CHAPTER 123 Electrolyte Disturbances

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PERSPECTIVE

An electrolyte is any substance that has free ions and therefore can conduct an electrical charge when in solution. The principle electrolytes in human physiology are sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), magnesium (Mg^{2+}), chloride (Cl^-), and hydrogen phosphate (HPO_4^{2-}). Gradients of electrolytes between the intracellular and extracellular spaces are carefully maintained and are responsible for the electrical conduction required for muscles and nerves to function. The electrolyte concentrations of the body are maintained principally through kidney function, but also through action of hormones such as antidiuretic hormone, aldosterone, and parathyroid hormone. Dysfunction of any of these mechanisms or even severe physiologic stress, can disrupt electrolyte balance and result in a life-threatening emergency.

SODIUM

Normal Physiology

Since electrolytes exist in solution in the human body, fluid balance and electrolyte balance are linked, and under hormonal control. Water makes up approximately 60% of body weight and is distributed in three compartments: the intracellular space, the interstitial space, and the intravascular space. The intracellular space makes up approximately two thirds of total body water, with the remaining one third in the interstitial and intravascular spaces. The concentration of sodium [Na^+], the predominant extracellular cation, governs the movement of water among these three compartments. When the extracellular [Na^+] decreases, water shifts to the intracellular space to restore osmotic equilibrium. When the extracellular [Na^+] rises, water shifts out of the intracellular space. Under normal conditions, Na^+ leaks passively into cells down a concentration gradient and is transported back out of the cell by the sodium-potassium adenosine triphosphatase (Na^+-K^+ ATPase) pump.

Na^+ homeostasis and water balance are under the hormonal regulation of the renin-angiotensin system and antidiuretic hormone, respectively. Renin, an enzyme produced by the kidney, is released in response to decreases in circulating intravascular volume. Renin catalyzes the production of angiotensin I, which is then converted to angiotensin II in the lung. Angiotensin II stimulates the production of aldosterone, a mineralocorticoid hormone produced by the zona glomerulosa of the adrenal glands. Aldosterone enhances Na^+ reabsorption and K^+ excretion in the distal nephron.

Antidiuretic hormone (ADH, vasopressin, arginine vasopressin) is synthesized in the hypothalamus and secreted from the posterior pituitary. ADH is released primarily in response to rises in serum osmolality but also to decreases in intravascular volume or arterial pressure. Volume depletion is the most potent stimulus for ADH production, and with decreases in plasma volume, ADH may be secreted even in the face of hypotonicity. ADH enhances renal water reabsorption by increasing tubular water permeability. Other factors that may stimulate ADH release include angiotensin, catecholamines, opiates, caffeine, hypoglycemia, hypoxia, and stress.

Hyponatremia

Principles of Disease

Hyponatremia is defined as a serum [Na^+] of less than 135 mEq/L. Hyponatremia can be classified into three categories based on the patient's clinical volume status: (1) hypovolemic hyponatremia, (2) euvolemic hyponatremia, and (3) hypervolemic hyponatremia (Box 123-1). When assessing the patient with a low serum Na^+ level, it is also important to consider the possibility of sampling errors (e.g., phlebotomy from a venous site proximal to an infusion of hypotonic solution), as well as pseudohyponatremia and redistributive hyponatremia.

Pseudohyponatremia. *Pseudohyponatremia* refers to a falsely low serum Na^+ measurement in patients whose plasma contains excessive protein or lipid. The relative percentage of water in plasma is reduced. Flame photometry, which determines Na^+ content per unit of plasma, shows an artifactually low Na^+ level, although both the total Na^+ content and the serum osmolarity remain within the normal range. Measurement of the serum Na^+ by direct potentiometry avoids this problem.[1]

Redistributive Hyponatremia. Redistributive hyponatremia is caused by osmotically active solutes in the extracellular space that draw water from the cell, diluting the serum [Na^+]. Common situations causing such hyperosmolar states include hyperglycemia (e.g., diabetic ketoacidosis [DKA]) and parenteral administration of mannitol or glycerol for the management of intracranial hypertension or glaucoma. The measured serum Na^+ in patients with hyperglycemia can be corrected by adding approximately 1.6 mEq/L for every 100-mg/dL rise in the serum glucose over 100 mg/dL.

Hypovolemic Hyponatremia. Hypovolemic hyponatremia results from the loss of water and Na^+ with a greater relative loss of Na^+. Typical causes include vomiting, diarrhea, gastrointesti-

BOX 123-1 CAUSES OF HYPONATREMIA

- Sampling error
- Pseudohyponatremia
  - Hyperlipidemia
  - Hyperproteinemia
- Redistributive type
  - Hyperglycemia
  - Mannitol
- Hypovolemic type
  - Renal losses
  - Gastrointestinal
  - Third-space losses
  - Excessive sweating
  - Addison's disease
- Euvolemic type
  - SIADH
  - Psychogenic polydipsia
- Hypervolemic type
  - Congestive heart failure
  - Hepatic cirrhosis
  - Nephrotic syndrome

SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

nal suction or drainage tubes, fistulas, and "third spacing" of fluids (e.g., burns, intra-abdominal sepsis, bowel obstruction, pancreatitis). Causes specifically attributable to renal losses include diuretic use, mineralocorticoid deficiency, renal tubular acidosis, and salt-wasting nephropathy. When Na^+ losses are sufficient to decrease the glomerular filtration rate (GFR) significantly, the amount of filtrate delivered to the loop of Henle (where free water is generated) is decreased, and little free water appears in the urine. Also, because ADH is released in response to intravascular volume deficits despite hypotonicity, hyponatremia may be maintained even in patients whose GFR would otherwise be adequate to excrete excess free water. Hypovolemic hyponatremia can also be worsened when fluid losses are replaced with hypotonic fluids.

Euvolemic Hyponatremia. The many causes of euvolemic hyponatremia include the syndrome of inappropriate secretion of ADH (SIADH), defined as the secretion of ADH in the absence of an appropriate physiologic stimulus. Its hallmark is an inappropriately concentrated urine despite the presence of a low serum osmolality and a normal circulating blood volume. Causes of SIADH include central nervous system (CNS) disorders, pulmonary disease, drugs, stress, pain, and surgery (Box 123-2). Before the diagnosis of SIADH can be confirmed, other potential causes of euvolemic hyponatremia (e.g., hypoadrenalism, hypothyroidism, renal failure) should be ruled out. Psychogenic polydipsia is a rare cause of euvolemic hyponatremia. This is most often seen in patients with psychiatric disorders who consume large volumes of water, usually in excess of 1 L/hr, overwhelming the capacity of the kidneys to excrete free water in the urine.[2] In contrast to SIADH, the urine in patients with psychogenic polydipsia is maximally dilute.

Hypervolemic Hyponatremia. Hypervolemic hyponatremia results when Na^+ is retained but retention of water exceeds that of Na^+. This is seen in edematous states such as congestive heart failure, hepatic cirrhosis, and renal failure. In these conditions, decreased effective renal perfusion causes the secretion of both ADH and aldosterone. This leads to increased tubular reabsorption of both Na^+ and water, decreased delivery of water to the distal nephron, and inability to produce hypotonic urine.

BOX 123-2 CAUSES OF SYNDROME OF INAPPROPRIATE SECRETION OF ANTIDIURETIC HORMONE

CNS Disease
- Brain tumor, infarction, injury, or abscess
- Meningitis
- Encephalitis

Pulmonary Disease
- Pneumonia
- Tuberculosis
- Lung abscess
- Pulmonary aspergillosis

Drugs
- Exogenous vasopressin
- Diuretics
- Chlorpropamide
- Vincristine
- Thioridazine
- Cyclophosphamide

CNS, central nervous system.

Clinical Features

The primary symptoms of hyponatremia are CNS symptoms, including lethargy, apathy, confusion, disorientation, agitation, depression, and psychosis. Focal neurologic deficits, ataxia, and seizures have been reported.[3] Other nonspecific signs and symptoms include muscle cramps, anorexia, nausea, and weakness.

The signs and symptoms of hyponatremia depend on the rapidity with which the serum $[Na^+]$ declines, as well as on its absolute level. The acutely hyponatremic patient is almost always symptomatic when the serum Na^+ level falls below 120 mEq/L, whereas patients with chronic hyponatremia may tolerate much lower levels. Very young and very old patients typically develop symptoms with lesser decreases in the serum Na^+ level.

