urinary potassium excretion will increase, leading to hypokalemia if the urinary losses are greater than intake.

The incidence and severity of hypokalemia are dose dependent, occurring much less frequently with lower doses [56,57]. Thus, lower doses of thiazides (eg, 12.5 to 25 mg/day of chlorthalidone or hydrochlorothiazide) are now widely used in the treatment of hypertension because they are as effective in blood pressure reduction (figure 5) with a lesser effect on electrolyte balance (figure 6) [58]. In two large hypertension trials of low-dose chlorthalidone, hypokalemia requiring therapy occurred in 7 to 8 percent of patients [59,60]. (See "Use of thiazide diuretics in

patients with primary (essential) hypertension" and "Loop diuretics: Dosing and major side effects".)

Overall, hypokalemia is more frequent with thiazide diuretics than with loop diuretics, despite having a less potent natriuretic effect [3,61,62]. One potential explanation is the differential effect on calcium excretion. Whereas thiazide diuretics decrease calcium excretion [63], loop diuretics lead to a significant increase in calcium excretion [64]. The higher luminal calcium concentration in the distal nephron produced by loop diuretics reduces the lumen-negative driving force for potassium excretion [65,66], thereby blunting their kaliuretic effect of loop diuretics.

In stable patients on a fixed diuretic dose, potassium loss, like other diuretic-induced fluid and electrolyte complications, occurs only during the first two weeks of therapy before a new steady state is established (figure 7). Thus, a stable patient with a normal serum potassium concentration at three weeks is not at risk of late hypokalemia unless the diuretic dose is increased, extrarenal potassium losses increase, or dietary potassium intake is reduced. (See "Time course of loop and thiazide diuretic-induced electrolyte complications".)

Once a steady state is reached, further monitoring is not required, unless the diuretic dose is increased, extrarenal potassium losses increase, or dietary potassium intake is reduced. As an example, increased losses and decreased intake may be seen with gastroenteritis. In such patients, temporary cessation of diuretic therapy for a few days may be appropriate.

In patients with hypertension who develop diuretic-induced hypokalemia, either another agent can be used, or the hypokalemia can be treated with a potassium-sparing diuretic or potassium supplementation. (See "Clinical manifestations and treatment of hypokalemia in adults", section on 'Treatment'.)

Increased mineralocorticoid activity — Urinary potassium wasting is characteristic of any condition associated with primary hypersecretion of a mineralocorticoid, as with an aldosterone-producing adrenal adenoma. These patients are usually hypertensive, and the differential diagnosis includes diuretic therapy (which may be surreptitious) in a patient with underlying hypertension, and renovascular disease, in which increased secretion of renin leads to enhanced aldosterone release. (See "Pathophysiology and clinical features of primary aldosteronism" and "Diagnosis of primary aldosteronism".)

Increased mineralocorticoid activity with suppressed circulating aldosterone concentrations (called apparent mineralocorticoid excess) is an uncommon condition due to autosomal recessive, loss-of-function mutations in the 11β-hydroxysteroid dehydrogenase-2 (11-betaHSD2) gene or to inhibition of this enzyme due to chronic licorice ingestion or use of antifungal agents

(itraconazole and posaconazole) [67-69]. (See "Apparent mineralocorticoid excess syndromes (including chronic licorice ingestion)".)

The anti-androgen drug abiraterone, which is used to treat prostate cancer, can also cause apparent mineralocorticoid excess with hypokalemia and hypertension [70,71], albeit through a different mechanism than 11-betaHSD2 inhibition. Abiraterone inhibits the CYP17A1 enzyme, 17-alpha hydroxylase, decreases cortisol, and increases plasma corticotropin (ACTH) [72]. Increased ACTH leads to the generation of excessive amounts of deoxycorticosterone, which has potent mineralocorticoid effects, causing hypokalemia and hypertension. This ACTH-dependent mineralocorticoid excess can be mitigated by coadministration of glucocorticoids with abiraterone [71,73], use of mineralocorticoid receptor antagonists, or salt restriction [74].

Nonreabsorbable anions — The lumen-negative electrical gradient created by sodium reabsorption in the cortical collecting tubule is partially attenuated by chloride reabsorption. There are, however, a number of clinical settings in which sodium is presented to the distal nephron with relatively large quantities of a nonreabsorbable anion, including bicarbonate with vomiting or proximal renal tubular acidosis, beta-hydroxybutyrate in diabetic ketoacidosis, hippurate following toluene use (glue sniffing), or a penicillin derivative in patients receiving high-dose penicillin therapy. In these settings, more of the delivered sodium will be reabsorbed in exchange for potassium, leading to a potentially marked increase in potassium excretion [75,76]. As an example, the serum potassium concentration is below 2 mEq/L in approximately one-fourth of patients with toluene-induced metabolic acidosis [77]. (See "The delta anion gap/delta HCO3 ratio in patients with a high anion gap metabolic acidosis", section on 'D-lactic acidosis and toluene inhalation'.)

The effect of nonreabsorbable anions is likely to be most prominent when there is concurrent volume depletion. In this setting, the decrease in distal chloride delivery (thereby limiting the ability of chloride reabsorption to dissipate the lumen-negative gradient) and the enhanced secretion of aldosterone both promote potassium secretion [76]. In diabetic ketoacidosis, for example, increased distal sodium and water delivery (due to the glucose osmotic diuresis), hypovolemia-induced hyperaldosteronism, and beta-hydroxybutyrate acting as a nonreabsorbable anion all can contribute to potassium wasting [5]. (See "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Clinical features, evaluation, and diagnosis", section on 'Serum potassium'.)

Loss of gastric secretions — The mechanism by which loss of gastric secretions leads to urinary potassium wasting is described above, in which there is an increase in sodium bicarbonate delivery to the collecting tubule. This problem is usually apparent from the history. If, however, the history is not helpful, the differential diagnosis of a normotensive patient with

hypokalemia, urinary potassium wasting, and metabolic alkalosis includes surreptitious vomiting, as well as diuretic use and Bartter syndrome. (See "Clinical manifestations and evaluation of metabolic alkalosis", section on 'Diagnostic approach in unexplained metabolic alkalosis'.)

