Fatal Electrolyte Abnormalities Following Enema Administration

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CASE

A 90-year-old man was admitted to the Emergency Department with severe congestive heart failure and kidney failure. His medical history included successful surgery for prostatic carcinoma, aortocoronary bypass surgery, and cardiac pacemaker implantation. The patient was regularly taking digoxin, enalapril, aspirin, transdermal nitrate, and furosemide. At admission, the patient was hyperkalemic (Table 1), and therapy with sodium polystyrene sulfonate and ethacrynic acid was started immediately. The diuretic therapy was continued after his admission to the Nephrology and Dialysis Department on the second day of hospitalization. An ultrasound examination in which the kidneys appeared small and hyperechoic confirmed chronic renal impairment. On the evening of the sixth day of hospitalization, 2 enemas (120 mL each) were administrated 30 min apart to relieve prolonged constipation. The patient vomited the following night, and a nasogastric tube was inserted. The next morning, the patient showed signs of dehydration and was hypotensive (blood pressure, 90/40 mmHg). The patient's abdominal distension prompted an abdominal radiograph, which showed signs of intestinal obstruction. Laboratory findings revealed severe hypocalcemia [3.7 mg/dL (0.93 mmol/L); reference interval, 8.5–10.5 mg/dL (2.13–2.63 mmol/L)] and alterations in the plasma concentrations of other major plasma ions (Table 1). An intravenous infusion of calcium gluconate was started immediately, and an abdominal computed tomography evaluation was requested. The severe electrolyte abnormalities were confirmed after analysis of a second blood sample drawn after 1.5 h, which revealed severe hyperphosphatemia [30.0 mg/dL (9.69 mmol/L); reference interval, 2.5–4.5 mg/dL (0.81–1.45 mmol/L)] without signs of overt acidosis. In the meantime, the abdominal computed tomography scan revealed paralytic ileus. Emergent hemodialysis was planned, but despite intensive treatment, the patient's electrocardiogram showed an increased QT interval. He finally went into cardiac arrest and died before hemodialysis could begin.

DISCUSSION

In the absence of autopsy confirmation, we cannot exclude the possibility that the small-bowel obstruction and a subsequent septic condition were responsible for the patient's death; however, the relatively small increase in the plasma C-reactive protein concentration (approximately 8-fold the upper reference limit) and the modest increase in the patient's temperature (37.6 °C) and neutrophil count did not support the possibility of septic shock.

The patient was given 2 sodium phosphate (NaP) enemas. Each enema contained 19.2 g of monobasic NaP and 7.2 g of dibasic NaP. Given the patient's age, renal status, and laboratory findings, NaP toxicity due to the enemas is the most likely diagnosis. NaP enemas are widely used for bowel cleansing and constipation treatment because of their hyperosmolar characteristics. In healthy adults, approximately 60%–65% of dietary phosphate is absorbed in the form of inorganic phosphate (1). The main site of absorption is the upper small intestine, although phosphate can certainly be absorbed by the colon as well, especially if an NaP enema is retained (2). Moderate hypocalcemia and hyperphos-

QUESTIONS TO CONSIDER

1. Which laboratory tests are useful in the evaluation of a patient with severe hypocalcemia?
2. What are several causes of severe hyperphosphatemia?
3. What treatment should be used in patients with severe hyperphosphatemia and hypocalcemia?
phatemia in association with other electrolyte changes, such as hypernatremia, hypokalemia, and hypomagnesemia, are well recognized after NaP enemas \( (3) \). These alterations are temporary and asymptomatic in most cases, and the development of hyperphosphatemic acidosis is not expected in well-hydrated adults with a preserved kidney function \( (4, 5) \). Life-threatening or fatal plasma concentrations of calcium and phosphate have been sporadically reported, however \( (6) \). Several risk factors for NaP intoxication that have been identified include impaired renal function, decreased intestinal motility, increased intestinal permeability, Hirschprung disease, enteric fistulas, congestive heart failure, liver cirrhosis, preexisting electrolyte disturbances, and an inability to maintain adequate fluid intake \( (3, 6, 7) \). Age is another aggravating condition. Administrations of oral laxatives or adult-sized hypertonic phosphate enemas in children can produce extremely high serum phosphate concentrations \( (3, 8) \). Patients \( \geq 65 \) years of age also require careful monitoring \( (5, 6) \).