Diagnostic Strategies

The urinary $[Na^+]$ can be a useful tool in the assessment of the patient with hyponatremia. Patients with hypovolemic hyponatremia caused by renal Na^+ wasting typically have an inappropriately high urinary $[Na^+]$ (>20 mEq/L); those with extrarenal Na^+ wasting and intact renal Na^+-conserving mechanisms have a low urinary $[Na^+]$ (<10 mEq/L). Patients with euvolemic hyponatremia generally have a urinary Na^+ concentration greater than 20 mEq/L. Patients with hypervolemic hyponatremia caused by congestive heart failure or cirrhosis typically have a $[Na^+]$ below 10 mEq/L, and those with renal failure have a concentration above 20 mEq/L.[4]

Management

Because tolerance for hyponatremia is highly variable, treatment should be guided by the severity of symptoms, the estimated duration of illness, and the patient's volume status rather than by the serum Na^+ level alone. Severe neurologic dysfunction and seizures are an indication for immediate treatment. Patients with signs of shock or symptomatic fluid overload also require rapid intervention. Because individuals with acute hyponatremia typically develop more prominent symptoms than those with chronic hyponatremia and are more tolerant of rapid correction of Na^+ deficits, vigorous treatment is a

reasonable goal in these patients. In contrast, patients with chronic hyponatremia are usually less symptomatic and are more susceptible to complications when the serum Na^+ level is corrected rapidly, making vigorous treatment both less necessary and less desirable.

Hypovolemic Hyponatremia. Patients with hypovolemic hyponatremia should have volume deficits corrected with an isotonic saline solution (NaCl, 0.9%). Isotonic saline is hypertonic compared with the hyponatremic patient's serum and will therefore cause a modest elevation of the serum $[Na^+]$.

Euvolemic Hyponatremia. Patients with hyponatremia and a normal total circulating volume can usually have free water intake restricted while the cause of the hyponatremia is determined and specific treatment for the underlying disorder is begun. Significantly, patients with SIADH who are given normal saline may actually experience a further decrease in the serum Na^+ as free water is retained and a hypertonic urine is excreted. Lithium and demeclocycline, which inhibits the action of ADH, can also be used in the treatment of SIADH.

Hypervolemic Hyponatremia. The cornerstone of therapy for patients with hypervolemic hyponatremia is fluid restriction, which is effective in most patients. The addition of diuretics may accelerate water excretion, although this approach should be used with caution because Na^+ excretion is also enhanced. Dialysis may be required to remove large amounts of water in patients with advanced renal failure.

Symptomatic Hyponatremia. Patients with severely symptomatic hyponatremia (e.g., seizures) may require administration of 3% saline (513 mEq of Na^+/L). In general, the serum Na^+ level should not be corrected to above 120 mEq/L or increased by more than 10 mEq/L in a 24-hour period. The rate of correction of hyponatremia should be dictated by the rapidity of its onset. Acute hyponatremia can be corrected at rates of up to 1 to 2 mEq/L/hr, and chronic hyponatremia should be corrected at a rate not greater than 0.5 mEq/L/hr. Hypertonic saline should be administered through a controlled intravenous (IV) infusion, paying careful attention to fluid input and output and frequently assessing serum electrolytes. The approximate required dose of hypertonic saline can be calculated with the following formula:

$$(\text{Desired } [Na^+] - \text{measured } [Na^+]) \times (0.6)\ (\text{weight in kg}) = \text{mEq } [Na^+] \text{ administered}$$

Overly aggressive correction of the serum Na^+ level can have serious consequences. Central pontine myelinolysis, also known as cerebral demyelination, involves the destruction of myelin in the pons and is thought to result from rapid elevation of the serum Na^+. Patients may develop cranial nerve palsies, quadriplegia, or coma. Central pontine myelinolysis is more likely to occur in patients with chronic hyponatremia than in those with acute hyponatremia. Most cases have been associated with rapid correction of serum Na^+ in alcoholic, malnourished, and elderly patients, although it has also been described in otherwise healthy patients.

Hypernatremia

Principles of Disease

Hypernatremia is defined as a serum $[Na^+]$ above 145 mEq/L. Patients at the extremes of age and those with chronic disorders are particularly vulnerable.[5] Hypernatremia is most often the result of a decrease in free water because of either reduced water intake or increased water loss. Less often, hypernatremia is caused by an increase in total Na^+ (Box 123-3). This classification scheme helps in identifying the underlying cause and guiding therapy.

BOX 123-3 CAUSES OF HYPERNATREMIA

- Reduced water intake
  - Disorders of thirst perception
  - Inability to obtain water
    - Depressed mentation
    - Intubated patient
- Increased water loss
  - Gastrointestinal
    - Vomiting, diarrhea
    - Nasogastric suctioning
    - Third spacing
  - Renal
    - Tubular concentrating defects
    - Osmotic diuresis (e.g., hyperglycemia, mannitol)
    - Diabetes insipidus
    - Relief of urinary obstruction
  - Dermal
    - Excessive sweating
    - Severe burns
  - Hyperventilation
- Gain of sodium
  - Exogenous sodium intake
    - Salt tablets
    - Sodium bicarbonate
    - Hypertonic saline solutions
    - Improper formula preparation
    - Salt water drowning
    - Hypertonic renal dialysate
  - Increased sodium reabsorption
    - Hyperaldosteronism
    - Cushing's disease
    - Exogenous corticosteroids
    - Congenital adrenal hyperplasia

Reduced water intake may be the result of limited access, inability to tolerate oral fluids, defective thirst mechanisms, or depressed mentation.

Increased water loss can occur through several different organ systems, including the gastrointestinal tract, skin, respiratory tract, or kidney. Gastrointestinal losses can occur from protracted diarrhea, vomiting, nasogastric tube suction, or third spacing. Renal causes of water loss include osmotic diuresis (e.g., hyperglycemia, mannitol administration) and renal tubular concentrating defects. Diabetes insipidus (DI) results in the loss of large amounts of dilute urine from the loss of concentrating ability in the distal nephron. DI may be central (lack of ADH secretion from the pituitary) or nephrogenic (lack of responsiveness to circulating ADH) (Box 123-4). Central DI is seen with CNS disease or surgery involving the hypothalamus and pituitary. Common mechanisms include stroke, infection, tumor, trauma, and systemic diseases. Nephrogenic DI can be caused by congenital disease, renal failure, sickle cell anemia, hypercalcemia, hypokalemia, and certain drugs, including lithium, cisplatin, amphotericin B, aminoglycosides, and demeclocycline. With a normal thirst mechanism and access to water, DI patients are generally able to maintain near-normal serum levels.[6,7] However, they quickly become hypernatremic when removed from a water source, and any sodium-containing IV fluids will exacerbate the problem.

Excessive Na^+ intake, accidentally, intentionally, or iatrogenically, can cause hypernatremia in the absence of corresponding intake of water. Because the kidney can usually

BOX 123-4 CAUSES OF DIABETES INSIPIDUS

Central
Idiopathic
Head trauma
Suprasellar/infrasellar tumors (e.g., craniopharyngioma)
Cerebral hemorrhage
CNS infections (e.g., meningitis, encephalitis)
Granulomatous disorders (e.g., tuberculosis, sarcoid, Wegener's, histiocytosis)

Nephrogenic
Congenital renal disorders
Obstructive uropathy
Renal dysplasia
Polycystic disease

Systemic Disease with Renal Involvement
Sickle cell disease
Sarcoidosis
Amyloidosis

Drugs
Amphotericin B
Phenytoin
Lithium
Aminoglycosides
Methoxyflurane

CNS, central nervous system.

excrete an increased Na^+ load effectively, most cases are seen in patients with renal insufficiency. Examples include hypertonic enteral or parenteral nutritional fluids, saline absorption, administration of large amounts of sodium bicarbonate, seawater drowning, and salt ingestion.[6] The administration of ticarcillin and carbenicillin, which contain large amounts of NaCl, is another potential cause.

Clinical Features

In cases of hypernatremia, free water is lost in excess of Na^+, so patients may be significantly dehydrated before signs of volume depletion are evident. Total free water deficits are often underestimated in this setting. Common symptoms include anorexia, nausea, vomiting, fatigue, and irritability.[3] Physical findings include lethargy, confusion, stupor, coma, muscle twitching, hyper-reflexia, spasticity, tremor, ataxia, or focal findings such as hemiparesis or extensor-plantar reflexes.

