Current Review

A clinical approach to common electrolyte problems: 2. Potassium imbalances

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A clinical approach to potassium imbalances is presented. Hypokalemia is rarely due solely to a reduced intake of potassium; instead, it usually results from a potassium flux into the cells or increased loss of the element, at times combined with a decreased intake. The clinician must seek the cause of the intracellular flux or the source of the gastrointestinal or renal loss. The causes of gastrointestinal losses are generally self evident. Renal potassium wasting, though, generally results from increased mineralocorticoid activity, an increased rate of urinary flow or of sodium delivery to the distal nephron, or both, hypomagnesemia or a combination of these factors. Hyperkalemia may be factitious, but usually it is caused by a flux of potassium from the cells or a decrease in the renal loss of potassium, the latter being mediated by a reduction in renal function, mineralocorticoid activity, or the rate of urinary flow or sodium delivery, or both. In both hypokalemia and hyperkalemia, treatment must be guided by the specific clinical circumstances.

On propose une attitude à prendre devant un déséquilibre potassique. L'hypokaliémie est rarement causée seulement par une réduction de l'apport potassique; habituellement elle résulte plutôt d'un écoulement de potassium dans les cellules ou d'une déperdition accrue de cet élément, parfois accompagnée d'une réduction d'apport. Le clinicien doit rechercher la cause de l'écoulement intracellulaire ou l'origine des pertes gastro-intestinales ou rénales. Les causes des pertes gastro-intestinales sont généralement évidentes. Les pertes rénales résultent généralement d'une activité minéralocorticoïde augmentée, d'une augmentation du débit urinaire ou du taux de l'arrivée du sodium au néphron distal, ou tous les deux, d'une hypomagnésiémie ou d'une combinaison de ces facteurs. L'hyperkaliémie peut être artificielle, mais elle est habituellement causée par une fuite du potassium à l'extérieur des cellules ou à une diminution de la déperdition potassique par le rein, cette dernière étant provoquée par une diminution de la fonction rénale, de l'activité minéralocorticoïde, du débit urinaire ou du taux de la filtration du sodium, ou les deux derniers. Que l'on soit placé devant une hypokaliémie ou une hyperkaliémie, le traitement doit être guidé par les circonstances cliniques spécifiques.

Potassium, the major intracellular cation, is known to play an important role in many biochemical processes and in the excitatory properties of the membranes of muscle and nerve cells. An imbalance in the supply or distribution of this cation may produce significant organ dysfunction. Hypokalemia (serum potassium level 3.5 mmol/l or lower) is perhaps the commonest electrolyte abnormality confronted by the clinician. Hyperkalemia (serum potassium level 5.0 mmol/l or higher), while less common, is no less important, by virtue of its attendant dangers. We present a simplified clinical approach, along with diagnostic algorithms, for the most common causes of these disorders.

Hypokalemia

A potassium deficiency develops when there is a reduction in total body potassium in relation to total body nitrogen; clinically, it is defined by the presence of hypokalemia. Mild hypokalemia is usually not associated with clinical sequelae. Severe hypokalemia, however, may lead to generalized muscle weakness or paralysis, rhabdomyolysis, enhanced sensitivity to digitalis, neuropsychiatric disturbances and disturbances in renal function[1] (Table I). In determining the cause of hypokalemia the clinician must consider the possibilities of a decreased potassium intake, a shift of the cation into the cells or an increased loss of the element.

Table I—Clinical features of hypokalemia

Impaired neuromuscular function
Weakness
Paralysis
Myonecrosis
Impaired gastrointestinal function
Paralytic ileus
Cardiac abnormalities
Conduction defects
Arrhythmias
Altered sensitivity to digitalis
Myocardial cell necrosis
Renal abnormalities
Decreased concentrating ability
Chloride-resistant metabolic alkalosis
Increased ammoniagenesis
Renal insufficiency
Neuropsychiatric disturbances
Depression
Decreased memory
Confusion

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Possible causes

Decreased intake: Hypokalemia is rarely caused by decreased intake alone. The ingestion of a potassium-free diet for several weeks induces renal conservation of potassium to the point that less than 5 mmol is lost each day.[1] In addition, such restricted diets are likely to be associated with catabolic states in which potassium will be released from the tissues.

