Chapter 8 / Capítulo 8

Electrolyte and Internal Environment Imbalances in Emergencies (English Edition)
ISBN: 978-9915-9680-3-2
DOI: 10.62486/978-9915-9680-3-2.Ch08

Hypophosphatemia in Emergency Care

Hipofosfatemia en emergencia

Jhossmar Cristians Auza-Santivañez[1], Carlos Alberto Paz-Roman[2], Alberto Martin Diaz-Seminario[3]

[1]Hospital de Tercer Nivel Fray Quebracho, Tarija, Bolivia
[2]Hospital de Niños Mario Ortiz / Clínica de las Américas, Santa Cruz, Bolivia
[3]Instituto Nacional Materno Perinatal (INMP), Perú

INTRODUCCIÓN

This chapter will examine phosphorus disorders, which primarily affect the skeleton (80 %). Phosphorus levels are regulated by the gastrointestinal tract based on intake, the kidneys, and parathyroid hormone (PTH). Daily requirements range from 0,2–0,5 mmol/kg, or 7–10 mmol/1000 kcal.

Its functions are varied: it is a substrate for ATP formation, a constituent of cell membrane phospholipids, regulates intracellular calcium, influences some enzymatic reactions, and plays a role in regulating hemoglobin's oxygen-carrying capacity.

Hypophosphatemia is defined as a serum phosphorus concentration below the normal range for age (less than 2,5 mg/dL (0,81 mmol/L) in adults). Hypophosphatemia can be induced by a decrease in net intestinal absorption, an increase in urinary phosphate excretion, or an acute shift of extracellular phosphate into cells.

Clinical findings of severe hypophosphatemia include neurologic (seizures), cardiac (arrhythmias, cardiomyopathy), renal (acute tubular necrosis), and musculoskeletal (muscle weakness, rhabdomyolysis) symptoms, as well as acute respiratory failure. Table 8.1 shows the main causes of hypophosphatemia.

Table 8.1. Main causes of hypophosphatemia

Internal redistribution	Decreased Intestinal Absorption	Increased Urinary Excretion
• Increased insulin secretion, especially during refeeding. • Acute respiratory alkalosis. • Hungry bone syndrome.	• Inhibition of phosphate absorption (antacids, phosphate binders, niacin). • Steatorrhea and chronic diarrhea. • Vitamin D deficiency or resistance.	• Primary and secondary hyperparathyroidism. • Vitamin D deficiency or resistance. • Hereditary hypophosphatemic rickets. • Oncogenic osteomalacia. • Fanconi syndrome. • Others: acetazolamide, tenofovir, intravenous iron, chemotherapeutic agents.

Source: Own elaboration

DIAGNOSIS

Clinical manifestations

The evaluation of hypophosphatemia begins by ruling out spurious hypophosphatemia (pseudohypophosphatemia). Patients with true hypophosphatemia should be assessed through their medical history and laboratory testing to identify the underlying cause. If the cause is not evident, measurement of urinary phosphate excretion may be useful to

distinguish between gastrointestinal and renal phosphate losses. Spurious hypophosphatemia (pseudohypophosphatemia) may occur in certain clinical settings and should be ruled out to avoid unnecessary testing and treatment. It is usually caused by paraproteins (for example, in patients with multiple myeloma or other monoclonal gammopathies) or medications (liposomal amphotericin, high-dose intravenous [IV] mannitol) that interfere with phosphate assays.

Neuromuscular manifestations: Weakness. Paresthesias. Lethargy, stupor, and coma. Seizures. Disorientation, confusion, and hallucinations. Proximal myopathy. Dysphagia. Paralytic ileus.

Cardiovascular manifestations: Alterations in cardiac contractility. Altered response to vasopressors

Respiratory manifestations: Weakness of respiratory muscles. Respiratory failure. Difficulty in weaning from mechanical ventilation.

Renal manifestations: Alterations in tubular function.