The mechanism of NaP intoxication is evident. Hypernatremia and hyperphosphatemia develop because of the absorption of these ions by the small intestine or colon. Extracellular phosphate concentrations depend mainly on the phosphate load and its renal excretion. Phosphate is freely filtered by the glomerulus, and about 80%–90% is reabsorbed by the tubules. Consequently, if the glomerular filtration rate is decreased, hyperphosphatemia can easily develop after NaP administration \( (5) \). High serum phosphate concentrations can lead to the precipitation of insoluble calcium phosphate in both intracellular and extracellular compartments, causing hypocalcemia \( (9) \). Hypomagnesemia and hypokalemia may develop via intestinal loss. Hypokalemia can be severe if it is associated with inadequate renal potassium-concentrating capacity or with the administration of potassium-losing diuretics \( (5) \).

Low serum calcium concentrations may be due to a reduction in free calcium (i.e., ionized calcium), albumin-bound calcium, or both. Hypoalbuminemia is the most common cause of pseudohypocalcemia \( (1) \). Acute symptomatic hypocalcemia has various causes \( (1) \). A laboratory evaluation should include measurements of ionized calcium, serum albumin, magnesium,
and parathyroid hormone concentrations, and assessment of renal function (1).

Hyperphosphatemia can have several causes. Increased phosphate intake can occur via oral or intravenous routes or be due to the administration of phosphate-containing laxatives or enemas. Decreased renal phosphate excretion can be caused by a decrease in the glomerular filtration rate, which occurs in acute or chronic renal failure, or by an increase in tubular reabsorption, which is seen mainly in pseudohypoparathyroidism. A third mechanism, an increased extracellular phosphate load, consists of a transcellular shift in lactic, respiratory, or untreated diabetic acidosis, and cell lysis in rhabdomyolysis, intravascular hemolysis, or tumor lysis syndrome (1). Concomitant hypocalcemia and hyperphosphatemia can occur in renal failure or in pseudohypoparathyroidism. In the absence of alterations in renal function and parathyroid hormone concentrations, the possibility of NaP intoxication has to be considered. Even severe hyperphosphatemia is largely a clinically asymptomatic condition. Among the short-term complications of hyperphosphatemia, acute hypocalcemia is the most important; more rarely, acute deposition of calcium phosphate precipitates into joints, subcutaneous tissues, vessels, and other soft-tissue areas can occur (8). The signs and symptoms of hypocalcemia include seizures, neuromuscular irritability, tetany, bronchospasm, hypotension, and an increased QT interval in the electrocardiogram. In fatal cases, cardiac arrest caused by electrolyte alterations is the most common cause of death (2, 9).

Treatment should aim to correct metabolic alterations, primarily any hypocalcemia and hyperphosphatemia. Because calcium administration can aggravate the calcium phosphate precipitation in vital organs, its use requires caution. In a life-threatening situation, however, the risk of soft-tissue calcification in response to calcium administration may be less important than restoring at least low-normal serum calcium concentrations to control the cardiovascular consequences of hypocalcemia (10). Correction of high serum phosphate concentrations has different approaches, depending on the severity of the hyperphosphatemia and the patient’s renal function. The treatment strategy for patients with a preserved renal function and moderate hyperphosphatemia aims to enhance renal excretion or to redistribute phosphate into the intracellular compartment by administration of dextrose/insulin, and, if possible, to deposit phosphate into the bone matrix by administering calcium (10). In cases of toxic ingestions, gastric lavage and oral phosphate binders can prevent further absorption. Direct removal of phosphate by hemodialysis is indicated in patients with severe hyperphosphatemia and kidney failure. This type of intervention, together with intravenous calcium administration, may be lifesaving (6).