Less common causes of urinary potassium wasting — Less common causes of hypokalemia due to urinary losses include a variety of acquired and genetic disorders.

Polyuria — Potassium-depleted subjects can normally reduce the urine potassium concentration to a minimum of 5 to 10 mEq/L [1]. If, however, the urine output is over 5 to 10 L/day, then obligatory potassium losses can exceed 50 to 100 mEq per day. This problem is most likely to occur in primary (often psychogenic) polydipsia, in which the urine output may be elevated over a prolonged period of time [78]. An equivalent degree of polyuria can also occur in arginine vasopressin deficiency (previously called central diabetes insipidus), but patients with this disorder typically seek medical care soon after the polyuria has begun.

Renal tubular acidosis — Potassium wasting can occur in both distal (type 1) and proximal (type 2) renal tubular acidosis. In each of these disorders, the degree of potassium depletion is masked by the tendency of acidemia to promote potassium movement out of the cells. Thus, the serum potassium concentration is higher than it should be in relation to the degree of potassium depletion. In some patients, the serum potassium concentration is normal or even elevated, although correction of the acidemia will uncover the true state of potassium balance. (See "Overview and pathophysiology of renal tubular acidosis and the effect on potassium balance" and "Potassium balance in acid-base disorders".)

Prior to treatment with bicarbonate, patients with a proximal renal tubular acidosis usually demonstrate mild hypokalemia, due primarily to baseline hyperaldosteronism [79]. However, treatment with sodium bicarbonate to correct the acidemia increases distal tubular sodium and bicarbonate delivery, which can cause a marked increase in renal potassium wasting [79]. (See "Treatment of distal (type 1) and proximal (type 2) renal tubular acidosis", section on 'Proximal (type 2) renal tubular acidosis'.)

Hypomagnesemia — Hypomagnesemia is present in up to 40 percent of patients with hypokalemia [80]. In many cases, as with diuretic therapy, vomiting, diarrhea, or certain tubular toxins such as gentamicin and iphosphamide [3,81], there are concurrent potassium and magnesium losses.

However, hypomagnesemia can itself lead to increased urinary potassium losses via an uncertain mechanism, possibly involving an increase in the number of open potassium channels [82,83]. This mechanism, as well as the causes of hypomagnesemia, is discussed

separately. (See "Hypomagnesemia: Clinical manifestations of magnesium depletion", section on 'Hypokalemia' and "Hypomagnesemia: Causes of hypomagnesemia".)

Determining whether hypomagnesemia is present is important clinically because the hypokalemia often cannot be corrected until the magnesium deficit is reversed [80].

Amphotericin B — Hypokalemia occurs in up to one-half of patients treated with amphotericin B [84]. Amphotericin interacts with membrane sterols, leading to an increase in membrane permeability that can promote potassium secretion across the luminal membrane. Concurrent distal renal tubular acidosis may play a contributory role. (See "Amphotericin B nephrotoxicity".)

Salt-wasting nephropathies — Kidney diseases associated with decreased proximal, loop, or distal sodium reabsorption can infrequently lead to hypokalemia via a mechanism similar to that induced by diuretics. This problem can be seen with Bartter or Gitelman syndrome, tubulointerstitial diseases (such as reflux nephropathy or interstitial nephritis due to Sjögren's disease), hypercalcemia, tubular injury due to drugs such as cisplatin, and tubular injury that may be induced by lysozyme in patients with leukemia, particularly acute monocytic or myelomonocytic leukemia [3,28,85-87]. (See "Inherited hypokalemic salt-losing tubulopathies: Pathophysiology and overview of clinical manifestations" and "Acute myeloid leukemia: Overview of complications".)

Liddle's syndrome — In patients with Liddle's syndrome, an autosomal dominant, gain-of-function mutation in ENaC leads to hereditary hypokalemia and hypertension, mimicking the syndrome of mineralocorticoid excess. (See "Genetic disorders of the collecting tubule sodium channel: Liddle syndrome and pseudohypoaldosteronism type 1", section on 'Liddle syndrome' and "Apparent mineralocorticoid excess syndromes (including chronic licorice ingestion)".)

Bartter and Gitelman syndromes — Mutations in a variety of tubular transport proteins can mimic the effects of chronic therapy with loop diuretics (Bartter syndrome) or thiazide diuretics (Gitelman syndrome), resulting in hypokalemia and metabolic alkalosis. (See "Inherited hypokalemic salt-losing tubulopathies: Pathophysiology and overview of clinical manifestations".)

Low-calorie diets — Ingestion of low-calorie diets (200 and 800 kcal/day) can result in hypokalemia, particularly in patients who do not consume supplementary potassium or who have an underlying predisposition to renal potassium wasting such as primary aldosteronism in which many patients are normokalemic at baseline [88-90]. These diets, intended to produce rapid weight loss, are usually carbohydrate poor and protein rich, such as the Atkins diet. (See

"Obesity in adults: Dietary therapy", section on 'Low-carbohydrate diets' and "Ketogenic dietary therapies for the treatment of epilepsy".)

The mechanism of the hypokalemia in patients consuming low-calorie diets is not completely understood. Urinary potassium wasting is thought to be important since patients with obesity demonstrate a significant kaliuresis over the first two weeks of fasting or ingesting a low-carbohydrate diet [91]. The kaliuresis may be due at least in part to the ketogenesis that results from a decrease in carbohydrate intake. As noted above, increased urinary excretion of ketoacid anions can increase urinary potassium excretion. (See 'Nonreabsorbable anions' above.)

INCREASED SWEAT LOSSES

Daily sweat losses are normally negligible since the volume is low and the potassium concentration is only 5 to 10 mEq/L. However, individuals exercising in a hot climate can produce 10 L or more of sweat per day, leading to potassium depletion if these losses are not replaced [92]. Significant loss of potassium in sweat can also occur in cystic fibrosis [93]. Urinary potassium excretion may contribute to the hypokalemia associated with increased sweat loss since aldosterone release is enhanced by exercise (via catecholamine-induced renin secretion) [92,94].

