Review Article

Current Concepts

HYPOKALEMIA

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A LOW serum potassium concentration is perhaps the most common electrolyte abnormality encountered in clinical practice. When defined as a value of less than 3.6 mmol of potassium per liter, hypokalemia is found in over 20 percent of hospitalized patients.[1] The majority of these patients have serum potassium concentrations between 3.0 and 3.5 mmol per liter, but as many as one quarter have values below 3.0 mmol per liter. Comparable data are not available for outpatients, but a low serum potassium concentration has been found in 10 to 40 percent of patients treated with thiazide diuretics.[2] Hypokalemia is usually well tolerated in otherwise healthy people, but it can be life-threatening when severe. Even mild or moderate hypokalemia increases the risks of morbidity and mortality in patients with cardiovascular disease. As a result, when hypokalemia is identified, the underlying cause should be sought and the disorder treated.

NORMAL REGULATION OF POTASSIUM BALANCE

Both the total body stores of potassium and its distribution within the body are closely regulated by key hormones. The normal transcellular distribution of potassium (a high ratio of intracellular to extracellular potassium) is maintained by at least two hormonal signals that promote the entry of this cation into cells (Fig. 1). Both insulin and β-adrenergic catecholamines increase cellular potassium uptake by stimulating cell-membrane Na^+/K^+–ATPase.[4] For insulin, there is a feedback system in which hyperkalemia stimulates insulin secretion and hypokalemia inhibits it.[5,6] No feedback system has been identified for β-adrenergic stimulation, but β-blockade increases serum potassium and β-agonists decrease it, an effect that is independent of body stores of potassium. Synthesis of Na^+/K^+–ATPase is also stimulated by thyroid hormone,[4] which may contribute to the hypokalemia that occurs in patients with hyperthyroidism (see below). Administration of alkali causes a shift of potassium into cells, but the response is quite variable.[7,8] In patients with end-stage renal disease, administration of bicarbonate has only a slight effect on the transcellular distribution of potassium.[8]

It remains unclear whether aldosterone affects the transcellular distribution of potassium, but this hormone is clearly the major regulator of body stores of potassium through its effect on the excretion of potassium by the kidney.[9] As in the case of insulin, there is a feedback control; hyperkalemia stimulates the release of aldosterone (with synergy from angiotensin II) (Fig. 1), and hypokalemia inhibits it.[10,11] Other hormonal and nonhormonal factors modulate renal potassium excretion,[3,12] but they do not appear to have a role in normal potassium homeostasis.

The regulation of extracellular potassium concentration and body stores of potassium is asymmetric. Depletion of potassium and hypokalemia can occur simply through a reduction in potassium intake[13,14] and can persist for long periods, despite normal hormone signaling and renal function. Hyperkalemia, by contrast, elicits a brisk response and is only sustained when there is continued disruption or impairment of the normal regulatory systems.

CLINICAL SPECTRUM

Patients with hypokalemia often have no symptoms, particularly when the disorder is mild (serum potassium, 3.0 to 3.5 mmol per liter). With more severe hypokalemia, nonspecific symptoms, such as generalized weakness, lassitude, and constipation, are more common. When serum potassium decreases to less than 2.5 mmol per liter, muscle necrosis can occur, and at serum concentrations of less than 2.0 mmol per liter, an ascending paralysis can develop, with eventual impairment of respiratory function. The likelihood of symptoms appears to correlate with the rapidity of the decrease in serum potassium. In patients without underlying heart disease, abnormalities in cardiac conduction are extremely unusual, even when the serum potassium concentration is below 3.0 mmol per liter. In patients with cardiac ischemia, heart failure, or left ventricular hypertrophy, however, even mild-to-moderate hypokalemia increases the likelihood of cardiac arrhythmias.[2,15] Hypokalemia increases the arrhythmogenic potential of digoxin. Potassium depletion and hypokalemia increase both systolic and diastolic blood