This case serves to remind clinicians that NaP enemas and laxatives should be used with caution. The role of the clinical laboratory is fundamental in the recognition and diagnosis of NaP intoxication. In a case of unexpected hypocalcemia, serum phosphate should be measured in addition to measuring serum albumin, parathyroid hormone, magnesium, and electrolyte concentrations and evaluating renal function parameters. If hypocalcemia and hyperphosphatemia are found together with hypernatremia and hypokalemia, NaP intoxication should be suspected. Concomitant hypocalcemia and hyperphosphatemia are common in renal insufficiency. These alterations are generally moderate, however, and serum potassium concentrations tend to be high. We recommend careful consideration of the patient’s clinical situation, as well as the results of appropriate evaluations of serum electrolyte concentrations and renal function, before administering NaP-containing laxatives or enemas. If risk factors are present, the replacement of NaP with other cathartics should be considered. The use of magnesium-containing enemas also requires caution, because magnesium is also excreted by the kidney and an impaired renal function would increase the risk for potentially lethal hypermagnesemia.

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<td>• The intestinal status, renal function, and the age of the patient should be considered before administering NaP-containing enemas or laxatives.</td>
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<td>• When low calcium and increased phosphate concentrations are found, such interfering factors as low albumin concentrations in hypocalcemia or the presence of cell lysis or monoclonal immunoglobulins in hyperphosphatemia should be excluded.</td>
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<td>• In cases of concomitant hypocalcemia and hyperphosphatemia, consider the possibility of iatrogenic administration or abuse of NaP-containing enemas or laxatives.</td>
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<td>• Before and after NaP administration, it is good practice to monitor patients by using a panel of laboratory tests that includes measurements of plasma sodium, potassium, calcium, phosphate, albumin, and creatinine, because prompt diagnosis of NaP toxicity and appropriate therapy can be lifesaving.</td>
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Clinical Case Study

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

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References


Commentary

Seth Goldberg*

This fatal case of hyperphosphatemia with hypocalcemia in an elderly patient after administration of sodium phosphate enemas highlights the potential risks of these commonly used bowel cleansers. Under normal conditions, phosphorus can be readily excreted by the kidneys. Hyperphosphatemia stimulates parathyroid hormone secretion, which has a phosphaturic effect on the kidneys. More recently, fibroblast growth factor 23 (FGF-23) has been identified as a major phosphaturic hormone that exerts its effect by inhibiting sodium phosphate cotransporters in the renal proximal tubule (1). This factor also inhibits activation of vitamin D.

When renal function has been compromised, phosphorus retention is typically mild, gradual, and asymptomatic, although the long-term consequences are not fully understood and may ultimately contribute to cardiovascular mortality. In the case presented, the hyperphosphatemia was acute and severe, suggesting massive intestinal absorption, rather than renal retention, as the most likely cause. In addition to the conventional risk factors of advanced age, chronic kidney disease, and decreased intestinal motility, the patient likely had decreased glomerular filtration due to a “pre-renal” state, given the underlying congestive heart failure. Furthermore, an angiotensin-converting enzyme inhibitor may have further impaired glomerular autoregulation in a volume-depleted state. When given as an enema, polystyrene sulfonate has been associated with colonic ischemia, which could also have promoted substantial sodium phosphate absorption (2).

The laboratory abnormalities described are typical of extreme hyperphosphatemia, with hypocalcemia caused by calcium–phosphorus complex formation. These complexes can deposit in various tissues, including in the renal interstitium, which causes acute kidney injury (3). Also of note is the sudden widening of the anion gap, from 16 mmol/L at presentation to 28 mmol/L. This finding likely does not represent an accumulation of excess metabolic acid but rather an artifact of the hyperphosphatemia (excess unmeasured anion) and hypocalcemia (loss of unmeasured cation).

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