DIALYSIS

Although patients with end-stage kidney disease typically retain potassium and tend to be mildly hyperkalemic, hypokalemia can be induced in some patients by maintenance dialysis. As an example, dialysis potassium losses can reach 30 mEq per day in patients on chronic peritoneal dialysis. This can become clinically important if intake is reduced or if there are concurrent gastrointestinal losses [95]. However, mild hypokalemia immediately following a session of hemodialysis is expected and should not be treated with potassium supplementation.

A different mechanism may be operative in patients treated with hemodialysis who have underlying potassium depletion. In this setting, the metabolic acidosis induced by kidney failure can result in a relatively normal predialysis serum potassium concentration due to potassium movement out of the cells. However, the high flows attained during hemodialysis can rapidly correct the acidemia, leading to potassium entry into cells and a potentially large reduction in the serum potassium concentration [96].

PLASMAPHERESIS

Plasmapheresis removes potassium in the same concentration as in the plasma. If, however, albumin is used as the replacement fluid, transient hypokalemia can be induced by dilution. This problem can be avoided by adding 4 mEq of potassium to each liter of albumin solution given. (See "Therapeutic apheresis (plasma exchange or cytapheresis): Complications", section on 'Hypokalemia'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Fluid and electrolyte disorders in adults".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Hypokalemia (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Pathogenesis** – Hypokalemia is a common clinical problem that can result from decreased intake, increased translocation into the cells, or, most often, increased losses of potassium from the gastrointestinal tract or in the urine (table 1). (See 'Introduction' above.)

Potassium intake is normally 40 to 120 mEq per day. Since the kidney can reduce potassium excretion to 5 to 25 mEq per day in the presence of potassium depletion, decreased intake alone rarely causes hypokalemia. (See 'Decreased potassium intake' above.)

- **Major causes of hypokalemia**

  - **Translocation into cells** – Total body potassium is predominantly intracellular, a distribution maintained principally by the Na-K-ATPase pump. Increased activity of the Na-K-ATPase and/or alterations in other potassium transport pathways can result in hypokalemia due to increased potassium entry into cells. Common examples of this phenomenon include (see 'Increased entry into cells' above):

    - Increased insulin action (see 'Increased availability of insulin' above)
    - Elevated beta-adrenergic activity (see 'Elevated beta-adrenergic activity' above)
    - Elevated extracellular pH (see 'Elevated extracellular pH' above)

  - **Gastrointestinal loss** – Loss of gastric or intestinal secretions from any cause (vomiting, diarrhea, laxatives, or tube drainage) is associated with potassium losses and, possibly, hypokalemia:

    - Upper gastrointestinal losses (eg, vomiting) lead to hypokalemia through urinary potassium wasting. This occurs because the metabolic alkalosis resulting from gastric acid loss increases the filtered bicarbonate load above its reabsorptive threshold. As a result, more sodium bicarbonate and water are delivered to the distal potassium secretory site. (See 'Upper gastrointestinal losses' above.)

    - In contrast to gastric secretions, the potassium concentration in lower intestinal losses is relatively high. Hypokalemia due to lower gastrointestinal tract losses (usually from diarrhea) are typically associated with bicarbonate wasting and metabolic acidosis rather than the metabolic alkalosis observed with upper gastrointestinal losses. Hypokalemia from lower gastrointestinal losses is most common when the losses occur over a prolonged period. (See 'Lower gastrointestinal losses' above.)

  - **Renal loss** – Hypokalemia from urinary potassium wasting usually requires either mineralocorticoid excess (often from an increase in aldosterone) and/or an increase in distal flow. (See 'Increased urinary losses' above.)

    The major causes of urinary potassium wasting include:

- Diuretics – Any diuretic that acts proximal to the potassium secretory site will both increase distal delivery and, via the induction of volume depletion, activate the renin-angiotensin-aldosterone system. (See 'Diuretics' above.)

- Increased mineralocorticoid activity – Urinary potassium wasting is characteristic of any condition associated with primary hypersecretion of a mineralocorticoid, as with an aldosterone-producing adrenal adenoma. (See 'Increased mineralocorticoid activity' above.)

- Excretion of nonreabsorbable anions – When sodium is delivered to the distal nephron with relatively large quantities of a nonreabsorbable anion, such as bicarbonate or beta-hydroxybutyrate, more of the delivered sodium will be reabsorbed in exchange for potassium, leading to a potentially marked increase in potassium excretion. (See 'Nonreabsorbable anions' above.)

- **Other causes** – Hypokalemia can occur in patients who sweat excessively, and in patients undergoing dialysis or plasmapheresis. (See 'Increased sweat losses' above and 'Dialysis' above and 'Plasmapheresis' above.)

REFERENCES

1. SQUIRES RD, HUTH EJ. Experimental potassium depletion in normal human subjects. I. Relation of ionic intakes to the renal conservation of potassium. J Clin Invest 1959; 38:1134.
2. Gallen IW, Rosa RM, Esparaz DY, et al. On the mechanism of the effects of potassium restriction on blood pressure and renal sodium retention. Am J Kidney Dis 1998; 31:19.
3. Mount DB, Zandi-Nejad K. Disorders of potassium balance. In: Brenner and Rector's The Kid ney, 11th ed, Brenner BM (Ed), WB Saunders Co, Philadelphia 2020. p.537.
4. Clausen T. Hormonal and pharmacological modification of plasma potassium homeostasis. Fundam Clin Pharmacol 2010; 24:595.
5. Adrogué HJ, Lederer ED, Suki WN, Eknoyan G. Determinants of plasma potassium levels in diabetic ketoacidosis. Medicine (Baltimore) 1986; 65:163.
6. Bradberry SM, Vale JA. Disturbances of potassium homeostasis in poisoning. J Toxicol Clin Toxicol 1995; 33:295.
7. Fuentebella J, Kerner JA. Refeeding syndrome. Pediatr Clin North Am 2009; 56:1201.

