

Hypophosphatemia associated with coma

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In three cases of severe hypophosphatemia profound coma was associated. Although the occurrence of hypophosphatemia appeared to coincide with a high rate of intravenous administration of glucose and water, two of the three patients had liver disease and the other had hypothermia. In two instances the neurologic status improved with intravenous phosphate therapy. These case reports emphasize the importance of early recognition and treatment of profound hypophosphatemia in critically ill patients.

Trois cas d'hypophosphatémie sévère se sont compliqués d'un coma profond. Bien que l'apparition de l'hypophosphatémie semble avoir coïncidé avec l'administration de glucose et d'eau par voie intraveineuse, deux des trois patients souffraient de maladie hépatique et l'autre présentait une hypothermie. Dans deux cas une amélioration de l'état neurologique a suivi l'administration intraveineuse de phosphate. Ces observations cliniques soulignent l'importance de reconnaître tôt et de traiter rapidement l'hypophosphatémie profonde chez les patients gravement malades.

Among other manifestations¹ hypophosphatemia has been reported to result in paresthesias, profound myopathy, seizures and even coma.² It must be remembered as a potential cause of coma that is clinically thought to have a metabolic basis, for such awareness can be life-saving.³

In this report we describe three cases of hypophosphatemia associated with coma; in two cases intravenous phosphate therapy was followed by improvement in clinical neurologic status.

Case reports

Case 1

A 59-year-old man was admitted to the general surgical service with weakness, vomiting and excessive thirst. He

had vomited on several occasions in the previous 2 weeks and four times the day before admission. Since a laryngectomy 5 years previously he had been consuming alcohol heavily. He had not taken antacids.

He was alert and well oriented, though clinically dehydrated, with orthostatic hypotension, decreased tissue turgor and a dry tongue. His liver was enlarged but not tender. Palpation of the right lower quadrant of the abdomen elicited pain. Measurement of the serum electrolyte concentrations and arterial blood gas tensions revealed hyponatremia with metabolic acidosis. The blood glucose and serum creatinine concentrations were normal (the latter was 1.5 mg/dL).

Because of profound oliguria and presumed fluid depletion, aggressive replacement was begun with intravenous fluids, primarily 0.9% NaCl alternated with 5% dextrose in water.

Over the next 24 hours the patient's level of consciousness progressively decreased. Neurologic findings were consistent with those of "metabolic" coma, no lateralizing signs being noted. An SMA 12 biochemical profile the morning after admission showed the following serum values: inorganic phosphorus 0.3 mg/dL (normal 2.5 to 4.5 mg/dL), total bilirubin 2.2 mg/dL (normal 0.15 to 1.0 mg/dL), serum glutamic oxaloacetic transaminase (SGOT) 85 mU/mL (normal 7 to 40 mU/mL) and alkaline phosphatase 65 mU/mL (normal 30 to 150 mU/mL). A clinical diagnosis of pancreatitis was confirmed by an elevated serum amylase value.

In the next 48 hours the metabolic acidosis and oliguria were treated vigorously with high-volume infusions monitored by a central venous pressure line; 5% dextrose in water and 0.9% NaCl was alternated with 5% dextrose in water, NaHCO₃ and KCl (for the profound hypokalemia). An SMA 12 biochemical profile 48 hours after admission again showed a serum inorganic phosphorus value of 0.3 mg/dL. Phosphorus was never given during the illness.

The patient remained deeply comatose, and 72 hours after admission had a cardiac arrest and died. Autopsy showed acute and chronic pancreatitis, a fatty liver and a previously unsuspected stone obstructing the common bile duct.

Case 2

A 56-year-old woman was admitted

to the critical care unit deeply comatose and unresponsive to pain. A history of increasing confusion, lethargy, vomiting and diarrhea in the 3 days prior to admission was obtained from a friend. The patient was known to be an alcoholic.

She was dehydrated, with postural hypotension and poor tissue turgor; the blood pressure was 90/50 mm Hg with the woman supine, and the pulse rate was 130 beats/min. No lateralizing neurologic signs were present, and lumbar puncture revealed no diagnostic abnormalities. Profound metabolic encephalopathy was diagnosed.