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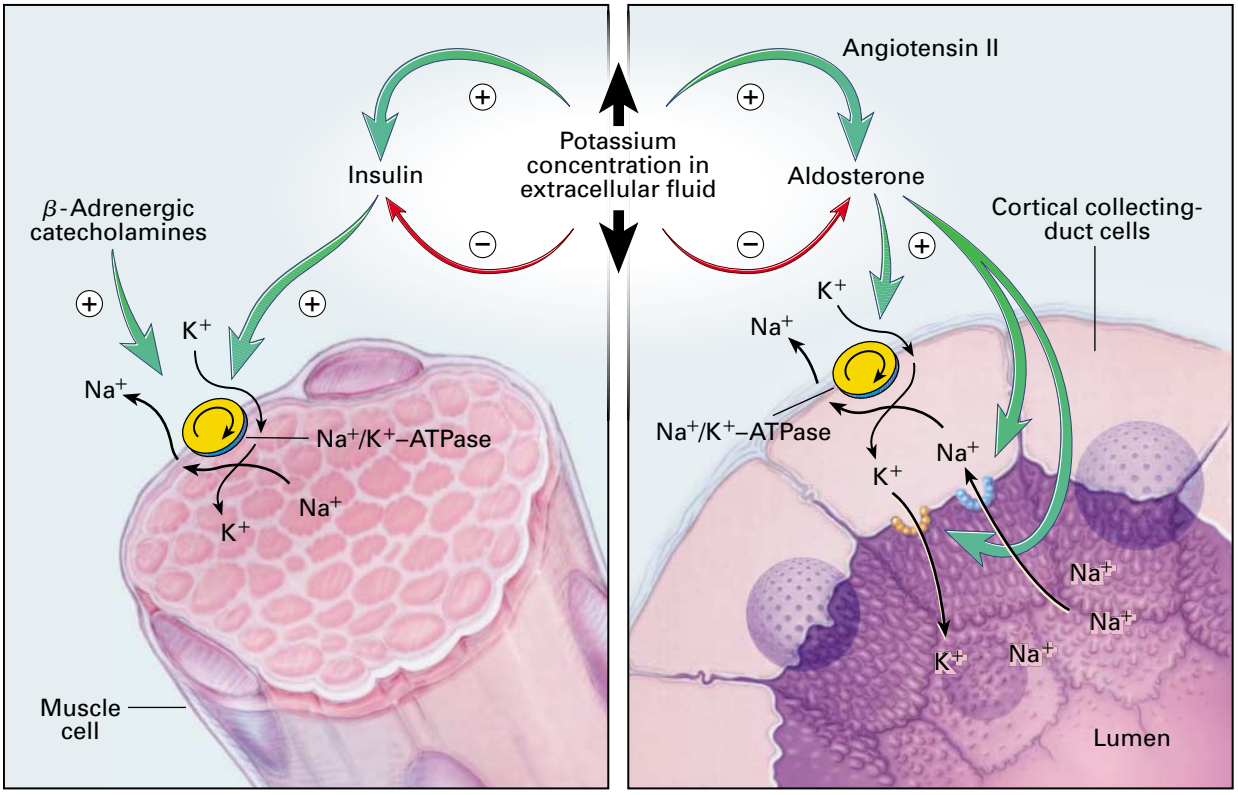

Figure 1. Key Hormones Involved in Normal Potassium Homeostasis.

Insulin and β-adrenergic catecholamines promote the entry of potassium into muscle cells by stimulating NA^+/K^+–ATPase. Aldosterone promotes potassium excretion through its effects on NA^+/K^+–ATPase and epithelial sodium and potassium channels in collecting-duct cells. There is a feedback mechanism for insulin and aldosterone: an increase in the potassium concentration of the extracellular fluid stimulates the secretion of each of these hormones, and a decrease inhibits their secretion. Angiotensin II has a synergistic effect on the stimulation of aldosterone production induced by hyperkalemia. Plus signs denote stimulation, and minus signs inhibition. Modified from Gennari.[3]

pressure when sodium intake is not restricted, presumably by promoting renal sodium retention.[16]

Hypokalemia is rarely suspected on the basis of clinical presentation; the diagnosis is made by measurement of serum potassium. A low serum potassium concentration indicates disruption of normal homeostasis, with one very rare exception. In some patients with leukemia and markedly elevated white-cell counts, potassium is taken up by the abnormal cells if the blood is left at room temperature for several hours.[17] More commonly, hypokalemia in patients with leukemia is the result of renal potassium wasting (see below).