8. Brown MJ, Brown DC, Murphy MB. Hypokalemia from beta2-receptor stimulation by circulating epinephrine. N Engl J Med 1983; 309:1414.
9. Clausen T, Everts ME. Regulation of the Na,K-pump in skeletal muscle. Kidney Int 1989; 35:1.
10. Gosmanov AR, Wong JA, Thomason DB. Duality of G protein-coupled mechanisms for beta-adrenergic activation of NKCC activity in skeletal muscle. Am J Physiol Cell Physiol 2002; 283:C1025.
11. Schnack C, Podolsky A, Watzke H, et al. Effects of somatostatin and oral potassium administration on terbutaline-induced hypokalemia. Am Rev Respir Dis 1989; 139:176.
12. Williams ME, Gervino EV, Rosa RM, et al. Catecholamine modulation of rapid potassium shifts during exercise. N Engl J Med 1985; 312:823.
13. Tønnesen E. Delirium tremens and hypokalemia. Lancet 1982; 2:97.
14. Morgan DB, Young RM. Acute transient hypokalaemia: new interpretation of a common event. Lancet 1982; 2:751.
15. Schaefer M, Link J, Hannemann L, Rudolph KH. Excessive hypokalemia and hyperkalemia following head injury. Intensive Care Med 1995; 21:235.
16. Shannon M, Lovejoy FH Jr. Hypokalemia after theophylline intoxication. The effects of acute vs chronic poisoning. Arch Intern Med 1989; 149:2725.
17. Kearney TE, Manoguerra AS, Curtis GP, Ziegler MG. Theophylline toxicity and the beta-adrenergic system. Ann Intern Med 1985; 102:766.
18. Lipworth BJ, McDevitt DG, Struthers AD. Prior treatment with diuretic augments the hypokalemic and electrocardiographic effects of inhaled albuterol. Am J Med 1989; 86:653.
19. Wong CS, Pavord ID, Williams J, et al. Bronchodilator, cardiovascular, and hypokalaemic effects of fenoterol, salbutamol, and terbutaline in asthma. Lancet 1990; 336:1396.
20. Goldenberg IF, Olivari MT, Levine TB, Cohn JN. Effect of dobutamine on plasma potassium in congestive heart failure secondary to idiopathic or ischemic cardiomyopathy. Am J Cardiol 1989; 63:843.
21. Braden GL, von Oeyen PT, Germain MJ, et al. Ritodrine- and terbutaline-induced hypokalemia in preterm labor: mechanisms and consequences. Kidney Int 1997; 51:1867.
22. de Wijkerslooth LR, Koch BC, Malingré MM, et al. Life-threatening hypokalaemia and lactate accumulation after autointoxication with Stacker 2, a 'powerful slimming agent'. Br J Clin Pharmacol 2008; 66:728.
23. Struthers AD, Whitesmith R, Reid JL. Prior thiazide diuretic treatment increases adrenaline-

induced hypokalaemia. Lancet 1983; 1:1358.

24. Adrogué HJ, Madias NE. Changes in plasma potassium concentration during acute acid-base disturbances. Am J Med 1981; 71:456.
25. Lin SH, Lin YF, Chen DT, et al. Laboratory tests to determine the cause of hypokalemia and paralysis. Arch Intern Med 2004; 164:1561.
26. Shiang JC, Cheng CJ, Tsai MK, et al. Therapeutic analysis in Chinese patients with thyrotoxic periodic paralysis over 6 years. Eur J Endocrinol 2009; 161:911.
27. Sung CC, Cheng CJ, Chiang WF, et al. Etiologic and therapeutic analysis in patients with hypokalemic nonperiodic paralysis. Am J Med 2015; 128:289.
28. Rose BD, Post TW. Clinical Physiology of Acid-Base and Electrolyte Disorders, 5th ed, McGra w-Hill, New York 2001. p.836.
29. Viens P, Thyss A, Garnier G, et al. GM-CSF treatment and hypokalemia. Ann Intern Med 1989; 111:263.
30. Lawson DH, Murray RM, Parker JL, Hay G. Hypokalaemia in megaloblastic anaemias. Lancet 1970; 2:588.
31. Adams PC, Woodhouse KW, Adela M, Parnham A. Exaggerated hypokalaemia in acute myeloid leukaemia. Br Med J (Clin Res Ed) 1981; 282:1034.
32. Zydlewski AW, Hasbargen JA. Hypothermia-induced hypokalemia. Mil Med 1998; 163:719.
33. Schaller MD, Fischer AP, Perret CH. Hyperkalemia. A prognostic factor during acute severe hypothermia. JAMA 1990; 264:1842.
34. Sigue G, Gamble L, Pelitere M, et al. From profound hypokalemia to life-threatening hyperkalemia: a case of barium sulfide poisoning. Arch Intern Med 2000; 160:548.
35. Ahlawat SK, Sachdev A. Hypokalaemic paralysis. Postgrad Med J 1999; 75:193.
36. Wells JA, Wood KE. Acute barium poisoning treated with hemodialysis. Am J Emerg Med 2001; 19:175.
37. Melnikov P, Zanoni LZ. Clinical effects of cesium intake. Biol Trace Elem Res 2010; 135:1.
38. Gay LA, Stanfield PR. Cs(+) causes a voltage-dependent block of inward K currents in resting skeletal muscle fibres. Nature 1977; 267:169.
39. Malik AR, Wolf PK, Ravasia S. Hypokalemia from risperidone and quetiapine overdose. Can J Psychiatry 2005; 50:76.
40. Lin YC, Chen HZ, Chang TJ, Lane HY. Hypokalemia following rapid titration of quetiapine treatment. J Clin Psychiatry 2008; 69:165.