Hematologic manifestations: Hemolysis. Thrombocytopenia. Alteration in phagocytosis. Alterations in granulocyte chemotaxis. Reduced oxygen release to tissues

Other manifestations: Rhabdomyolysis. Hepatic dysfunction. Alteration in protein synthesis. Alteration in skeletal mineralization. Insulin resistance

Physical examination

It is necessary to pay attention to the neurological examination, as severe hypophosphatemia can cause neurological manifestations such as weakness, paresthesia, delirium, and coma.

Similarly, a focus on the cardiopulmonary examination is relevant, since severe hypophosphatemia impairs myocardial contractility and can cause heart failure.

Differential diagnosis

The symptoms of hypophosphatemia are highly variable depending on the clinical context; however, it is important to consider associated electrolyte disorders (for example, hypokalemia, hypomagnesemia, hypocalcemia) and thiamine deficiency (in the setting of chronic malnutrition).

Diagnostic tests

It is necessary to determine the serum phosphorus level, since, from the definition, it is understood that hypophosphatemia is defined as a total serum phosphate level <2,5 mg/dL (0,81 mmol/L). Based on laboratory values, it can be classified as follows:

- Mild: 2–2,5 mg/dL (0,65–0,81 mmol/L).
- Moderate: 1–2 mg/dL (0,32–0,65 mmol/L).
- Severe: <1 mg/dL (0,32 mmol/L).

A complete metabolic panel should be performed to assess renal function, as well as serum potassium, calcium, and albumin levels. Serum magnesium levels should be determined, as it is a commonly associated electrolyte disorder. Similarly, obtain a complete blood count to detect associated anemia and thrombocytopenia.

Some additional tests should be considered. Obtain an ECG to evaluate the intervals and rhythm in patients with any cardiopulmonary symptoms or associated electrolyte disturbances (e.g., potassium, calcium, or magnesium). Measure troponin levels if there are clinical findings of heart failure or cardiomyopathy.

Tips

Determine serum creatine kinase (CK) levels, since severe hypophosphatemia may precipitate rhabdomyolysis.

- *Evaluate parathyroid hormone levels to aid in diagnosis if the etiology of hypophosphatemia is unclear.*

- *Perform point-of-care cardiac ultrasound to assess cardiac function and pulmonary edema.*
- *Obtain a chest radiography to evaluate for pulmonary edema if there are any clinical findings of heart failure.*
- *Perform a head computed tomography to assess alternative etiologies of central nervous system manifestations.*

TREATMENT

Treatment of the underlying cause of hypophosphatemia is usually sufficient to resolve it. Some patients will require phosphate supplementation, depending on the serum phosphate concentration and the presence of hypophosphatemia symptoms.

Treatment of the underlying cause

Patients with hypophosphatemia should receive therapy directed at the underlying cause. In many cases, treatment of the underlying cause will be sufficient to resolve hypophosphatemia without the need for phosphate replacement.

For example:

- Hypophosphatemia occurring during the correction of diabetic ketoacidosis is resolved spontaneously with normal dietary intake.
- Patients with hypophosphatemia due to gastrointestinal losses should correct spontaneously once the underlying cause is resolved (diarrhea, chronic antacid therapy, or vitamin D deficiency). Specific recommendations for vitamin D supplementation are presented elsewhere.
- Patients undergoing surgical treatment for primary hyperparathyroidism should experience resolution of hypophosphatemia, unless they develop hungry bone syndrome after parathyroidectomy.

Phosphate replacement

In addition to treatment of the underlying cause of hypophosphatemia, some patients will require phosphate supplementation.

Our approach to phosphate replacement takes into account the serum phosphate concentration, the presence of overt symptoms of hypophosphatemia, and whether the patient can receive oral therapy.

In general, patients with a serum phosphate concentration below 2 mg/dL (0,64 mmol/L) should receive phosphate supplements.