Management

Hypovolemic Hypernatremia. The primary goals in the emergency management of hypovolemic hypernatremia are to restore volume deficits and to maintain organ perfusion. Treatment should be initiated with an infusion of isotonic saline solution (0.9%). Once the patient is hemodynamically stable, the remaining free water deficits can be replaced.

Euvolemic Hypernatremia. Euvolemic hypernatremic patients may have had either hypotonic fluid losses (e.g., with DI) or hypertonic fluid losses from increased insensible fluid loss. Patients with DI generally have a low urine specific gravity (<1.005) and low urine osmolality. The DI is usually the result of a previously recognized disorder, and patients can usually maintain their serum osmolality if they have access to water. Treatment is with oral fluids or 0.45% saline. Patients with central DI require parenteral or intranasal vasopressin. The response to vasopressin can be monitored by checking urine osmolality, urine specific gravity, and serum electrolytes.[7]

Hypervolemic Hypernatremia. The treatment of hypervolemic hypernatremia should focus on increasing renal Na^+ excretion while maintaining free water intake. A strategy of diuretic administration (e.g., furosemide) followed by infusion of hypotonic fluids gradually restores the serum Na^+ to the normal range. Dialysis may be needed for patients with renal failure.

Symptomatic Hypernatremia. Patients with acute hypernatremia usually tolerate rapid correction of free water deficits. On the other hand, aggressive treatment of chronic hypernatremia with hypotonic fluids may result in life-threatening complications. It is recommended that in this setting free water deficits be corrected over at least a 48-hour period. When hypernatremia develops over days, brain cells produce osmotic substances (*idiogenic osmoles*) that hold water in the cell and help maintain cellular volume and tonicity.[6] Overzealous administration of hypotonic fluids may cause rapid shifts of water into brain cells, cellular swelling, and cerebral edema.

Assuming only loss of free water, the free water deficit can be calculated as follows:

$$\text{FW deficit} = 0.6 \times \text{weight (kg)} \times \left(\frac{\text{current } Na^+}{4} - 1 \right)$$

POTASSIUM

Normal Physiology

The relative concentrations of potassium [K^+] in the intracellular fluid and extracellular fluid are the major determinants of the normal osmotic and electrochemical gradients of all living cells. Precisely controlled transcellular movement of K^+ in excitable tissues is required for neuronal transmission, cardiac conduction, and excitation-contraction coupling. K^+ is also important for acid-base balance; the exchange of K^+ and hydrogen ions H^+ across the cell membrane serves as a first-line buffering system during acute acidosis and alkalosis. K^+ is also required for intracellular glucose metabolism, oxidative phosphorylation, and protein synthesis.[8]

The adult human body contains between 2500 and 3500 mmol of K^+, 98% of which is found in the intracellular compartment. For this reason, the serum K^+ level is not an accurate indicator of total K^+ stores. The normal range of the serum [K^+] is 3.5 to 5.0 mEq/L.[9]

Ingested potassium is absorbed in the small intestine through passive transport mechanisms. Renal excretion is the major route of K^+ elimination; less than 8% of losses occur in the feces and sweat. In the kidneys, 90% of the filtered load of K^+ is reabsorbed in the proximal tubule, and K^+ balance is determined by the handling of the cation in the distal nephron. The Na^+-K^+ ATPase pump transports K^+ from the serum into distal tubular cells against a concentration gradient. K^+ then moves passively into the tubular lumen in exchange for Na^+ and is excreted in the urine. When the serum K^+ level increases, pump activity increases and renal K^+ excretion increases. When the serum K^+ level falls, the pump is less active and excretion decreases. Aldosterone also controls K^+ homeostasis. Increased aldosterone release causes retention of Na^+ and excretion of K^+ at the distal tubule. Decreased aldosterone release or inhibition of aldosterone (by drugs such as angiotensin-converting enzyme inhibitors or spironolactone) promotes K^+ retention. Acidosis and alkalosis also affect renal K^+ handling. Acidosis promotes secretion of H^+ into the distal tubule, with retention of K^+, and alkalosis tends to favor renal K^+ excretion.[10]

The serum K^+ level depends on the distribution of K^+ between the serum and cells, as well as the balance between

K^+ intake and excretion. Acute decreases in the plasma pH cause K^+ to shift out of the cell in exchange for H^+. Conversely, alkalosis promotes movement of extracellular K^+ into the cell in exchange for intracellular H^+. In general, a change of 0.1 pH unit causes an inverse change of approximately 0.6 mEq in the serum K^+. Respiratory acid-base disturbances affect serum K^+ in the same manner as metabolic changes, but not as predictably. K^+ levels are also influenced by hormones and hormone receptor stimulation. Insulin increases cellular K^+ uptake by means of the Na^+-K^+ ATPase pump. Insulin release is stimulated by hyperkalemia, and hypokalemia inhibits insulin release. Alpha-adrenergic stimulation promotes hyperkalemia, and beta-stimulation causes uptake of K^+ into cells.[9]

Hypokalemia

Principles of Disease

Hypokalemia is relatively common, although life-threatening hypokalemia is much less common.[10] Hypokalemia may be the result of decreased K^+ intake, increased K^+ excretion, or transcellular K^+ shifts (Box 123-5).

Hypokalemia resulting from decreased dietary intake is rare. However, when poor intake is combined with other factors (e.g., vomiting or diarrhea, high insulin or aldosterone levels), severe hypokalemia can result. Patients suffering from prolonged starvation may become hypokalemic when they are fed because insulin secretion and increased cellular uptake cause K^+ to move into cells.

Pronounced renal or gastrointestinal K^+ losses can result in hypokalemia. Diuretic therapy, the most common cause of hypokalemia in clinical practice, increases Na^+ delivery to the distal tubule, promoting K^+ excretion. Associated volume depletion and high levels of aldosterone cause K^+ and H^+ excretion and may worsen hypokalemia. In addition, alkalosis from H^+ excretion promotes cellular K^+ uptake, further lowering the serum K^+ level.[10]

Other disorders can cause significant renal K^+ loss. These include osmotic diuresis, high mineralocorticoid states, Mg^{2+} depletion, and high urinary concentrations of anions such as penicillin. Intrinsic renal causes of K^+ loss include renal tubular acidosis (RTA), chronic interstitial disease, and drugs that affect tubular potassium reabsorption. RTA type 1 is caused by a defect in H^+ secretion in the distal tubule, and RTA type 2 is associated with a similar defect in the proximal tubule. In both cases, increased K^+ excretion at the distal tubule is the result. Other causes of increased renal K^+ loss include hypercalcemia, toxins (e.g., cisplatin, amphotericin B, aminoglycosides), leukemia, interstitial nephritis, and postobstructive diuresis.

Primary hyperaldosteronism (Conn's syndrome), which is typically caused by adrenal adenoma, is characterized by hypertension and hypokalemia.[11] Secondary hyperaldosteronism, due to increased renin release, causes hypokalemia in the face of volume depletion as K^+ is exchanged for Na^+ at the distal tubule. In Bartter's syndrome, a disorder causing hyperplasia of the juxtaglomerular apparatus and hyper-reninism, patients typically have weakness and hypokalemia.