41. Older J, Older P, Colker J, Brown R. Secretory villous adenomas that cause depletion syndrome. Arch Intern Med 1999; 159:879.
42. Agarwal R, Afzalpurkar R, Fordtran JS. Pathophysiology of potassium absorption and secretion by the human intestine. Gastroenterology 1994; 107:548.
43. Sitprija V. Altered fluid, electrolyte and mineral status in tropical disease, with an emphasis on malaria and leptospirosis. Nat Clin Pract Nephrol 2008; 4:91.
44. Rose BD, Post TW. Clinical Physiology of Acid-Base and Electrolyte Disorders, 5th ed, McGra w-Hill, New York 2001. p.333.
45. Ho JM, Juurlink DN, Cavalcanti RB. Hypokalemia following polyethylene glycol-based bowel preparation for colonoscopy in older hospitalized patients with significant comorbidities. Ann Pharmacother 2010; 44:466.
46. Beloosesky Y, Grinblat J, Weiss A, et al. Electrolyte disorders following oral sodium phosphate administration for bowel cleansing in elderly patients. Arch Intern Med 2003; 163:803.
47. Gonzalez JJ, Owens W, Ungaro PC, et al. Clay ingestion: a rare cause of hypokalemia. Ann Intern Med 1982; 97:65.
48. Bennett A, Stryjewski G. Severe hypokalemia caused by oral and rectal administration of bentonite in a pediatric patient. Pediatr Emerg Care 2006; 22:500.
49. Ukaonu C, Hill DA, Christensen F. Hypokalemic myopathy in pregnancy caused by clay ingestion. Obstet Gynecol 2003; 102:1169.
50. Wang WH, Giebisch G. Regulation of potassium (K) handling in the renal collecting duct. Pflugers Arch 2009; 458:157.
51. Young DB. Quantitative analysis of aldosterone's role in potassium regulation. Am J Physiol 1988; 255:F811.
52. Welling PA, Chang YP, Delpire E, Wade JB. Multigene kinase network, kidney transport, and salt in essential hypertension. Kidney Int 2010; 77:1063.
53. Vallon V, Schroth J, Lang F, et al. Expression and phosphorylation of the Na+-Cl- cotransporter NCC in vivo is regulated by dietary salt, potassium, and SGK1. Am J Physiol Renal Physiol 2009; 297:F704.
54. Wang ZJ, Sun P, Xing W, et al. Decrease in dietary K intake stimulates the generation of superoxide anions in the kidney and inhibits K secretory channels in the CCD. Am J Physiol Renal Physiol 2010; 298:F1515.
55. Babilonia E, Wei Y, Sterling H, et al. Superoxide anions are involved in mediating the effect of low K intake on c-Src expression and renal K secretion in the cortical collecting duct. J

Biol Chem 2005; 280:10790.

56. Papademetriou V. Diuretics, hypokalemia, and cardiac arrhythmia: a 20-year controversy. J Clin Hypertens (Greenwich) 2006; 8:86.
57. Schmieder RE, Rockstroh JK. Efficacy and tolerance of low-dose loop diuretics in hypertension. Cardiology 1994; 84 Suppl 2:36.
58. Carlsen JE, Køber L, Torp-Pedersen C, Johansen P. Relation between dose of bendrofluazide, antihypertensive effect, and adverse biochemical effects. BMJ 1990; 300:975.
59. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002; 288:2981.
60. Franse LV, Pahor M, Di Bari M, et al. Hypokalemia associated with diuretic use and cardiovascular events in the Systolic Hypertension in the Elderly Program. Hypertension 2000; 35:1025.
61. Kaplan NM, Carnegie A, Raskin P, et al. Potassium supplementation in hypertensive patients with diuretic-induced hypokalemia. N Engl J Med 1985; 312:746.
62. Schnaper HW, Freis ED, Friedman RG, et al. Potassium restoration in hypertensive patients made hypokalemic by hydrochlorothiazide. Arch Intern Med 1989; 149:2677.
63. Bettinelli A, Bianchetti MG, Girardin E, et al. Use of calcium excretion values to distinguish two forms of primary renal tubular hypokalemic alkalosis: Bartter and Gitelman syndromes. J Pediatr 1992; 120:38.
64. Suki WN, Yium JJ, Von Minden M, et al. Acute treatment of hypercalcemia with furosemide. N Engl J Med 1970; 283:836.
65. Okusa MD, Velázquez H, Ellison DH, Wright FS. Luminal calcium regulates potassium transport by the renal distal tubule. Am J Physiol 1990; 258:F423.
66. Sands JM, Naruse M, Baum M, et al. Apical extracellular calcium/polyvalent cation-sensing receptor regulates vasopressin-elicited water permeability in rat kidney inner medullary collecting duct. J Clin Invest 1997; 99:1399.
67. Beck KR, Bächler M, Vuorinen A, et al. Inhibition of 11β-hydroxysteroid dehydrogenase 2 by the fungicides itraconazole and posaconazole. Biochem Pharmacol 2017; 130:93.
68. Hoffmann WJ, McHardy I, Thompson GR 3rd. Itraconazole induced hypertension and hypokalemia: Mechanistic evaluation. Mycoses 2018; 61:337.

69. Boughton C, Taylor D, Ghataore L, et al. Mineralocorticoid hypertension and hypokalaemia induced by posaconazole. Endocrinol Diabetes Metab Case Rep 2018; 2018.
70. Attard G, Reid AH, Auchus RJ, et al. Clinical and biochemical consequences of CYP17A1 inhibition with abiraterone given with and without exogenous glucocorticoids in castrate men with advanced prostate cancer. J Clin Endocrinol Metab 2012; 97:507.
71. Fizazi K, Tran N, Fein L, et al. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med 2017; 377:352.
72. Olson CA, Crudo DF. Pubertal delay, hypokalemia, and hypertension caused by a rare form of congenital adrenal hyperplasia. J Pediatr Adolesc Gynecol 2011; 24:e29.
73. Attard G, Merseburger AS, Arlt W, et al. Assessment of the Safety of Glucocorticoid Regimens in Combination With Abiraterone Acetate for Metastatic Castration-Resistant Prostate Cancer: A Randomized, Open-label Phase 2 Study. JAMA Oncol 2019; 5:1159.
74. Pia A, Vignani F, Attard G, et al. Strategies for managing ACTH dependent mineralocorticoid excess induced by abiraterone. Cancer Treat Rev 2013; 39:966.
75. Mohr JA, Clark RM, Waack TC, Whang R. Nafcillin-associated hypokalemia. JAMA 1979; 242:544.
76. Carlisle EJ, Donnelly SM, Ethier JH, et al. Modulation of the secretion of potassium by accompanying anions in humans. Kidney Int 1991; 39:1206.
77. Carlisle EJ, Donnelly SM, Vasuvattakul S, et al. Glue-sniffing and distal renal tubular acidosis: sticking to the facts. J Am Soc Nephrol 1991; 1:1019.
78. Hariprasad MK, Eisinger RP, Nadler IM, et al. Hyponatremia in psychogenic polydipsia. Arch Intern Med 1980; 140:1639.
79. Sebastian A, McSherry E, Morris RC Jr. On the mechanism of renal potassium wasting in renal tubular acidosis associated with the Fanconi syndrome (type 2 RTA). J Clin Invest 1971; 50:231.
80. Whang R, Whang DD, Ryan MP. Refractory potassium repletion. A consequence of magnesium deficiency. Arch Intern Med 1992; 152:40.
81. Husband DJ, Watkin SW. Fatal hypokalaemia associated with ifosfamide/mesna chemotherapy. Lancet 1988; 1:1116.
82. Huang CL, Kuo E. Mechanism of hypokalemia in magnesium deficiency. J Am Soc Nephrol 2007; 18:2649.
83. Yang L, Frindt G, Palmer LG. Magnesium modulates ROMK channel-mediated potassium secretion. J Am Soc Nephrol 2010; 21:2109.