Shift into cells: A shift of potassium into the cells occurs in alkalemic states (when there is respiratory or metabolic alkalosis), as a result of insulin therapy or β-adrenergic stimulation (e.g., through an epinephrine excess[2] or salbutamol therapy), in association with intense anabolism (e.g., as a result of intravenous hyperalimentation or treatment of pernicious anemia) and, rarely, in barium carbonate poisoning or hypokalemic periodic paralysis. With respect to the potassium shifts associated with anabolic states, approximately 3 mmol of potassium will be required for every gram of new tissue.

Increased loss: Increased losses of potassium are generally gastrointestinal or renal; the loss through the skin is negligible, as the concentration in sweat is only 5 to 10 mmol/l. The cause of any excessive gastrointestinal loss is generally obvious (e.g., diarrhea, vomiting or the presence of an enteric or biliary fistula). Under these circumstances renal potassium wasting caused by volume contraction and secondary aldosteronism often contributes in a major way to the hypokalemia. More subtle causes of gastrointestinal potassium loss, such as surreptitious vomiting, laxative abuse and villous adenoma, pose somewhat more difficult diagnostic problems. In the face of hypokalemia the presence of renal potassium conservation (urinary potassium concentration less than 20 mmol/l) is an important clue to the presence of an occult gastrointestinal loss of potassium. In addition, the presence of accompanying acid–base disorders may provide diagnostic clues.

High renal losses of potassium will generally be found to result from increased mineralocorticoid activity (primary or secondary), an increased rate of urinary flow or of delivery of sodium to the distal nephron, or both, hypomagnesemia or a combination of these factors. Volume depletion caused by diuretics, for instance, can lead to an increased urinary excretion of sodium and also to increased mineralocorticoid activity. There are other, rare causes, such as Liddle's syndrome (pseudohyperaldosteronism) and tubular damage of uncertain nature due to acute or chronic leukemia. The concentration of potassium in the urine is an important diagnostic measurement, for if it is greater than 20 mmol/l in the face of hypokalemia it will confirm renal potassium wasting.

Increased mineralocorticoid activity promotes the electroequivalent exchange of sodium for potassium and hydrogen ions in the distal nephron; this is suggested by certain clinical circumstances (Fig. 1) and by markedly increased urinary potassium levels.

Increases in the urinary flow rate and the sodium concentration in the urine lead to hypokalemia by creating an electrochemical gradient favourable for potassium secretion in the distal nephron; random samples of urine will generally show sodium levels exceeding 75 mmol/l. The major causes of increased sodium delivery to the distal nephron are detailed in Fig. 1. Several of these deserve special comment. The genesis of hypokalemia in proximal and distal renal tubular acidosis is not clearly understood but may involve sodium wasting.[1] The hypokalemia accompanying the administration of amphotericin B may result from the renal tubular acidosis induced by this medication. Hypercalciuria leads to reduced sodium reabsorption in the proximal tubule and in Henle's loop, accounting for the hypokalemia that commonly accompa-