Hypokalemia is almost always the result of potassium depletion induced by abnormal losses of potassium. More rarely, hypokalemia occurs because of an abrupt shift of potassium from the extracellular compartment into cells. In either case, drugs prescribed by physicians are the most common causes of hypokalemia. Thus, the first step in the management of hypokalemia is to review the patient's drug record.

In the absence of an inciting drug, hypokalemia can result from an acute shift of potassium from the extracellular compartment to cells, from inadequate intake, or from abnormal losses. Most commonly, hypokalemia is the result of either abnormal loss through the kidney induced by metabolic alkalosis or loss in the stool induced by diarrhea.

DRUG-INDUCED CAUSES DUE TO TRANSCELLULAR SHIFTS

β_2-Sympathomimetic Drugs

A wide range of drugs have β_2-sympathomimetic activity, including decongestants, bronchodilators, and inhibitors of uterine contraction (Table 1). A standard dose of nebulized albuterol reduces serum potassium by 0.2 to 0.4 mmol per liter, and a second dose taken within one hour reduces it by almost 1 mmol per liter.[18,19] The hypokalemia caused by these drugs is sustained for up to four hours. Intentional ingestion of excess amounts of pseudoephedrine can cause severe hypokalemia.[20] Ritodrine and

TABLE 1. DRUG-INDUCED HYPOKALEMIA.

HYPOKALEMIA DUE TO TRANSCELLULAR POTASSIUM SHIFT	HYPOKALEMIA DUE TO INCREASED RENAL POTASSIUM LOSS	HYPOKALEMIA DUE TO EXCESS POTASSIUM LOSS IN STOOL
β_2-Adrenergic agonists	Diuretics	Phenolphthalein
Epinephrine	Acetazolamide	Sodium polystyrene sulfonate
Decongestants	Thiazides	
Pseudoephedrine	Chlorthalidone	
Phenylpropanolamine	Indapamide	
Bronchodilators	Metolazone	
Albuterol	Quinethazone	
Terbutaline	Bumetanide	
Pirbuterol	Ethacrynic acid	
Isoetharine	Furosemide	
Fenoterol	Torsemide	
Ephedrine	Mineralocorticoids	
Isoproterenol	Fludrocortisone	
Metaproterenol	Substances with mineralocorticoid effects	
Tocolytic agents	Licorice	
Ritodrine	Carbenoxolone	
Nylidrin	Gossypol	
Theophylline	High-dose glucocorticoids	
Caffeine	High-dose antibiotics	
Verapamil intoxication	Penicillin	
Chloroquine intoxication	Nafcillin	
Insulin overdose	Ampicillin	
	Carbenicillin	
	Drugs associated with magnesium depletion	
	Aminoglycosides	
	Cisplatin	
	Foscarnet	
	Amphotericin B	

terbutaline, inhibitors of uterine contraction, can reduce serum potassium to as low as 2.5 mmol per liter after four to six hours of intravenous administration.[21]

Xanthines

Theophylline and caffeine are not sympathomimetic drugs, but these agents stimulate the release of sympathetic amines and may also increase Na^+/K^+–ATPase activity by inhibiting cellular phosphodiesterase.[22] Severe hypokalemia is an almost invariable feature of acute theophylline toxicity.[22,23] The caffeine in a few cups of coffee can decrease serum potassium by as much as 0.4 mmol per liter.[24]

Other Drugs

Although calcium-channel blockers increase cellular uptake of potassium in experimental studies,[25] these drugs have no effect on serum potassium concentrations at usual doses. Intentional ingestion of large amounts of verapamil, however, can cause severe hypokalemia.[26] Ingestion of large amounts of chloroquine also causes hypokalemia, by inhibiting potassium from exiting cells.[22] Because insulin moves potassium into cells (Fig. 1), the administration of this hormone always causes a transient reduction in serum potassium. Hypokalemia is not an important clinical problem, however, except in the case of intentional overdose of insulin[22] or during the treatment of diabetic ketoacidosis (see below).