Gastrointestinal losses of K^+ occur in patients with protracted vomiting and diarrhea. Vomiting itself does not cause K^+ loss; rather, hypokalemia results from hypovolemia, secondary hyperaldosteronism, and alkalosis. Diarrhea can cause

BOX 123-5 CAUSES OF HYPOKALEMIA

- Decreased intake
  - Decreased dietary potassium
  - Impaired absorption of potassium
  - Clay ingestion
  - Kayexalate
- Increased loss
  - Renal
    - Hyperaldosteronism
      - Primary
        - Conn's syndrome
        - Adrenal hyperplasia
      - Secondary
        - Congestive heart failure
        - Cirrhosis
        - Nephrotic syndrome
        - Dehydration
      - Bartter's syndrome
    - Glycyrrhizic acid (licorice, chewing tobacco)
    - Excessive adrenocorticosteroids
      - Cushing's syndrome
      - Steroid therapy
      - Adrenogenital syndrome
    - Renal tubular defects
      - Renal tubular acidosis
      - Obstructive uropathy
      - Salt-wasting nephropathy
    - Drugs
      - Diuretics
      - Aminoglycosides
      - Mannitol
      - Amphotericin B
      - Cisplatin
      - Carbenicillin
  - Gastrointestinal
    - Vomiting
    - Nasogastric suction
    - Diarrhea
    - Malabsorption
    - Ileostomy
    - Villous adenoma
    - Laxative abuse
  - Increased losses from skin
    - Excessive sweating
    - Burns
- Transcellular shifts
  - Alkalosis
    - Vomiting
    - Diuretics
    - Hyperventilation
    - Bicarbonate therapy
  - Insulin
    - Exogenous
    - Endogenous response to glucose
  - $Beta_2$-agonists (albuterol, terbutaline, epinephrine)
  - Hypokalemic periodic paralysis
    - Familial
    - Thyrotoxic
- Miscellaneous
  - Anabolic state
  - Intravenous hyperalimentation
  - Treatment of megaloblastic anemia
  - Acute mountain sickness

hypokalemia from losses in the stool and secondary hyperaldosteronism. Patients with villous adenomas classically have tremendous losses of K^+ from diarrheal fluid.

Loss of K^+ from the skin in sufficient quantities to cause hypokalemia is unusual unless the patient has experienced extreme sweating or is a victim of extensive burns or toxic epidermal necrolysis.[10]

Hypokalemia may result from transcellular K^+ shifts, most often because of alterations in acid-base balance. Acidosis causes K^+ to move out of the cell in exchange for H^+, and the reverse is true for alkalosis. Although acidosis is typically associated with hyperkalemia, acidosis may also be associated with hypokalemia in the presence of increased urinary K^+ losses (e.g., DKA). Beta-receptor stimulation is another common cause of hypokalemia resulting from transcellular shifts. In the emergency department, this is most likely to occur in the patient receiving large doses of beta-agonists for the treatment of asthma or chronic obstructive pulmonary disease.[12,13]

The periodic paralyses are associated with varying serum K^+ levels, including hypokalemia. They often are associated with thyroid disease and are distinguished by symmetrical proximal weakness.[14]

Clinical Features

Hypokalemia can affect the neuromuscular, cardiovascular, gastrointestinal, and renal systems, as well as acid-base balance. Signs and symptoms of neuromuscular dysfunction usually occur when the serum K^+ level is less than 2.5 mEq/L.[15] CNS signs include lethargy, depression, irritability, and confusion. Peripheral manifestations include paresthesias, depressed deep tendon reflexes, fasciculations, myalgias, and prominent muscle weakness. Muscular paralysis can occur with serum levels below 2.0 mEq/L.

Patients with severe hypokalemia may develop rhabdomyolysis because of impaired energy metabolism, membrane pump dysfunction, and local muscle ischemia.[16] K^+ is released from injured muscle, so the responsible hypokalemia may not be clinically evident, with serum levels normal or even elevated.

Cardiovascular manifestations of hypokalemia include palpitations, postural hypotension, ectopy, and dysrhythmias. First- and second-degree heart block, atrial fibrillation, paroxysmal ventricular contractions, ventricular fibrillation, and asystole have all been reported. The electrocardiogram (ECG) shows flattening of T waves, ST segment depression, and the appearance of U waves.[16]

Hypokalemia impairs intestinal smooth muscle activity and may cause nausea, vomiting, and abdominal distention. Severe hypokalemia may produce paralytic ileus.[10] The renal manifestations of hypokalemia include polyuria, polydipsia, and impaired ability to concentrate urine or excrete an acid load.

The effect of hypokalemia on acid-base balance is to promote metabolic alkalosis. In response to a low serum K^+ level, K^+ moves out of the cell in exchange for H^+, causing an extracellular alkalosis and an intracellular acidosis. In response to the drop in intracellular pH, renal tubular cells excrete H^+, leading to paradoxical aciduria and exacerbating the extracellular alkalosis.

Management

Because K^+ is an intracellular cation, a low serum K^+ level reflects a much greater total K^+ deficit. In the absence of acute shifts caused by acid-base disturbances, a decrease of the serum K^+ by 1.0 mEq/L may reflect a 370-mEq deficit of total K^+. Because up to 50% of administered K^+ is excreted in the urine, correction of large deficits may require several days.

Whenever possible, oral therapy is preferable to IV therapy because the risk of hyperkalemia is significantly less. However, patients with prominent symptoms (e.g., dysrhythmias) and those who are unable to tolerate oral supplements should receive IV K^+ replacement. IV K^+ is usually given at a rate of 10 to 20 mEq/hr, but larger doses can be given to patients with severe depletion or severely symptomatic hypokalemia (e.g., respiratory muscle weakness). Doses greater than 20 mEq/hr should be given in a monitored setting through a large-bore peripheral venous catheter or a central venous access site.[17]

Burning at the infusion site is the most common side effect of IV K^+ administration. Slowing the rate of infusion usually decreases venous irritation. The most important potential risk of IV K^+ administration is acute hyperkalemia, which is most likely in patients with renal insufficiency. If dysrhythmias (e.g., frequent premature ventricular contractions, heart block, tachycardia, widening of the QRS complex) develop, the K^+ infusion should be discontinued immediately.

Oral potassium is preferred for mild hypokalemia. Several oral preparations are available in liquid or tablet form. Although liquid preparations are typically better absorbed, matrix tablets are often better tolerated. Hypokalemia can be effectively corrected with oral supplements, and large amounts of oral potassium can be given to increase serum levels rapidly.

Potassium can be given as the chloride salt in most patients. Potassium phosphate, rather than potassium chloride, can be given if there is associated hypophosphatemia (e.g., in DKA). Patients with distal RTA should be treated with potassium bicarbonate, potassium citrate, or potassium gluconate, which provide both K^+ and base equivalents. The hypokalemia of proximal RTA may be better treated with potassium chloride because the administered base cannot be reabsorbed well proximally and can obligate K^+ loss when it reaches the distal tubule.

Hyperkalemia

Principles of Disease

Hyperkalemia may be the result of increased K^+ intake, enhanced K^+ absorption, impaired K^+ excretion, or shifts of K^+ out of cells into the serum (Box 123-6).

When faced with a report of a high serum K^+ level, the emergency physician should first consider the possibility of laboratory error. Hemolysis during phlebotomy, as can occur when blood is obtained with a small needle or sampled in a high-vacuum tube, releases K^+ into the sample and causes a spuriously high K^+ measurement. Laboratory technicians usually note the presence of pink serum, indicating hemolysis. Pseudohyperkalemia can also occur when K^+ is released from platelets in patients with severe thrombocytosis or from leukocytes in patients with extreme leukocytosis.[18]

Hyperkalemia rarely results from increased K^+ intake. This is more common when K^+ supplements are inadvertently taken by patients with renal insufficiency or in those taking a K^+-sparing diuretic or an angiotensin-converting enzyme inhibitor.[18] Parenteral medications such as penicillin and carbenicillin, as well as transfused blood, also contain significant amounts of K^+ and can precipitate hyperkalemia.

Renal insufficiency (i.e., decreased GFR), defects in tubular K^+ secretion, or hypoaldosteronism can cause hyperkalemia. As GFR decreases to approximately 5 to 15 mL/min, excretion of the normal daily K^+ load is impaired. Defects in tubular K^+ excretion are associated with a number of conditions. Hypoaldosteronism may be the result of causes as varied as RTA type

BOX 123-6 CAUSES OF HYPERKALEMIA

- Pseudohyperkalemia
  - Hemolysis of sample
  - Thrombocytosis
  - Leukocytosis
  - Laboratory error
- Increased potassium intake and absorption
  - Potassium supplements (oral and parenteral)
  - Dietary (salt substitutes)
  - Stored blood
  - Potassium-containing medications
- Impaired renal excretion
  - Acute renal failure
  - Chronic renal failure
  - Tubular defect in potassium secretion
    - Renal allograft
    - Analgesic nephropathy
    - Sickle cell disease
    - Obstructive uropathy
    - Interstitial nephritis
    - Chronic pyelonephritis
    - Potassium-sparing diuretics
    - Miscellaneous (lead, systemic lupus erythematosus, pseudohypoaldosteronism)
  - Hypoaldosteronism
    - Primary (Addison's disease)
    - Secondary
      - Hyporeninemic hypoaldosteronism (renal tubular acidosis type 4)
      - Congenital adrenal hyperplasia
      - Drug-induced
        - Nonsteroidal anti-inflammatory drugs
        - Angiotensin-converting enzyme
        - Heparin
        - Cyclosporine
- Transcellular shifts
  - Acidosis
  - Hypertonicity
  - Insulin deficiency
  - Drugs
    - Beta-blockers
    - Digitalis toxicity
    - Succinylcholine
  - Exercise
  - Hyperkalemic periodic paralysis
- Cellular injury
  - Rhabdomyolysis
  - Severe intravascular hemolysis
  - Acute tumor lysis syndrome
  - Burns and crush injuries

4, Addison's disease, nonsteroidal anti-inflammatory drugs, and angiotensin-converting enzyme inhibitors.