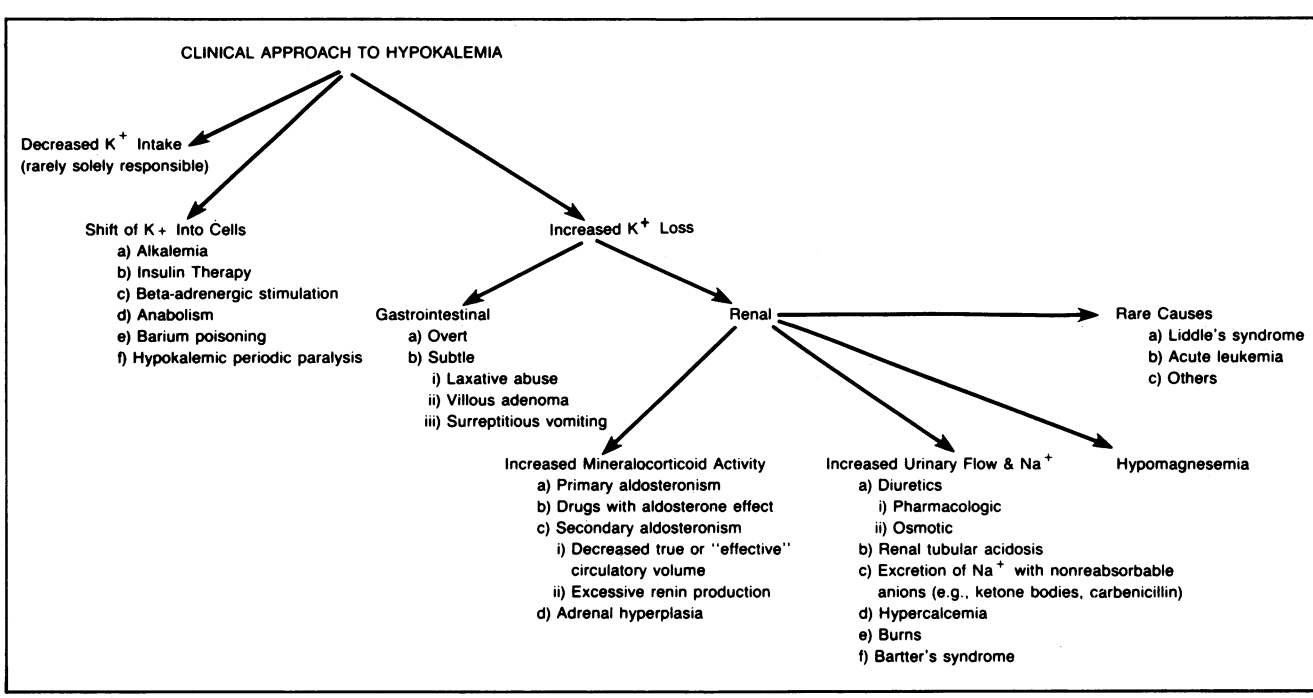

FIG. 1—Clinical approach to hypokalemia. K^+ = potassium; Na^+ = sodium.

nies chronic hypercalcemia.[3] Post-burn hypokalemia results from renal potassium wasting — a consequence of tissue wasting, osmotic diuresis and increased urinary sodium losses. Increased skin losses of potassium, respiratory alkalosis and hyperaldosteronism caused by volume contraction may also contribute to this disorder.[4]

Although the mechanism by which hypomagnesemia leads to hypokalemia is not evident, it is known that potassium replacement will not correct the hypokalemia until the magnesium deficit is repaired. Two commonly used drugs that may lead to hypokalemia through hypomagnesemia are gentamicin and cisplatinum.

Therapy

Hypokalemia resulting solely from an intracellular shift of potassium generally requires no therapy; an exception would be the hypokalemia caused by the intense tissue anabolism associated with intravenous hyperalimentation. Hypokalemia associated with substantial total body deficits must be corrected; since potassium is primarily an intracellular ion, though, the serum levels provide only a rough index of total body stores. A total body potassium deficit of 100 to 200 mmol will reduce the serum potassium concentration by about 1.0 mmol/l. Conversely, each 1.0 mmol/l reduction in the serum potassium concentration below 3 mmol/l reflects a further potassium deficit of 200 to 400 mmol.

Mild potassium deficiencies can be corrected by foods rich in the element or by supplemental potassium chloride. Most patients who are receiving thiazide diuretics need only increase their dietary intake of potassium, but patients taking digitalis should receive supplements if the serum potassium level falls. In cases of severe potassium deficiency or in patients unable to take the oral supplements, potassium chloride may be administered intravenously. The concentration should not exceed 40 mmol/l, though, nor should the administration be more rapid than 20 to 30 mmol/h. Most importantly, the underlying cause of the potassium wasting must be identified and corrected if at all possible.