DRUG-INDUCED CAUSES DUE TO ABNORMAL LOSSES OF POTASSIUM

Diuretics

The most common cause of hypokalemia is diuretic therapy. Both the thiazide and loop diuretics block chloride-associated sodium reabsorption (with each inhibiting a different membrane-transport protein) and, as a result, increase delivery of sodium to the collecting tubules, where its reabsorption creates a favorable electrochemical gradient for potassium secretion.[11,12] The degree of hypokalemia is directly related to the dose of the thiazide diuretic and is greater when dietary sodium intake is higher.[15] The combined use of furosemide or bumetanide with metolazone invariably causes moderate-to-severe hypokalemia, despite potassium supplementation. Diuretic-induced hypokalemia is usually but not always associated with a mild-to-moderate metabolic alkalosis (serum bicarbonate concentration, 28 to 36 mmol per liter). The diuretic drug acetazolamide, however, promotes potassium excretion by impeding hydrogen-linked sodium reabsorption and thus causes a metabolic acidosis along with hypokalemia. Identifying a diuretic

drug as the cause of hypokalemia is straightforward, except when patients take these agents surreptitiously.[27,28] The diagnosis of the cause of the hypokalemia in these patients may require urinary assays for specific diuretic drugs.

Drugs with Mineralocorticoid or Glucocorticoid Effects

Fludrocortisone is an oral mineralocorticoid that promotes renal potassium excretion and can cause potassium wasting if used inappropriately. Glucocorticoids, such as prednisone and hydrocortisone, have no direct effect on renal potassium secretion, but they increase potassium excretion nonspecifically through their effect on the filtration rate and distal sodium delivery.[8] When given over the long term, these drugs reduce serum potassium only slightly (by 0.2 to 0.4 mmol per liter). Gossypol (an oral inhibitor of spermatogenesis), carbenoxolone, and licorice all cause hypokalemia by inhibiting the enzyme 11β-hydroxysteroid dehydrogenase.[29,30]

Other Drugs

Penicillin and its synthetic derivatives, when given intravenously in large doses, promote renal potassium excretion by increasing sodium delivery to the distal nephron. The aminoglycoside antibiotics, the antitumor drug cisplatin, and the antiviral drug foscarnet all cause renal potassium wasting by inducing depletion of magnesium.[31,32] Amphotericin B causes renal potassium wasting through the inhibition of the secretion of hydrogen ions by collecting-duct cells as well as by causing magnesium depletion.

Laxatives and Enemas

Large doses of laxatives cause excessive potassium loss in the stool and can cause hypokalemia. Repeated enemas will produce the same result. This diagnosis can be overlooked if these agents are used surreptitiously to control body weight.[33,34]

NONDRUG CAUSES DUE TO TRANSCELLULAR SHIFTS

Severe hypokalemia (serum potassium, $<$3.0 mmol per liter) can occur, although rarely, in association with hyperthyroidism, resulting in a clinical syndrome characterized by the sudden onset of severe muscle weakness and paralysis.[35] This presentation has a predilection for people of Asian origin, occurring in 2 to 8 percent of patients with hyperthyroidism in Asian countries. Signs and symptoms of hyperthyroidism usually accompany these acute episodes of muscle weakness and paralysis, but they may be subtle, and the misdiagnosis of familial periodic paralysis may be made (see below). As in the case of familial periodic paralysis, the symptoms respond rapidly to the administration of potassium.

Familial hypokalemic periodic paralysis is a rare autosomal dominant disease that has been associated with mutations of the gene encoding the dihydropyridine receptor, a voltage-gated calcium channel.[36] The disorder is characterized by sudden attacks of muscle paralysis associated with a decrease in serum potassium to low concentrations, often less than 2.5 mmol per liter. Attacks can be provoked by high intake of carbohydrates or sodium or by exertion and usually subside spontaneously in less than 24 hours. Although the hypokalemia is caused by a shift of potassium into cells, the administration of potassium can be lifesaving and should be given to treat acute attacks. Various approaches have been used to prevent recurrences with varying degrees of success, including the administration of spironolactone, triamterene, and acetazolamide.[37]

Serum potassium decreases abruptly in patients with delirium tremens, by 1.0 mmol per liter on average.[38] The severity of hypokalemia in this disorder is correlated with the plasma epinephrine concentration, and the presumption is that the reduction in potassium is due to β_2-adrenergic stimulation, which causes a shift of potassium into cells.