Transcellular K^+ shifts (e.g., acute acidosis, beta-receptor antagonism) are another major cause of hyperkalemia. Periodic paralysis is an inherited disorder characterized by hyperkalemia caused by cellular efflux of K^+ associated with stressors such as exercise, infection, and diet. Drugs may also be the cause of transcellular K^+ shifts. Digitalis poisons the Na^+-K^+ ATPase pump, with resultant hyperkalemia in severe cases. Succinylcholine causes transient K^+ efflux because of depolarization of the muscle cell membrane. High-dose trimethoprim-sulfamethoxazole has also been implicated in hyperkalemia, especially with concomitant renal insufficiency.[19,20]

Life-threatening hyperkalemia may result when large amounts of K^+ are released from damaged cells. Rhabdomyolysis, tumor cell necrosis, and hemolysis are important causes.[15] Acute renal failure that may be associated with these conditions impairs K^+ excretion, further exacerbating endogenous hyperkalemia.

Clinical Features

Cardiovascular and neurologic dysfunction is the primary manifestation of hyperkalemia.[18] Patients may have a variety of dysrhythmias, including second- and third-degree heart block, wide-complex tachycardia, ventricular fibrillation, and even asystole. The ECG can provide valuable clues to the presence of hyperkalemia. As K^+ levels rise, peaked T waves are the first characteristic manifestation. Further rises are associated with progressive ECG changes, including loss of P waves and widening and slurring of the QRS complex. Eventually, the tracing assumes a sine wave appearance, followed by ventricular fibrillation or asystole. Concomitant alkalosis, hypernatremia, or hypercalcemia antagonizes the membrane effects of hyperkalemia and may delay or diminish the characteristic ECG findings.

Neuromuscular signs and symptoms of hyperkalemia include muscle cramps, weakness, paralysis, paresthesias, tetany, and focal neurologic deficits, but these are rarely specific enough to suggest the diagnosis in themselves.[15,16]

Management

The treatment of hyperkalemia includes cardiovascular monitoring, administration of calcium chloride or gluconate to treat hemodynamic instability, initiation of measures to lower serum [K^+], and correction of the underlying cause.

All patients with suggested hyperkalemia should be on a cardiac monitor, and attention should be paid to the morphology of the T waves and QRS complex. Peaked T waves, loss of P waves, slurring of the QRS, and second- or third-degree heart block all suggest hyperkalemia and are indications for prompt therapy. Treatment of the hyperkalemia is directed toward antagonism of the membrane effects of hyperkalemia, promotion of transcellular K^+ shifts, and removal of K^+ from the body.

Calcium Chloride or Gluconate. Immediate antagonism of K^+ at the cardiac membrane is achieved with IV administration of calcium chloride or gluconate. This is indicated in patients with unstable dysrhythmia or hypotension. Several ampules of calcium (10 mL of 10% solution) may be required.[16,18] Because of the brief duration of action (approximately 20–40 minutes), other measures should also be instituted promptly.[18]

Sodium Bicarbonate. Sodium bicarbonate infusion promotes a shift of K^+ into cells. One ampule (44 mEq) should be given by slow IV push over 5 to 15 minutes. The duration of action is approximately 2 hours. Sodium bicarbonate should be used with caution when hypertonicity, volume overload, or alkalosis poses a risk to the patient. Bicarbonate therapy is less efficacious than insulin or albuterol.[21,22]

Glucose and Insulin. Cellular uptake of K^+ can also be induced with a regimen of IV glucose and insulin. Regular insulin (10–20 U) can be given by bolus infusion. Dextrose should be administered to euglycemic and diabetic patients with a blood glucose level below 250 mg/dL to prevent hypoglycemia. This combination lasts 4 to 6 hours.[18] Rapid infusion of hypertonic glucose solution may transiently exacerbate hyperkalemia by its osmotic effect on cells.

Beta$_2$-agonists. The known effect of beta$_2$-agonists to cause movement of K^+ into cells can be harnessed to lower the

serum K^+ level acutely. Treatment with nebulized albuterol (5–20 mg) lowers the serum K^+ level for at least 2 hours.[22,23]

Exchange Resins. Definitive treatment for hyperkalemia remains the removal of K^+ from the body. Exchange resins (e.g., sodium polystyrene sulfonate [Kayexalate]) and hemodialysis are two such options. Given orally or rectally, each gram of Kayexalate can remove approximately 1.0 mEq of K^+. An oral dose of 20 g of Kayexalate in a sorbitol produces effects in 1 to 2 hours. Rectal enemas of 50 g of Kayexalate, retained for 30 minutes, work in approximately 30 minutes. Kayexalate should be used with caution in patients with poor cardiovascular reserve because of the potential to exacerbate volume overload.

Dialysis. Hemodialysis corrects hyperkalemia rapidly, and consultation with a nephrologist is indicated in the unstable hyperkalemic patient with newly diagnosed or chronic renal failure. Hyperkalemia resulting from severe rhabdomyolysis is difficult to treat with the usual measures and also mandates consultation for emergency dialysis. Dialysis removes K^+ from the blood only, and subsequent shifts of intracellular K^+ may cause rebound hyperkalemia. Dialysis can be effective in treating hyperkalemia-induced cardiac arrest.[24]

Underlying Cause. Treatment of any underlying causative disorder should be initiated at the same time as therapy for hyperkalemia. This may include the treatment of rhabdomyolysis with fluids and bicarbonate; treatment of Addison's disease with corticosteroids, IV fluids, and glucose; treatment of digitalis toxicity with digoxin-binding antibodies; or discontinuation of drugs that may have precipitated the hyperkalemia.

Patients with hyperkalemia should be admitted to a monitored bed with care provided by a clinician skilled in the treatment of electrolyte disorders.

CALCIUM

Normal Physiology

Hundreds of enzymatic reactions are mediated by changes in intracellular calcium. Cellular growth and reproduction, membrane integrity, receptor activation, neurotransmission, glandular secretion, enzyme activation, muscle contraction, cardiac contractility, platelet aggregation, and immune function all depend on the precise regulation of free calcium. Evidence also indicates that cellular injury and ultimately cell death are mediated by changes in free intracellular calcium.[25]

The adult human body contains approximately 1200 g of calcium, with more than 99% in the mineral component of bone. The remaining 1% is distributed in three different plasma fractions: (1) approximately 50% is bound to serum proteins, primarily albumin; (2) 10% is complexed with serum anions (phosphate, bicarbonate, citrate, lactate); and (3) 40% is in the free ionized state (Ca^{2+}). Ca^{2+} is the physiologically active form, and concentrations are tightly regulated by the endocrine system.

Dietary calcium is absorbed in the proximal intestine through both active and passive processes. Absorption is enhanced by the action of vitamin D. In the kidneys, 99% of the filtered load of calcium is reabsorbed. Approximately 90% of calcium reabsorption occurs passively in the proximal tubule and loop of Henle. The remaining 10% occurs in the distal tubule under the control of *parathyroid hormone* (PTH, parathormone). A fall in free serum calcium stimulates the release of PTH, which in turn increases reabsorption. PTH also mediates the hydroxylation of vitamin D to its active form, 1,25-dihydroxycholecalciferol (1,25-DHCC).

The skeleton acts as a calcium pool that buffers acute changes in serum concentration. When the serum calcium level falls, PTH stimulates an increase in bone turnover and the release of calcium into the serum. A rise in serum calcium suppresses PTH production and causes the release of calcitonin. *Calcitonin* decreases osteoclastic activity and enhances skeletal deposition of calcium.