Hyperkalemia

Hyperkalemia may be clinically silent or it may present with clinical features such as paresthesia, muscle weakness and gastrointestinal symptoms (Table II). Marked hyperkalemia (serum levels greater than 7.5 mmol/l) can be associated with the abrupt onset of life-threatening cardiac abnormalities, including conduction defects, ventricular tachycardia and ventricular fibrillation.

Possible causes

Factitious: In diagnosing the cause of hyperkalemia the clinician must exclude the factitious hyperkalemia caused by hemolysis. Artificially induced increases in potassium levels may also be found when potassium has been released from leukocytes or platelets in clotted blood from patients with leukocytosis or thrombocytosis. If it is appropriate to do so, these hematologic problems can be ruled out by obtaining simultaneous potassium determinations in clotted and unclotted blood. Once factitious hyperkalemia has been excluded the clinician must consider other possible causes: an increased potassium intake, a shift of potassium out of the cells or a decrease in potassium losses.

Increased intake: An increased potassium intake is a relatively uncommon cause of hyperkalemia unless coupled with decreased losses. The normal dietary intake varies between 50 and 100 mmol/d. In people who are accustomed to a low intake, a sudden increase in dietary

Table II—Clinical features of hyperkalemia

Impaired neuromuscular function
Weakness
Paresthesias
Ascending paralysis
Flaccid quadriplegia
Gastrointestinal symptoms
Nausea and vomiting
Abdominal pain
Ileus
Cardiac abnormalities
Conduction defects
Arrhythmias

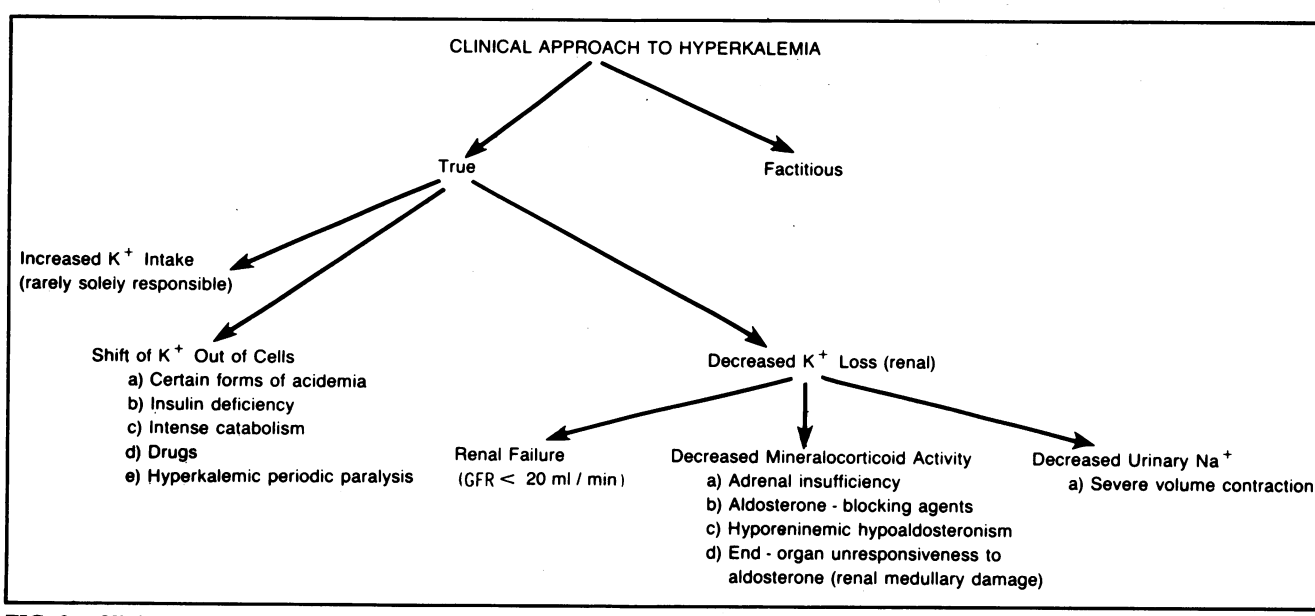

FIG. 2—Clinical approach to hyperkalemia. GFR = glomerular filtration rate.

potassium may lead to hyperkalemia, although this is rarely of clinical significance.[1] Salt-poor food is often high in potassium and should be avoided by people who have an impaired ability to excrete potassium. Hyperkalemia can also result from inordinately rapid intravenous potassium therapy[5] or from administration of the element in blood or as potassium penicillin.