Accidental ingestion of barium compounds causes hypokalemia by blocking the exit of potassium from cells, and in severe cases it can lead to muscle weakness, paralysis, and rhabdomyolysis.[22] Barium also causes vomiting and diarrhea, both of which exacerbate hypokalemia by causing loss of potassium. Treatment with intravenous potassium should be initiated rapidly.

Treatment of severe pernicious anemia (hematocrit, $<$20 percent) with vitamin B_{12} causes an acute reduction in serum potassium because of a rapid uptake of potassium by the new cells that are formed.[39] Hypokalemia can also occur after the transfusion of previously frozen washed red cells, presumably because of the uptake of potassium by these cells.[40]

NONDRUG CAUSES DUE TO INADEQUATE DIETARY INTAKE

When the dietary intake of potassium is reduced to less than 1 g per day (25 mmol per day), depletion of potassium and hypokalemia result because the renal excretion of potassium fails to decrease promptly.[13,14] An isolated reduction of this magnitude in the dietary intake of potassium requires a specially prepared diet, and therefore, hypokalemia is rarely the result of decreased intake. With starvation or near-starvation, body potassium stores become depleted but the breakdown of tissues releases potassium into the extracellular compartment, mitigating the hypokalemia.

NONDRUG CAUSES DUE TO ABNORMAL LOSSES OF POTASSIUM

Losses in Stool

The concentration of potassium in stool is 80 to 90 mmol per liter, but because of the low volume of

water in normal stool, only about 10 mmol is usually lost each day. In diarrheal states, the potassium concentration in stool decreases, but large quantities of potassium can nonetheless be lost as the volume of stool increases. Anything that increases stool volume, from infectious diarrhea to cancer chemotherapy, can result in clinically significant potassium depletion and hypokalemia (Table 2).

Table 2. Causes of Potassium Loss in Stool.

Infectious diarrhea
Cholera
Salmonella
Strongyloides
Yersinia
Diarrhea associated with AIDS*
Tumors
Vipoma
Villous adenoma of the colon
Zollinger–Ellison syndrome
Jejunoileal bypass
Enteric fistula
Malabsorption
Intestinal ion-transport defects
Congenital chloride diarrhea
Cancer therapy
Chemotherapy
Radiation enteropathy
Geophagia

*AIDS denotes the acquired immunodeficiency syndrome.

Loss through the Kidney

Large amounts of potassium are lost through the kidney in patients with a variety of disorders. For ease of diagnosis, these disorders are categorized according to acid–base status.

Metabolic Alkalosis

Hypokalemia is an almost invariable consequence of metabolic alkalosis. In the most common form of this disorder, induced by selective chloride depletion due to vomiting or nasogastric drainage, hypokalemia develops during the induction of alkalosis as a result of increased renal potassium loss.[41] In the chloride-sensitive form of metabolic alkalosis, the administration of chloride corrects the alkalosis and allows the repletion of body stores of potassium if potassium intake is adequate.

More rarely, metabolic alkalosis occurs independently of chloride depletion, as a result of systemic or intrarenal abnormalities that augment sodium reabsorption in the distal nephron (Table 3). The most common of these abnormalities is primary hyperaldosteronism, a disorder often heralded by severe hypokalemia (serum potassium, <3.0 mmol per liter). In the few affected patients who do not have hypokalemia, the serum potassium concentration is virtually always below 4.0 mmol per liter.[42] Hypokalemia can also develop in patients with Cushing's syndrome, but it is usually milder than in patients with hyperaldosteronism.[12]

Genetic abnormalities that influence the activity of renal ion transporters are rare causes of metabolic alkalosis and hypokalemia.[43-46] Two of these disorders (Liddle's syndrome and 11β-hydroxysteroid dehydrogenase deficiency) stimulate reabsorption of sodium by collecting-duct cells and cause the syndrome of apparent mineralocorticoid excess, so named because this transport abnormality results in hypertension and hypokalemia, but serum aldosterone concentrations are low rather than high.[44,45] In two other disorders, genetic mutations inactivate or impede the activity of chloride-associated sodium transporters in the loop of Henle (Bartter's syndrome) and early distal tubule (Gitelman's syndrome),[46] causing metabolic alkalosis and hypokalemia without hypertension.