The serum calcium level reflects the net outcome of several processes. On one hand, intestinal absorption and bone resorption add calcium to the blood; on the other, calcium is lost from the blood by renal excretion, skeletal uptake, or abnormal deposition in soft tissues. A decrease in the serum Ca^{2+} activates the PTH–vitamin D system to increase the entry of calcium into the blood from the bone and gastrointestinal tract. A rise in the serum calcium level suppresses the PTH–vitamin D system and increases the release of calcitonin, which decreases calcium entry into the blood.

Many hospital laboratories measure total serum calcium concentrations, which is a combination of both Ca^{2+} and calcium that is bound to proteins. Normal value of total serum calcium ranges from 8.5 to 10.5 mg/dL. However, the total serum calcium is often a poor indicator of the Ca^{2+} status, since abnormalities of serum protein concentrations (primarily albumin) affect the total calcium. A decrease in albumin concentration lowers the measured serum calcium, and an increase raises it, even as the Ca^{2+} level remains unchanged. A corrected serum calcium level that accounts for changes in serum albumin concentrations can be calculated as follows:

$$\begin{aligned}\text{Corrected calcium} &= \text{serum calcium (mg/dL)} \\ &\cong +0.8[4 - \text{serum albumin (g/dL)}]\end{aligned}$$

This formula is only an estimate, and the Ca^{2+} should be measured whenever hypocalcemia is suggested. Blood gas analyzers can measure Ca^{2+} from a sample of blood or serum. The normal range is 1.00 to 1.15 mmol/L.

Changes in acid-base status influence the ratio of bound to ionized calcium without altering the total measured calcium. Acidosis decreases calcium binding to albumin, and alkalosis increases binding. Thus, acute changes in blood pH may have important physiologic effects by changing the Ca^{2+} level even when the total serum calcium level remains unchanged.[25]

Hypocalcemia

Principles of Disease

The causes of ionized hypocalcemia are numerous (Box 123-7) and can be divided into disorders causing PTH insufficiency, vitamin D insufficiency, PTH resistance states, and calcium chelation.

Parathyroid Hormone Insufficiency. PTH insufficiency can be caused by either primary or secondary hypoparathyroidism. Primary hypoparathyroidism is rare and is usually congenital. Maternal hyperparathyroidism may result in fetal parathyroid hypoplasia and transient hypoparathyroidism.

Secondary hypoparathyroidism is more common and is most often iatrogenic, resulting from inadvertent removal of the parathyroid glands or disruption of the vascular supply during parathyroid, thyroid, or carotid surgery. Permanent hypocalcemia is the usual consequence. Excision of a functional parathyroid adenoma, leaving only the chronically suppressed but otherwise unaffected parathyroid tissue, causes hypocalcemia that usually resolves over several days. Metastatic carcinoma or infiltrative disorders (e.g., hemochromatosis, sarcoidosis, Wilson's disease) may destroy parathyroid tissue and cause hypocalcemia. Both severe hypomagnesemia and severe hypermagnesemia can impair PTH release. Drugs that may suppress parathyroid function include chemotherapeutic agents, cimetidine, and ethanol.

BOX 123-7 CAUSES OF HYPOCALCEMIA

- Parathyroid hormone insufficiency
  - Primary hypoparathyroidism
    - Congenital syndromes
    - Maternal hyperparathyroidism
  - Secondary hypoparathyroidism
    - Neck surgery
    - Metastatic carcinoma
    - Infiltrative disorders
    - Hypomagnesemia, hypermagnesemia
    - Sepsis
    - Pancreatitis
    - Burns
    - Drugs (chemotherapeutics, ethanol, cimetidine)
- Vitamin D insufficiency
  - Congenital rickets
  - Malnutrition
  - Malabsorption
  - Liver disease
  - Renal disease
    - Acute and chronic renal failure
    - Nephrotic syndrome
  - Hypomagnesemia
  - Sepsis
  - Anticonvulsants (phenytoin, primidone)
- Parathyroid hormone resistance states (pseudohypoparathyroidism)
- Calcium chelation
  - Hyperphosphatemia
  - Citrate
  - Free fatty acids
  - Alkalosis
  - Fluoride poisoning

Vitamin D. Vitamin D deficiency can result in hypocalcemia because of decreased gastrointestinal calcium absorption. Nutritional vitamin D deficiency is rare in the United States because of the fortification of milk but can occur when exposure to sunlight is limited, especially in elderly, chronically ill, and debilitated patients. Children of mothers with vitamin D deficiency may be born with congenital rickets. Characteristic findings include hypocalcemia, hypophosphatemia, and specific radiographic findings (widening of the distal radius and ulna, craniotabes). Vitamin D insufficiency resulting from intestinal malabsorption can occur in patients with small-bowel or biliary disease or pancreatic exocrine failure. Cholestyramine can also prevent adequate vitamin D absorption. Once absorbed, vitamin D is hydroxylated in the liver and kidney to its active form, 1,25-DHCC. Hepatic disease and renal disease may lead to inadequate activation of the vitamin. Hypercatabolism of vitamin D may occur in association with agents that stimulate the hepatic microsomal oxidase system, such as the anticonvulsants phenytoin and primidone.

Parathyroid Hormone Resistance States. PTH resistance states are termed *pseudohypoparathyroidism*. These rare familial syndromes are characterized by renal unresponsiveness to PTH and resultant parathyroid hyperplasia.[26] Differentiation from hypoparathyroidism is based on elevated PTH levels and a lack of increase in urinary cyclic adenosine monophosphate after PTH administration.

Hypocalcemia is common in patients with chronic renal failure. This results from vitamin D deficiency, impaired responsiveness to PTH, and phosphate retention. Generally, these patients are asymptomatic, possibly because of a protective effect of systemic acidosis. However, rapid correction of metabolic acidosis with exogenous sodium bicarbonate can precipitate severe hypocalcemia, often causing tetany and seizures.

Calcium Chelation. Calcium complexes with several different substances in serum, including proteins, fatty acids, and anions. Increases in the concentration of these substances may thus result in ionized hypocalcemia. Citrate is used as a blood preservative and anticoagulant. The citrate load associated with massive blood transfusion (>6 U) causes hypocalcemia in up to 94% of patients.[27] Hypocalcemia is usually short-lived, and Ca^{2+} levels return to normal shortly after transfusion. Because citrate is metabolized by temperature-dependent enzymes in tissues and excreted by the liver, hypothermia and hepatic failure are important risk factors for protracted hypocalcemia after blood transfusion. Citrate is also a constituent of radiocontrast material, and hypocalcemia has been associated with the administration of these agents.

Exogenous administration of phosphate and endogenous hyperphosphatemia (e.g., with acute renal failure, rhabdomyolysis, or tumor lysis syndrome) are well-known causes of hypocalcemia.[28] Exogenous bicarbonate also complexes with calcium and may cause symptomatic hypocalcemia. Alkalosis, either metabolic or respiratory, enhances the binding of calcium to serum proteins, resulting in ionized hypocalcemia. Free fatty acids liberated in various conditions (e.g., acute pancreatitis, hyperadrenergic states, acute ethanol ingestion) can chelate free Ca^{2+} to form calcium soaps. Fluoride poisoning can also cause hypocalcemia. This may occur after exposure to hydrofluoric acid or ammonium bifluoride, components of many household cleaners and rust removers. These compounds release free fluoride ion, a direct cellular toxin that binds Ca^{2+}, forming calcium fluoride. Numerous cases of severe hypocalcemia, cardiac dysrhythmias, and death have been reported after ingestion, inhalation, or cutaneous exposure to these products.

Clinical Features

The clinical manifestations of hypocalcemia depend not only on the serum level but also on the rapidity with which it declines. Although the signs and symptoms of hypocalcemia are numerous (Box 123-8), the effects on neuromuscular function predominate.

A declining serum calcium level is associated with progressive neuromuscular hyperexcitability. CNS manifestations include depression, irritability, confusion, and focal or generalized seizures. Peripheral nervous system manifestations include perioral paresthesias, muscle weakness and cramps, fasciculations, and tetany.[25] Latent tetany can often be demonstrated by eliciting Chvostek's or Trousseau's sign. *Chvostek's sign* is elicited by tapping over the facial nerve and causing twitching of the ipsilateral facial muscles. *Trousseau's sign* describes carpal spasm in response to inflation of an arm blood pressure cuff to 20 mm Hg above systolic blood pressure for 3 minutes.