If possible, we prefer oral phosphate therapy over intravenous (IV) therapy, since IV replacement may cause transient hyperphosphatemia that can lead to serious complications such as hypocalcemia, acute kidney injury, and arrhythmias. However, in patients who cannot take or tolerate oral phosphate supplementation, and in those with extremely low serum phosphate levels, particularly those with symptomatic hypophosphatemia, IV replacement is reasonable.

If the serum phosphate level is <1 mg/dL (0,32 mmol/L), intravenous phosphate is administered. Switch to oral phosphate once the serum phosphate level rises above 1,5 mg/dL (0,48 mmol/L).

If the serum phosphate level is 1–2 mg/dL (0,32–0,64 mmol/L), treatment varies depending on the presence or absence of overt symptoms of hypophosphatemia and the severity of hypophosphatemia:

In asymptomatic patients, we administer oral phosphate therapy. Many of these patients may have myopathy and weakness that are not clinically evident.

In symptomatic patients with a serum phosphate level of 1–1,5 mg/dL (0,32–0,48 mmol/L), we treat with intravenous phosphate and switch to oral phosphate once the serum phosphate

level rises above 1,5 mg/dL (0,48 mmol/L).

In symptomatic patients with a serum phosphate level >1,5–2 mg/dL (0,48 to 0,64 mmol/L), we treat with oral phosphate therapy.

Phosphate replacement is discontinued when the serum phosphate level is ≥2 mg/dL (0,64 mmol/L), unless there is an indication for chronic therapy, such as persistent urinary phosphate wasting. Oral replacement is most often achieved with a combined sodium–potassium phosphate preparation; sodium phosphate is preferred for intravenous therapy.

Phosphate replacement regimens

When oral dosing is used, we initiate the treatment with 30 to 80 mmol of phosphate per day in divided doses. Phosphate may also be supplemented with skim milk, which contains approximately 8 mmol of phosphate per 237 mL (1 cup).

The following regimen is a reasonable approach:

- If the serum phosphate level is >1,5 to 2 mg/dL (0,48 to 0,64 mmol/L), we administer 1 mmol/kg of elemental phosphate (minimum of 40 mmol and maximum of 80 mmol) in three or four divided doses over 24 hours.
- If the serum phosphate level is 1 to 1,5 mg/dL (0,32 to 0,48 mmol/L), we administer 1,3 to 1,4 mmol/kg of elemental phosphate (up to a maximum of 100 mmol) in three or four divided doses over 24 hours.
- Patients with severe obesity may receive the maximum initial doses or a dose adjusted according to their height and weight.
- Patients with reduced glomerular filtration rate should receive approximately half of the suggested initial dose.
- Serum phosphate concentration should be rechecked 2 to 12 hours after the last divided dose to determine whether repeat dosing is required.

That being the case, the same procedure may be repeated. Oral phosphate supplements (tablets and powders) contain variable proportions of sodium and potassium phosphate. Serious medication errors have occurred due to confusion between preparations and the lack of uniformity in product labeling units and ordering practices. Therefore, an oral phosphate supplement should be selected based on its sodium and potassium content, and dosed according to the mmol of phosphate. The most common oral potassium phosphate and sodium phosphate supplements contain 250 mg (8 mmol) of phosphate per tablet.

Intravenous dosing: Intravenous phosphate is potentially dangerous, as it may precipitate with calcium and produce a variety of adverse effects, including hypocalcemia due to calcium binding, renal failure due to calcium phosphate precipitation in the kidneys, and possibly fatal arrhythmias.

If intravenous therapy is required in patients with severe symptomatic hypophosphatemia or inability to receive oral therapy, we suggest a dose that varies according to the severity of hypophosphatemia and the patient's weight. We suggest the following regimen.