84. Douglas JB, Healy JK. Nephrotoxic effects of amphotericin B, including renal tubular acidosis. Am J Med 1969; 46:154.
85. Perazella MA, Eisen RN, Frederick WG, Brown E. Renal failure and severe hypokalemia associated with acute myelomonocytic leukemia. Am J Kidney Dis 1993; 22:462.
86. Mir MA, Brabin B, Tang OT, et al. Hypokalaemia in acute myeloid leukaemia. Ann Intern Med 1975; 82:54.
87. Aldinger KA, Samaan NA. Hypokalemia with hypercalcemia. Prevalence and significance in treatment. Ann Intern Med 1977; 87:571.
88. Liu T, Nagami GT, Everett ML, Levine BS. Very low calorie diets and hypokalaemia: the importance of ammonium excretion. Nephrol Dial Transplant 2005; 20:642.
89. Singh BN, Gaarder TD, Kanegae T, et al. Liquid protein diets and torsade de pointes. JAMA 1978; 240:115.
90. Advani A, Taylor R. Life-threatening hypokalaemia on a low-carbohydrate diet associated with previously undiagnosed primary hyperaldosteronism [corrected]. Diabet Med 2005; 22:1605.
91. Rabast U, Vornberger KH, Ehl M. Loss of weight, sodium and water in obese persons consuming a high- or low-carbohydrate diet. Ann Nutr Metab 1981; 25:341.
92. Knochel JP, Dotin LN, Hamburger RJ. Pathophysiology of intense physical conditioning in a hot climate. I. Mechanisms of potassium depletion. J Clin Invest 1972; 51:242.
93. Davé S, Honney S, Raymond J, Flume PA. An unusual presentation of cystic fibrosis in an adult. Am J Kidney Dis 2005; 45:e41.
94. Kosunen KJ, Pakarinen AJ. Plasma renin, angiotensin II, and plasma and urinary aldosterone in running exercise. J Appl Physiol 1976; 41:26.
95. Rostand SG. Profound hypokalemia in continuous ambulatory peritoneal dialysis. Arch Intern Med 1983; 143:377.
96. Wiegand CF, Davin TD, Raij L, Kjellstrand CM. Severe hypokalemia induced by hemodialysis. Arch Intern Med 1981; 141:167.

Topic 2341 Version 35.0

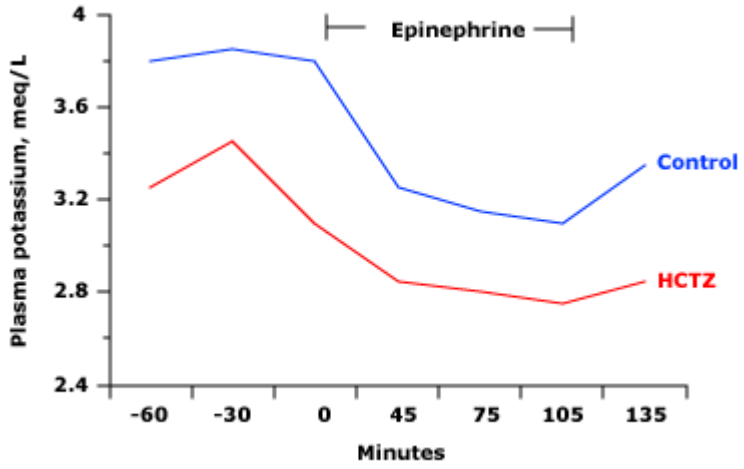
GRAPHICS

Major causes of hypokalemia

Decreased potassium intake
Increased entry into cells
An elevation in extracellular pH
Increased availability of insulin
Elevated β-adrenergic activity - stress or administration of beta agonists
Hypokalemic periodic paralysis
Marked increase in blood cell production
Hypothermia
Chloroquine intoxication
Increased gastrointestinal losses
Vomiting
Diarrhea
Tube drainage
Laxative abuse
Increased urinary losses
Diuretics
Primary mineralocorticoid excess
Loss of gastric secretions
Nonreabsorbable anions
Renal tubular acidosis
Hypomagnesemia
Amphotericin B
Salt-wasting nephropathies - including Bartter's or Gitelman's syndrome
Polyuria
Increased sweat losses
Dialysis
Plasmapheresis

Graphic 62892 Version 3.0

Epinephrine lowers the plasma potassium

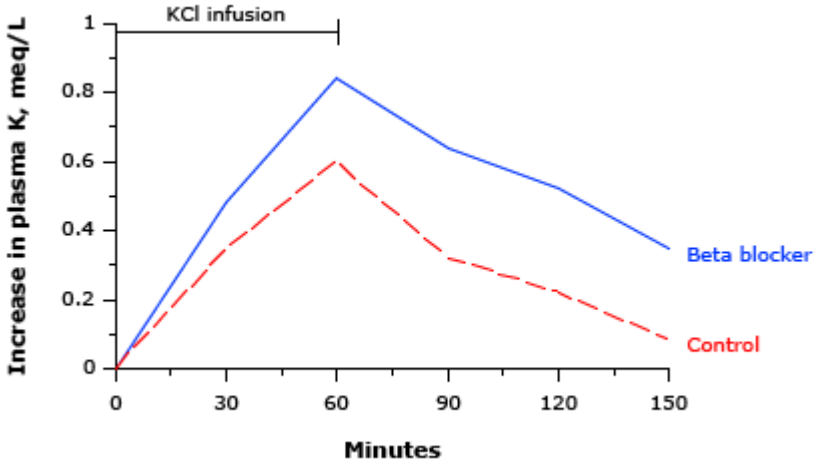


Plasma potassium concentration during an infusion of epinephrine (in physiologic doses) in six patients pretreated with a placebo or a thiazide diuretic for seven days. The plasma potassium concentration fell in both groups, but reached potentially dangerous levels in the diuretic-treated patients who had mild baseline hypokalemia.