Severe hypocalcemia causes a decrease in myocardial contractility and, rarely, bradycardia, hypotension, and symptomatic congestive heart failure. Patients with preexisting cardiac dysfunction and those taking digoxin or diuretics are especially at risk. The ECG may demonstrate QT prolongation, and an inverse relationship exists between the serum calcium level and the QT interval. However, the ECG is a poor predictor of hypocalcemia and should not be used to rule in or rule out this disorder.

Bronchospasm and laryngeal spasm occur rarely. Symptoms and signs ranging from anxiety and depression to psychosis and dementia can be seen.

BOX 123-8 CLINICAL FEATURES OF HYPOCALCEMIA

Neuromuscular
Paresthesias
Muscle weakness
Muscle spasm
Tetany
Chvostek's and Trousseau's signs
Hyper-reflexia
Seizures

Cardiovascular
Bradycardia
Hypotension
Cardiac arrest
Digitalis insensitivity
QT prolongation

Pulmonary
Bronchospasm
Laryngeal spasm

Psychiatric
Anxiety
Depression
Irritability
Confusion
Psychosis
Dementia

Management

In patients with suggested hypocalcemia or a documented low total serum calcium level, the first step in management should be verification of true ionized hypocalcemia. When hypocalcemia is the presumed cause of tetany, seizures, hypotension, or dysrhythmias, it may be appropriate to initiate treatment before the Ca^{2+} level is available. All patients with symptomatic hypocalcemia should be treated with parenteral calcium. Two different formulations are readily available in most emergency departments: (1) 10-mL ampules of 10% calcium chloride, which contain 360 mg of elemental calcium, and (2) 10-mL ampules of 10% calcium gluconate, which contain 93 mg of elemental calcium. For the adult patient, the recommended initial dose is 100 to 300 mg of elemental calcium given as calcium chloride or calcium gluconate. This dose of calcium increases the serum Ca^{2+} level for only a short time (1–2 hours) and should be followed by repeated doses or an infusion at a rate of 0.5 to 2 mg/kg/hr.[25] For neonates, infants, and children, the recommended initial dose is 0.5 to 1.0 mL/kg of 10% calcium gluconate over 5 minutes.[26]

The most common side effects of IV calcium administration are hypertension, nausea, vomiting, and flushing. Bradycardia and heart block occur in rare cases. Patients receiving IV calcium should be placed on a cardiac monitor, and administration should be discontinued if bradycardia ensues. Calcium should be administered with extra caution in patients taking digoxin because it may precipitate (or exacerbate) digoxin-induced cardiotoxicity. Because calcium can cause severe tissue irritation and necrosis if it extravasates, it should always be given through a well-functioning catheter. Whenever possible, calcium chloride should be diluted in 5% dextrose in water (D_5W).[25,26]

Symptoms refractory to appropriate doses of calcium may be caused by coexisting hypomagnesemia. In patients with normal renal function, administration of 2 to 4 g of 10% magnesium sulfate should be considered.

Patients with asymptomatic hypocalcemia can be treated with oral calcium supplements. Available preparations include calcium ascorbate, calcium gluconate, and calcium lactate. Most patients require 1 to 4 g of elemental calcium daily in divided doses.

Hypercalcemia

Principles of Disease

Hypercalcemia is a relatively common medical disorder. Routine laboratory screening can be expected to detect hypercalcemia in 0.1 to 1.0% of patients, depending on the population being screened.[29-31] Hypercalcemia is usually mild (<12 mg/dL) and asymptomatic and rarely requires emergency treatment. Nevertheless, hypercalcemia may be an important clue to a serious underlying medical disorder. *Hypercalcemic crisis* occurs in a subset of patients who have severe hypercalcemia (usually >14 mg/dL) and is generally associated with prominent signs and symptoms. In this situation, immediate measures to lower the serum calcium level are indicated.

Although hypercalcemia has many causes, more than 90% of cases result from primary hyperparathyroidism or malignancy (Box 123-9).[32]

Primary hyperparathyroidism is the most common cause of hypercalcemia in outpatients, accounting for 25 to 50% of cases.[33] This can result from parathyroid adenoma (80%), parathyroid hyperplasia (15%), or parathyroid carcinoma (5%).[34] Hyperparathyroidism can also occur in association with other endocrine tumors as part of one of the familial syndromes of

BOX 123-9 CAUSES OF HYPERCALCEMIA

Primary hyperparathyroidism
Malignant disease
  Parathyroid hormone–related protein
  Ectopic production of 1,25-dihydroxyvitamin D
  Other bone-resorbing substances
  Osteolytic bone metastasis
Medications
  Thiazide diuretics
  Lithium
  Estrogens
  Vitamin D toxicity
  Vitamin A toxicity
  Calcium ingestion
Granulomatous disorders
  Sarcoidosis
  Tuberculosis
  Coccidioidomycosis
  Berylliosis
  Histoplasmosis
  Leprosy
Nonparathyroid endocrine disorders
  Hyperthyroidism
  Adrenal insufficiency
  Pheochromocytoma
  Acromegaly
  Vasoactive intestinal polypeptide–producing tumor
Miscellaneous
  Milk-alkali syndrome
  Immobilization
  Idiopathic hypocalcemia of infancy
  Physiologic (in the newborn)

multiple endocrine adenomatosis. In primary hyperparathyroidism, the PTH level is elevated in more than 90% of cases; the remainder of patients have high-normal PTH levels that are inappropriate for the degree of hypercalcemia. An elevated PTH level leads to increased bone resorption, a relative decrease in renal calcium excretion, and increased intestinal calcium absorption. Patients typically develop hypercalcemia, phosphaturia, hypophosphatemia, and a hyperchloremic metabolic acidosis.

Malignancy is the most common cause of hypercalcemia in hospitalized patients, and hypercalcemia is the most common paraneoplastic complication of cancer. The reported prevalence of hypercalcemia in patients with cancer ranges from 15 to 60%.[35,36] A multitude of solid tumors can cause hypercalcemia, including cancers of breast, lung, colon, stomach, cervix, uterus, ovary, kidney, bladder, and head and neck. Hypercalcemia is also seen with hematologic malignancies such as multiple myeloma and lymphoma. Hypercalcemia in patients with cancer can result from several different mechanisms, including production of PTH-related protein by the tumor.[37,38] This polypeptide is homologous to PTH in its first 13 N-terminal amino acids and binds to the PTH receptor, mimicking all the actions of the hormone. PTH-related protein is secreted by solid malignancies and their metastases and is not subject to normal feedback control mechanisms.[39] Assays for PTH-related protein are available to confirm this cause of cancer-related hypercalcemia.[40] Less often, hypercalcemia results from the production of other bone-resorbing substances by the tumor (e.g., transforming growth factor-α) or the local effects of osteolytic skeletal metastasis. Virtually all patients with cancer-associated hypercalcemia have low concentrations of PTH, readily distinguishing this cause of hypercalcemia from primary hyperparathyroidism.

Thiazide diuretics are associated with up to 20% of cases of hypercalcemia. These agents can increase the reabsorption of calcium in the distal convoluted tubule by as much as 70%. Hypercalcemia is typically mild, although it may be exaggerated in patients with dehydration.

Granulomatous disorders (e.g., sarcoidosis, tuberculosis, coccidioidomycosis, histoplasmosis, leprosy) can cause hypercalcemia. In these conditions, activated macrophages convert 1,25-hydroxyvitamin D to its active form (1,25-DHCC), resulting in enhanced intestinal calcium absorption, hypercalcemia, and hypercalciuria.[41] Certain lymphomas cause severe hypercalcemia by a similar mechanism. Interestingly, hypercalcemia in patients with sarcoidosis occurs as a seasonal event in patients who live in the Northern Hemisphere, presumably because of increased production of vitamin D in the skin during longer exposure to the summer sun.[42]

Acute vitamin A intoxication is an uncommon but well-recognized cause of hypercalcemia, resulting from an increase in osteoclastic activity. This usually occurs after an accidental massive ingestion of a preparation containing vitamin A. Chronic hypervitaminosis A can occur in patients using large doses of the vitamin for a variety of dermatologic conditions (e.g., acne vulgaris). Because vitamin A is highly lipophilic, toxicity may take several weeks to resolve after discontinuation of the vitamin. Increased exogenous vitamin D intake may also result in hypercalcemia.