- If the serum phosphate concentration is ≥1,4 mg/dL (0,45 mmol/L), we administer 0,2 mmol/kg over four hours (up to a maximum initial dose of 20 mmol).
- If the serum phosphate concentration is ≥1,1 to 1,3 mg/dL (0,36 to 0,42 mmol/L), we administer 0,3 mmol/kg over four hours (up to a maximum initial dose of 30 mmol).
- If the serum phosphate concentration is ≤1 mg/dL (0,32 mmol/L), we administer 0,4 mmol/kg over six hours (up to a maximum initial dose of 50 mmol).

Serum phosphate concentration should be monitored every six hours when intravenous phosphate is administered, and the patient should be switched to oral replacement once the serum phosphate concentration reaches 1,5 mg/dL (0,48 mmol/L).

Intravenous phosphate is available as potassium phosphate or sodium phosphate; serum potassium levels may guide product selection. Potassium phosphate provides approximately 1,5 mEq of potassium per 1 mmol of phosphate. To avoid medication errors, the dose should be expressed in mmol of phosphate and the sodium or potassium salt should be specified.

Risks of long-term phosphate therapy

The main concern with chronic phosphate therapy is the increased risk of extraskeletal mineral deposition, particularly in the kidney. In patients with chronic phosphaturia, prolonged administration of phosphate supplements may increase the risk of nephrocalcinosis and presumably contribute to a gradual loss of renal function. Individuals receiving chronic phosphate supplementation should undergo periodic measurements of serum phosphate and creatinine to monitor phosphate balance and renal function, as well as intermittent renal ultrasound to assess for the development of nephrocalcinosis.

Special populations

Pediatric

- Moderate, serum phosphate level 1,5–2 mg/dL [0,48–0,65 mmol/L]: 0,16–0,32 mmol/kg intravenously over 4–6 hours.
- Severe, serum phosphate level <1,5 mg/dL [<0,48 mmol/L]: 0,32–0,64 mmol/kg intravenously over 4–6 hours.

Pregnancy

- Phosphate requirements are the same in pregnant and nonpregnant women. We recommend consultation with an obstetrician for any patient requiring parenteral phosphate therapy.

Disposition

The disposition of patients with hypophosphatemia depends on the severity of the symptoms, the degree of hypophosphatemia, and the patient's ability to tolerate oral medication.

- Asymptomatic patients, without severe hypophosphatemia and able to tolerate oral medication, can likely be safely discharged after oral phosphate replacement.
- Patients receiving intravenous phosphate, with persistent symptoms, or with any evidence of cardiorespiratory instability should be admitted for further treatment.
- Patients with severe hypophosphatemia in presence of chronic malnutrition often require prolonged phosphate replacement, accompanied by a gradual advancement of enteral feeding toward caloric goals.

BIBLIOGRAPHY

1. Molinaris V, Bianchetti MG, Milani GP, Lava SAG, Bruna RD, Simonetti GD, Faré PB. Interferences in the measurement of circulating phosphate: a literature review. Clin Chem Lab Med. 2020 Nov 26;58(12):1971–7. https://doi.org/10.1515/cclm-2020-0281

2. Taylor BE, Huey WY, Buchman TG, et al. Treatment of hypophosphatemia using a protocol based on patient weight and serum phosphorus level in a surgical intensive care unit. J Am Coll Surg. 2004;198(2):198–204.

3. Subramanian R, Khardori R. Severe hypophosphatemia: pathophysiologic implications, clinical presentations, and treatment. Medicine (Baltimore). 2000;79(1):1–8.

4. Weisinger JR, Bellorín-Font E. Magnesium and phosphorus. Lancet. 1998 Aug

1;352(9125):391–6. https://doi.org/10.1016/S0140-6736(97)10535-9

5. Gohil A, Imel EA. FGF23 and associated disorders of phosphate wasting. Pediatr Endocrinol Rev. 2019;17(1):17–24.

6. Verge CF, Lam A, Simpson JM, et al. Effects of therapy in X-linked hypophosphatemic rickets. N Engl J Med. 1991;325(24):1843–8.