Data from Struthers, AD, Whitesmith, R, Reid, JL, Lancet 1983; 1:1358.

Graphic 57078 Version 1.0

Beta blocker enhances kalemic response to a potassium load

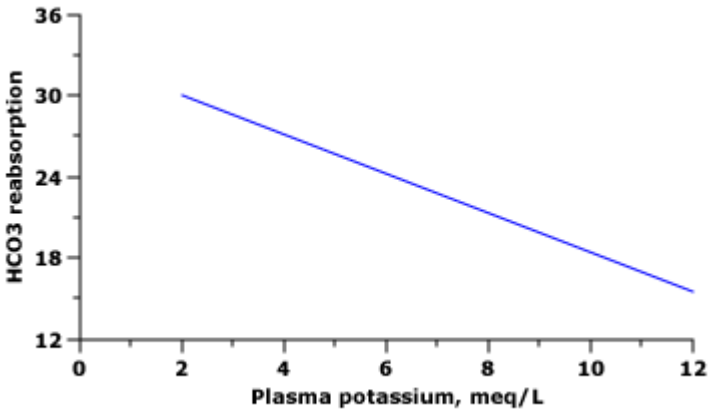


Change in the plasma potassium concentration after a potassium chloride infusion in control subjects (dashed line) and those treated with a beta blocker (solid line). The rise in the plasma potassium concentration was signficantly greater in the presence of beta blockade.

Data from: Rosa RM, Silva P, Young JB, et al. N Engl J Med 1980; 302:431.

Graphic 62538 Version 4.0

Inverse relation between plasma potassium and bicarbonate reabsorption

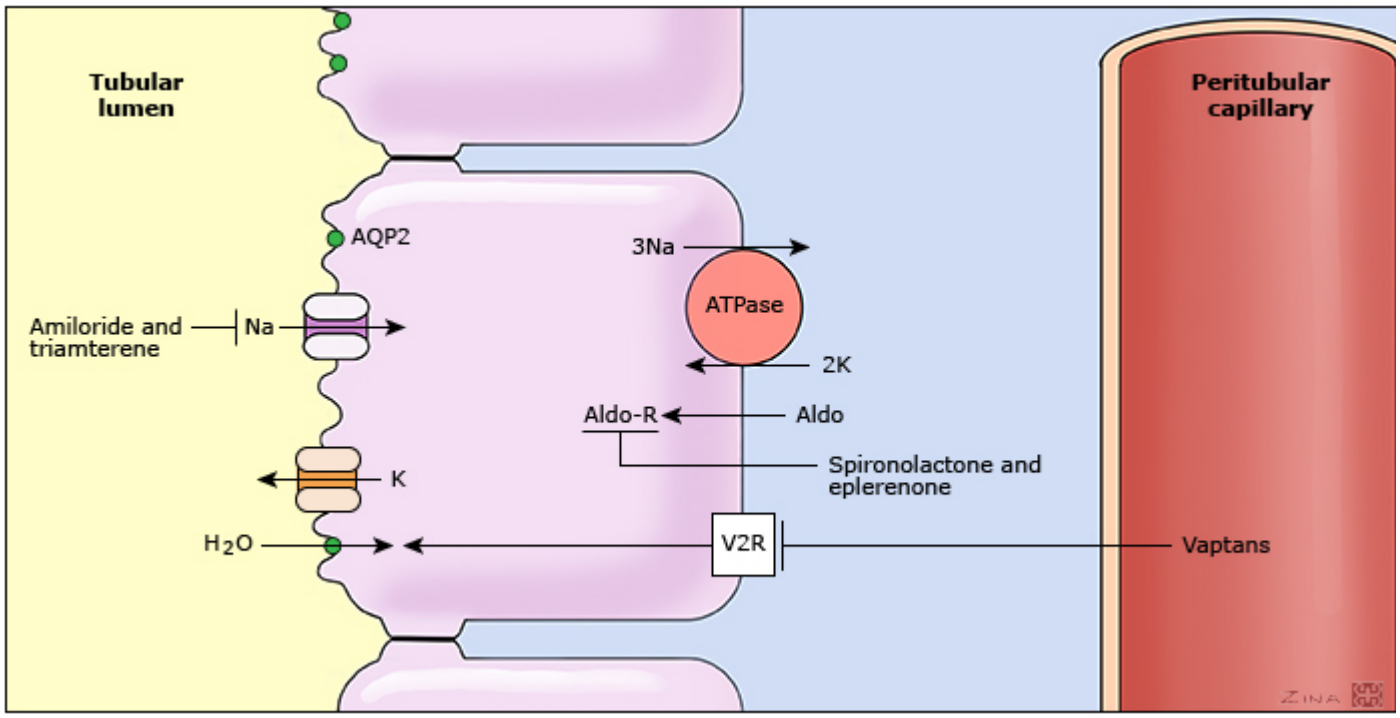


Renal tubular reabsorption of HCO3 (meq/L of glomerular filtrate) as a function of the plasma potassium concentration.

Data from Fuller, GR, MacLeod, MB, Pitts, RF, Am J Physiol,182:111, 1956.