Milk-alkali syndrome is caused by excessive ingestion of calcium and absorbable antacids such as milk or calcium carbonate and is characterized by hypercalcemia, alkalosis, and renal failure. The disorder is less common since nonabsorbable antacids and H_2-receptor antagonists became available for the treatment of peptic ulcer disease.

Lithium therapy for bipolar (manic-depressive) disorders can put patients at increased risk for developing hypercalcemia. Clinical and in vitro studies suggest that lithium alters the release of PTH by shifting the set point for inhibition of hormone secretion by circulating calcium.

Thyroid hormone causes hypercalcemia by increasing bone turnover through direct stimulation of osteoclastic bone resorption. In most cases, the symptoms of hyperthyroidism predominate, and hypercalcemia does not become apparent until hyperthyroidism is managed. Hypercalcemia can also be seen in patients after renal transplantation or in the early phase of acute tubular necrosis.

Clinical Features

The clinical manifestations of hypercalcemia are nonspecific and vary widely from patient to patient (Box 123-10). Severity of symptoms depends on both the level of serum calcium and the rapidity of its rise.

Hypercalcemia decreases neuronal conduction and in general causes CNS depression. Symptoms range from fatigue, weakness, and difficulty concentrating to confusion, lethargy, stupor, and even coma.

Hypercalcemia has several effects on the cardiovascular system. The volume depletion with which hypercalcemia is typically associated can result in hypotension. Because hypercalcemia causes an increase in vascular tone, however, the blood pressure may be misleadingly normal. Characteristic ECG changes include shortening of the QT interval and, to a lesser degree, prolongation of the PR interval and QRS widening. Rarely, severe hypercalcemia causes sinus bradycardia, bundle branch block, high-degree atrioventricular block, and even cardiac arrest. Calcium potentiates the action of digoxin, and the side effects of digoxin are accentuated when hypercalcemia is present.[34]

BOX 123-10 Clinical Features of Hypercalcemia

Neurologic
Fatigue, weakness
Confusion, lethargy
Ataxia
Coma
Hypotonia, diminished deep tendon reflexes

Cardiovascular
Hypertension
Sinus bradycardia, atrioventricular block
ECG abnormalities (short QT, bundle branch block)
Ventricular dysrhythmias
Potentiation of digoxin toxicity

Renal
Polyuria, polydipsia
Dehydration
Loss of electrolyte
Prerenal azotemia
Nephrolithiasis
Nephrocalcinosis

Gastrointestinal
Nausea, vomiting
Anorexia
Peptic ulcer disease
Pancreatitis
Constipation, ileus

ECG, electrocardiographic.

An acute rise in the serum calcium level impairs the reabsorption of fluid and electrolytes in the renal tubule, promoting the development of dehydration, which is worsened by vomiting and poor fluid intake. This may lead to a vicious cycle of volume depletion, reduced GFR and calcium excretion, intensified hypercalcemia, and further dehydration, culminating in oliguric renal failure, coma, and death. Chronically, hypercalcemia and associated volume depletion predispose the patient to renal calculi, nephrocalcinosis, and calcium-induced interstitial nephritis.

Anorexia, nausea, vomiting, and abdominal pain are common but nonspecific symptoms of hypercalcemia. Hypercalcemia decreases smooth muscle tone and may lead to constipation or intestinal ileus. An increased serum calcium level enhances the release of hydrochloric acid, gastrin, and pancreatic enzymes. Chronic hypercalcemia has been associated with an increased risk of peptic ulcer disease and pancreatitis.

Management

Treatment should be initiated at once in patients with evidence of significant dehydration, alteration of consciousness, or symptomatic dysrhythmias. Patients with severe hypercalcemia (>14 mg/dL) require rapid treatment regardless of symptoms. The four basic goals of therapy are (1) restoration of intravascular volume, (2) enhancement of renal calcium elimination, (3) reduction of osteoclastic activity, and (4) treatment of the primary disorder (Box 123-11). Although it may not be realistic to expect to achieve these goals in the emergency department, it is important for the emergency physician to initiate therapy and involve the appropriate consultants as early as possible.

Fluid Administration. The administration of isotonic saline is the first step in the management of severe hypercalcemia. Once the intravascular volume has been restored to normal, the serum calcium level will usually have decreased by 1.6 to 2.4 mg/dL, although hydration alone rarely leads to complete normalization. The expansion of intravascular volume increases renal calcium clearance by increasing GFR and Na^+ delivery to the distal tubules. The rate of fluid administration should be based on the severity of hypercalcemia, the degree of dehydration, and the patient's cardiovascular tolerance of acute volume expansion. In elderly patients and those with poor left ventricular function, central venous pressure monitoring can be used to adjust fluid administration rates. Two to 5 L per day is often required. Coexisting electrolyte deficiencies should also be corrected.

Furosemide. Loop diuretics such as furosemide inhibit the resorption of calcium in the thick ascending loop of Henle, increasing the calciuric effect of hydration. Volume expansion must precede the administration of furosemide, however, because the drug's effect depends on the delivery of calcium to the distal nephron. IV doses of 10 to 40 mg every 6 to 8 hours are usually sufficient. Thiazide diuretics should not be used because they enhance distal absorption of calcium and may worsen hypercalcemia.

Osteoclast Inhibitors. Therapy for severe hypercalcemia should also include agents that reduce the mobilization of calcium from bone. Drugs that inhibit osteoclast-mediated bone resorption include the bisphosphonates, calcitonin, glucocorticoids, and gallium nitrate. Because these drugs are used very infrequently in the emergency department, consultation with a specialist and/or pharmacist to select the best agent and dosing strategy is advised.

The bisphosphonates act by inhibiting osteoclastic bone resorption and decreasing the viability of osteoclasts.[43] Etidronate, palmidronate, and zoledronic acid have similar efficacy and a reasonable adverse effect profile.[44-47]

Calcitonin is a naturally occurring hormone that lowers serum calcium by inhibiting osteoclastic activity. Among the anticalcemic agents available, calcitonin has the most rapid onset of action, although it causes only a modest reduction in the serum calcium level.[48] When hypercalcemia is severe and the need to lower the serum calcium is urgent, it is reasonable to administer a dose of calcitonin in combination with a more potent agent such as a bisphosphonate.

The glucocorticoids act by inhibiting the action of vitamin D. They may be effective calcium-lowering agents in patients with hypercalcemia caused by hematologic malignancies, granulomatous disorders, or vitamin D intoxication.

Underlying Cause. Pharmacologic therapy does not permanently normalize the serum calcium concentration. The underlying cause of the hypercalcemia needs to be treated as well. Primary hyperparathyroidism is definitively managed by parathyroidectomy. In the hands of experienced surgeons, more than 90% of patients are cured. When hypercalcemia is caused by malignancy, treatment must be directed at the underlying tumor because normocalcemia is difficult to sustain without successful treatment of the underlying cause. Hypercalcemia caused by medication responds to discontinuation of the offending agent. Hypercalcemia caused by nonparathyroid endocrine disease responds to treatment of the underlying disorder.

BOX 123-11 MANAGEMENT OF HYPERCALCEMIA

- Restoration of intravascular volume
  - Correct dehydration with isotonic solution
  - Correct associated electrolyte abnormalities
- Enhancement of renal calcium elimination
  - Saline diuresis
  - Loop diuretics (e.g., furosemide)
  - *Avoid* thiazide diuretics
- Reduction of osteoclastic activity
  - (Consult specialist for agent selection dosing.)
  - Bisphosphonates
    - Etidronate
    - Pamidronate
  - Zoledronic acid
  - Calcitonin
  - Hydrocortisone
- Treatment of primary disorder
  - Parathyroidectomy for hyperparathyroidism
  - Withdrawal of causative medications
  - Treatment of nonparathyroid endocrine disorders

MAGNESIUM

Normal Physiology

Magnesium (Mg^{2+}) is the second most abundant intracellular cation. It is a cofactor in hundreds of enzymatic reactions, including all those involving adenosine triphosphate (ATP). Magnesium is essential for the production and use of energy, DNA, and protein synthesis, ion channel gating, hormone receptor binding, neurotransmission, cardiac excitability, and muscle contraction.[49]

The adult human body contains approximately 2000 mEq of magnesium. One half of total magnesium is in the mineral