Table 3. Causes of Potassium Loss in Urine Due to Mineralocorticoid Excess or Renal Transport Abnormalities.

Mineralocorticoid excess
Primary hyperaldosteronism
Adrenal adenoma
Adrenal carcinoma
Bilateral adrenal hyperplasia
Congenital adrenal hyperplasia*
11β-hydroxylase deficiency
17α-hydroxylase deficiency
Renin-secreting tumors
Ectopic corticotropin syndrome
Cushing's syndrome
Pituitary
Adrenal
Glucocorticoid-responsive aldosteronism*
Renovascular hypertension
Malignant hypertension
Vasculitis
Apparent mineralocorticoid excess
Liddle's syndrome*
11β-hydroxysteroid dehydrogenase deficiency*
Impaired chloride-associated sodium transport
Bartter's syndrome*
Gitelman's syndrome*

*This disease is hereditary.

Metabolic Acidosis

Hypokalemia is a cardinal feature of type I or classic distal renal tubular acidosis. The degree of hypokalemia in this disorder is not directly correlated to the degree of acidosis but more likely reflects dietary sodium and potassium intake and serum aldosterone concentrations. Life-threatening hypokalemia (serum potassium, <2.0 mmol per liter) can occur in patients with untreated distal renal tubular acidosis. The administration of sodium bicarbonate ameliorates the

hypokalemia,[47] but potassium supplementation is usually required on a long-term basis to manage this disorder.[48] In cases of type II or proximal renal tubular acidosis, hypokalemia only occasionally occurs in untreated patients but often develops when sodium bicarbonate is administered.[49]

Other Disorders

Magnesium depletion, induced either by dietary restriction or by abnormal loss, reduces the intracellular potassium concentration and causes renal potassium wasting.[31] The depletion of intracellular potassium stores appears to be due to impairment of the activity of cell-membrane NA^+/K^+–ATPase, but the mechanism by which magnesium depletion causes renal potassium loss is unclear. Magnesium depletion often coexists with potassium depletion as a result of drugs (e.g., diuretics and amphotericin B) or disease processes (e.g., hyperaldosteronism and diarrhea) that cause loss of both ions, making it difficult to assess whether the hypokalemia is caused by the hypomagnesemia or is an independent effect.[31] Regardless of the cause, the ability to correct potassium deficiency is impaired when magnesium deficiency is present, particularly when the serum magnesium concentration is less than 0.5 mmol per liter. Magnesium repletion improves the coexistent potassium deficit.

Severe and often refractory hypokalemia due to renal potassium wasting occurs in patients with acute myelogenous, monomyeloblastic, or lymphoblastic leukemia.[50,51] The cause of the defect in renal potassium excretion is unknown. If remission of the leukemia is achieved, the hypokalemia also remits.

In uncontrolled diabetes mellitus, renal glucose loss causes osmotic diuresis, increasing sodium delivery to the distal nephron and promoting potassium excretion. With prolonged glycosuria, there is considerable depletion of body stores of potassium,[52] but hypokalemia is usually mild or absent because both hypertonicity and insulin deficiency impede the entry of potassium into cells. The underlying potassium deficiency is rapidly unmasked when insulin is given, and severe hypokalemia can develop, particularly in patients with diabetic ketoacidosis, unless aggressive replacement of potassium stores is undertaken at the same time.

PRINCIPLES OF POTASSIUM REPLACEMENT

Potassium replacement is the cornerstone of therapy for hypokalemia. Unfortunately, supplemental potassium administration is also the most common cause of severe hyperkalemia in patients who are hospitalized,[53] and this risk must be kept in mind when one is initiating treatment. The risk is greatest with the administration of intravenous potassium, which should be avoided if possible. When potassium is given intravenously, the rate should be no more than 20 mmol per hour, and the patient's cardiac rhythm should be monitored. Oral potassium is safer, because potassium enters the circulation more slowly.