An endotracheal tube was inserted for airway protection and a Swan-Ganz catheter was positioned for monitoring an intravenous infusion of 5% dextrose in water at 300 mL/h. The pulmonary wedge pressure before therapy was 1 mm Hg.

Biochemical investigation of the serum revealed mildly elevated values of SGOT, lactate dehydrogenase, alkaline phosphatase and total bilirubin; these disturbances were thought to be due to liver disease, probably alcohol-induced. The serum inorganic phosphorus value was elevated, at 5.4 mg/dL, as was the serum osmolality, at 303 mOsm/kg. No drugs or their metabolites were detected, and the blood glucose value was normal. Plasma cortisol and serum thyroxine values, and triiodothyronine resin uptake were normal. An electrocardiogram was normal.

The day after admission the serum inorganic phosphorus value was 0.5 mg/dL. Aggressive therapy with intravenous fluids was continued to maintain an adequate blood pressure. The pulmonary wedge pressure was still low, although other signs of dehydration dissipated that day.

On the third hospital day the serum inorganic phosphorus value was 0.8 mg/dL. She was still deeply comatose, without lateralizing signs, and neurologic evaluation suggested "metabolic" or anoxic coma. The hypotension had been corrected for 48 hours. Without any other major change in therapy she was given 45 mg of potassium acid phosphate intravenously over 8 hours and the serum inorganic phosphate concentration increased to 1.5 mg/dL. Towards the end of the infusion the coma lightened. She became fully conscious the next day, when the serum inorganic phosphorus value was 1.7 mg/dL. Over the next 3 days the serum phosphorus concentration rose to 2.3

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mg/dL with continued phosphate replacement.

The diarrhea, found to be due to ischemic colitis, continued for several more days. Hyperalimentation was begun, with careful attention being paid to the serum phosphorus concentration, and following prolonged hospitalization the woman was discharged.

Case 3

A 22-year-old woman was admitted to the critical care unit deeply comatose, unresponsive to pain and hypothermic (rectal temperature 30°C); there was evidence of sexual assault. Drug overdose was also considered a possibility.

There were no lateralizing neurologic signs, and bilateral carotid angiograms were normal. Intubation, ventilation and application of a warming blanket raised her body temperature to normal. An SMA 12 biochemical profile soon after admission showed a serum inorganic phosphorus value of 10.4 mg/dL, which was thought to be due to bowel ischemia.⁴

An intravenous infusion of 5% dextrose in water at 125 mL/h was begun. After 5 hours the infusion was changed to 5% dextrose and 0.2% NaCl in water at 200 mL/h; at this time the serum inorganic phosphorus value was only 1.0 mg/dL, as it was 8 hours later.

Later in the day, when the attending physicians became aware of the low values, another blood sample was drawn and 40 mg of potassium acid phosphate was given intravenously over 4 hours. The patient was still comatose, though she was now responding to pain and her rectal temperature was 36°C. Towards the end of the infusion she became fully conscious and appeared to be neurologically normal. The serum inorganic phosphorus values at the beginning and end of the infusion were 1.0 and 3.5 mg/dL respectively. The patient said that she had taken an unknown amount of a tricyclic antidepressant prior to the assault; it was then apparent that the cause of her coma was probably multifactorial.

Discussion

Recently, increased awareness of the clinical manifestations and pathophysiologic consequences of hypophosphatemia has been repeatedly noted.^{1,5-7} This is likely due to the ease of obtaining laboratory values through the widespread use of multiple-channel autoanalysers⁵ and an increased appreciation of the occurrence of hypophosphatemia, particu-

larly secondary to intravenous hyperalimentation.^{2,8,9}

Recent studies have suggested that hypophosphatemia is somewhat more common than has been recognized;⁵ accordingly, some of its causes and effects have subsequently been delineated. Hypophosphatemia has been divided into two types: moderate (that associated with depression of the serum inorganic phosphorus concentration to values of 1.0 to 2.5 mg/dL) and profound (that associated with depression to values less than 1.0 mg/dL).⁷ Moderate hypophosphatemia has been associated with glucose infusion, recovery from hypothermia, hypomagnesemia, cirrhosis of the liver,¹⁰ gram-negative septicemia¹¹ and prolonged vomiting,⁵ among others. Profound hypophosphatemia, the type in our three cases, has been described in association with alcoholic withdrawal, diabetes mellitus with ketoacidosis, "hyperalimentation", "nutritional recovery syndrome" (malnutrition), pharmacologic binding of phosphate by antacids, diuretic or recovery phase of severe burns and severe respiratory alkalosis.⁷