Shift out of cells: Potassium can be shifted out of the cells by hyperosmolality, insulin or aldosterone deficiency, intense catabolism or treatment with certain drugs (the depolarizing agents used in anesthesia, β-blockers, digitalis and arginine hydrochloride), and, rarely, it occurs in hyperkalemic periodic paralysis. There may be a shift of potassium from the cells with certain forms of acidemia too. As Cohen and associates[1] pointed out, this may be more of a response to changes in bicarbonate concentration than a response to changes in pH.

The potassium shift caused by acute respiratory acidosis (in which the serum bicarbonate level rises) is much less striking than that seen in certain forms of acute metabolic acidosis, when there is a marked reduction in the serum bicarbonate concentration. Other forms of metabolic acidosis, however, are not accompanied by hyperkalemia. Acidemia will lead to hyperkalemia only when the anion accompanying the hydrogen ion cannot enter the intracellular space. Thus, lactic acidosis and diabetic ketoacidosis do not necessarily cause hyperkalemia through intracellular buffering.[6] Instead, hyperkalemia is more likely to occur in forms of acute metabolic acidosis characterized by bicarbonate loss. A notable exception is that, for reasons previously mentioned, chronic metabolic acidosis secondary to certain forms of renal tubular acidosis is accompanied by hypokalemia; also hyperkalemia is associated with hyporeninemic hypoaldosteronism (type 4 renal tubular acidosis), although this is more a consequence of hypoaldosteronism than a result of potassium shifts mediated by acidemia.[7]

Decreased loss: A decrease in the usual loss of potassium occurs only when the renal excretory mechanisms have been altered. A tendency to hyperkalemia is universal in patients with oliguric acute renal failure and occurs less frequently in nonoliguric forms of the disorder. In patients with chronic renal failure the capacity to excrete potassium is reasonably well maintained until renal failure is far advanced, and until then hyperkalemia may not be seen unless the intake of potassium is inappropriately high or certain medications, such as potassium-sparing diuretics, are administered. In addition to renal failure, a decrease in the loss of potassium through the kidneys may result from reduced mineralocorticoid activity or a decrease in the urinary flow rate or the delivery of sodium to the distal nephron, or both. The differential diagnosis of these factors is outlined in Fig. 2.

Note, however, that the conditions are not always mutually exclusive. A decrease in either the true or the "effective" intravascular volume, for instance, may lead to a sodium-ion-avid state, characterized by enhanced proximal tubular reabsorption of sodium; in this circumstance a failure to deliver adequate amounts of sodium to the distal nephron may markedly reduce renal potassium secretion, despite high levels of circulating mineralocorticoid.

Therapy

The treatment of severe hyperkalemia involves the intravenous administration of calcium to avert hyperkalemic cardiotoxicity. Administration of 10 to 30 ml of a 10% solution of calcium gluconate over a few minutes may be followed by an intravenous infusion of 30 ml of 10% calcium gluconate in a litre of 5% dextrose and water. Then, 50 ml of 50% dextrose, followed by the intravenous infusion of a 10% dextrose and water solution, will promote the release of endogenous insulin and the movement of potassium into the cells. In nondiabetic patients exogenous insulin is probably not required. The administration of bicarbonate will also promote a shift of potassium into the cells. Potassium can also be actively removed with cation exchange resins (calcium polystyrene, for instance) or dialysis. Dietary restriction of potassium may be useful. Obviously the underlying causes of hyperkalemia should be identified and corrected, if this is possible.

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The variable expression of disease

Certainly it is by their signs and symptoms, that internal diseases are revealed to the physician. But daily observation shows, that there is no uniform and invariable relationship between the extent and intensity of disease, and its external signs. The prominency, the number, and the combination, of these, depend upon many circumstances beside the disease with which they are connected.

—Elisha Bartlett (1804–1855)