In the absence of an independent factor causing transcellular potassium shifts, the magnitude of the deficit in body stores of potassium correlates with the degree of hypokalemia.[54] On average, serum potassium decreases by 0.3 mmol per liter for each 100-mmol reduction in total-body stores, but the response is extremely variable. Because potassium repletion is rarely an urgent undertaking, one should always err on the low end of this estimate to avoid inducing hyperkalemia. A portion of administered potassium is always excreted, even in the presence of serious potassium depletion. Thus, supplemental potassium is best administered in a moderate dose by mouth over a period of days to weeks to correct losses fully.

Three salts are available for repletion of body potassium stores: potassium chloride, potassium phosphate, and potassium bicarbonate (or an organic anion that is a metabolic precursor of bicarbonate). Potassium phosphate is used to replace phosphate losses, and potassium combined with bicarbonate or an organic anion is only recommended when potassium depletion occurs in the setting of metabolic acidosis. In all other settings, potassium chloride should be used because of its unique effectiveness in the most common causes of potassium depletion.

Potassium chloride can be given in either liquid or tablet form. Several liquid preparations are available, and there are two types of slow-release tablets — a wax matrix formulation and a microencapsulated formulation.[12] Potassium is readily absorbed regardless of the preparation used. The liquid forms are less expensive but have an unpleasant taste and are often not well tolerated. The slow-release tablets are well tolerated but have been associated with ulceration and bleeding of the gastrointestinal tract.[55] The risk of such a complication, however, is quite low and seems to be lowest with the microencapsulated preparation.

Although the calculation of the amount of potassium needed to replace the loss that has occurred before the onset of treatment is straightforward, there is no simple formula for calculating the amount needed in patients in whom potassium loss is continuing. Typically, 40 to 100 mmol of supplemental potassium chloride is needed each day to maintain serum potassium concentrations near or within the normal range in patients receiving diuretics, and hypokalemia persists despite aggressive potassium replacement in approximately 10 percent of such patients.[56,57] A more effective way to restore serum potassium to normal concentrations is to use a second diuretic drug that inhibits potassium excretion, such as amiloride, triamterene, or spironolactone. Although effective, these

TABLE 4. FOODS WITH HIGH POTASSIUM CONTENT.

Highest content (>1000 mg [25 mmol]/100 g)
Dried figs
Molasses
Seaweed
Very high content (>500 mg [12.5 mmol]/100 g)
Dried fruits (dates, prunes)
Nuts
Avocados
Bran cereals
Wheat germ
Lima beans
High content (>250 mg [6.2 mmol]/100 g)
Vegetables
Spinach
Tomatoes
Broccoli
Winter squash
Beets
Carrots
Cauliflower
Potatoes
Fruits
Bananas
Cantaloupe
Kiwis
Oranges
Mangos
Meats
Ground beef
Steak
Pork
Veal
Lamb

drugs can cause hyperkalemia, occasionally to a life-threatening degree, even when given in conjunction with a thiazide or loop diuretic.[11,12] The risk is greatest in patients with diabetes and renal insufficiency. Patients treated with one of these potassium-sparing diuretics should have their renal function and serum potassium concentrations monitored frequently.

The safest approach to minimizing hypokalemia is to ensure adequate dietary potassium intake. Table 4 lists foods that have a high potassium content. The potassium contained in these foods is almost entirely coupled with phosphate rather than with chloride and therefore is not effective in repairing potassium loss associated with chloride depletion (from diuretics, vomiting, or nasogastric drainage) unless chloride intake is adequate. The salt substitutes sold in supermarkets contain approximately 12 mmol of potassium per gram as the chloride salt. Although they are effective in correcting potassium losses, hyperkalemia is a real threat if excessive amounts are ingested. The best approach is to combine a diet high in potassium with either a prescribed dose of potassium chloride or a potassium-sparing diuretic agent, if necessary.

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