Graphic 76787 Version 1.0

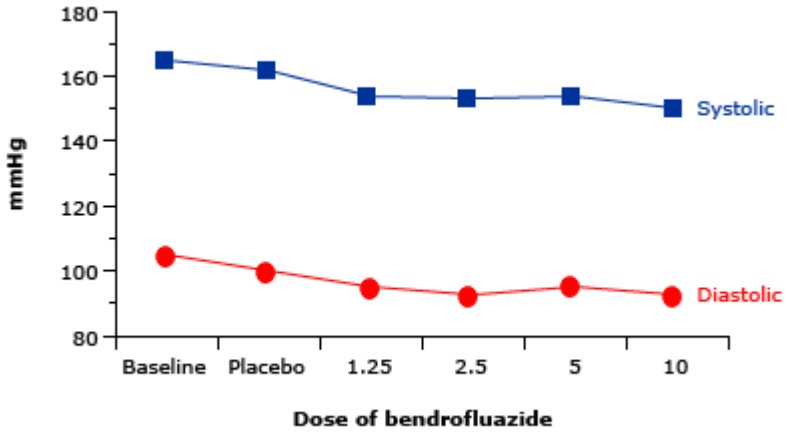
Ion transport in collecting tubule principal cells



Schematic representation of sodium (Na) and potassium (K) transport in the sodium-reabsorbing principal cells in the collecting tubules. The entry of filtered sodium into these cells is mediated by selective sodium channels in the apical (luminal) membrane (ENaC); the energy for this process is provided by the favorable electrochemical gradient for sodium (cell interior electronegative and low cell sodium concentration). Reabsorbed sodium is pumped out of the cell by the Na-K-ATPase pump in the basolateral (peritubular) membrane. The reabsorption of cationic sodium makes the lumen electronegative, thereby creating a favorable gradient for the secretion of potassium into the lumen via potassium channels (ROMK and BK) in the apical membrane. Aldosterone (Aldo), after combining with the cytosolic mineralocorticoid receptor (Aldo-R), leads to enhanced sodium reabsorption and potassium secretion by increasing both the number of open sodium channels and the number of Na-K-ATPase pumps. The potassium-sparing diuretics (amiloride and triamterene) act by directly inhibiting the epithelial sodium channel; spironolactone acts by competing with aldosterone for binding to the mineralocorticoid receptor.

Graphic 60693 Version 16.0

Antihypertensive dose response to thiazide therapy

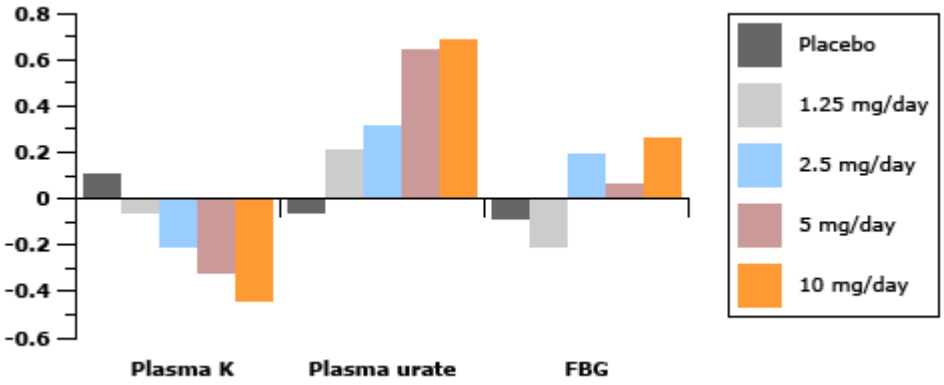


Antihypertensive response to bendrofluazide in relation to daily dose (in mg; multiply by 10 to get approximate equivalent doses of hydrochlorothiazide). The initial dose of 1.25 mg/day lowers the blood pressure in comparison with placebo; however, higher doses produced little further antihypertensive response. Each treatment group contained approximately 52 patients.

Data from: Carlsen JE, Kober L, Torp-Pedersen C, Johannsen P. Relation between dose of bendrofluazide, antihypertensive effect, and adverse biochemical effects. BMJ 1990; 300:975.

Graphic 61248 Version 4.0

Dose dependence of thiazide-induced side effects



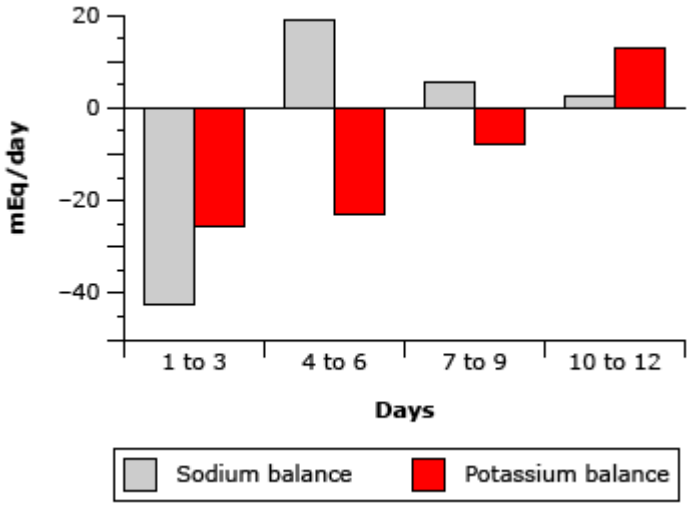
Metabolic complications induced by bendrofluazide in relation to daily dose (multiply by 10 to get equivalent doses of hydrochlorothiazide). Increasing the dose led to progressive hypokalemia and hyperuricemia and a greater likelihood of a mild elevation in the FBG, all without a further reduction in the systemic blood pressure. Each treatment group contained approximately 52 patients.

FBG: fasting blood glucose.

Data from: Carlsen JE, Kober L, Torp-Pedersen C, Johansen P. Relation between dose of bendrofluazide, antihypertensive effect, and adverse biochemical effects. BMJ 1990; 300:975.

Graphic 69912 Version 5.0

Steady state after initiation of a thiazide diuretic



Sodium and potassium balance (intake minus excretion) after the administration of 100 mg of hydrochlorothiazide to three normal subjects. Negative balance persisted for only three days for sodium and six days for potassium before a steady state was reestablished, in which intake and excretion were roughly equal.

Data from Maronde RF, Milgrom M, Vlachakis ND, Chan L. Response of thiazide-induced hypokalemia to amiloride. JAMA 1983; 249:237.

Graphic 74940 Version 8.0