With the widespread use of parenteral hyperalimentation and the need for serial biochemical analysis to detect occasional associated metabolic derangements, it has become evident that the sudden infusion of large quantities of carbohydrate may cause profound hypophosphatemia.³ In most cases, whether or not the total body content of phosphorus is depleted, hypophosphatemia appears to be triggered by a shift in phosphate from the extracellular to the intracellular compartment. Most of the conditions producing such a shift seem to have in common a large and relatively sudden increase in glucose metabolism and anabolic processes. The shift occurs because most of the intermediates in both glycogen formation and glycolysis are phosphorylated compounds. As a result, when these processes are extremely active, phosphate will translocate from the serum into tissue cells.

Although a relatively sudden decrease in serum phosphorus concentration in humans is believed to be due to a sudden increase in cellular uptake of phosphate,⁶ this has yet to be proven. Derr and Zieve¹² approached the problem in rats, aware

that previous studies of urine collections had shown that very little phosphorus is excreted through the kidneys during profound hypophosphatemia. Using radioactive phosphorus they found that with total parenteral nutrition the labelled phosphate shifted from the blood into liver, bone, muscle and carcass residue. On a weight basis liver cells took up as much phosphate as bone, and twice as much as muscle — a puzzling finding in view of the association of liver disease and hypophosphatemia in humans. It is evident that further clinical investigation is required.

Clinically hypophosphatemia is primarily manifested by abnormalities of the central nervous and musculoskeletal systems. Paresthesias, lethargy, seizures and coma associated with marked muscular weakness are seen.⁶ Proximal myopathy has been described,¹³ as have muscular pain and stiffness.¹³ The associated myopathy appears to be occasionally severe enough to cause respiratory failure.³

Less clinically obvious are the effects of hypophosphatemia on erythrocytes and leukocytes. In erythrocytes the adenosine triphosphate (ATP) concentration is directly dependent and the 2,3-diphosphoglycerate (2,3-DPG) concentration indirectly dependent on the plasma concentration of inorganic phosphate.⁹ It has been postulated that reduction in the erythrocyte ATP and 2,3-DPG concentrations is related to hemolytic anemia and possibly cellular hypoxia due to changes induced in the affinity of hemoglobin for oxygen. A low erythrocyte 2,3-DPG concentration is associated with a shift of the oxyhemoglobin dissociation curve¹⁴ to the left and a subsequent reduction in the ability of hemoglobin to release bound oxygen in the periphery.

Leukocyte function is also affected by hypophosphatemia; specifically the chemotactic, phagocytic and bactericidal activity is depressed.⁶ This is also believed to be due to impaired ATP synthesis in the leukocytes, which would produce improper function of the cellular microfilaments responsible for pseudopod and vacuole formation.

In two of our cases of profound hypophosphatemia deep coma was one of the primary clinical manifesta-

tions. All three patients received intravenous infusions of 5% dextrose in water as well as other crystalloid solutions for restoration of a clinically deficient intravascular volume before the onset of hypophosphatemia, and two patients had liver disease — obstruction of the common bile duct in one and cirrhosis in the other. Although reports^{5,10} have indicated that liver disease may be an etiologic factor in hypophosphatemia, as it may have been in two of our cases, it is also possible that the high rate of intravenous infusion precipitated the hypophosphatemia.^{5,15} In addition, patients 1 and 2 may have been extremely malnourished at the time of admission to hospital; patient 3 was hypothermic.

It seems reasonable to suggest that the profound hypophosphatemia in our patients had a multifactorial basis.

In conclusion, these cases emphasize that severe hypophosphatemia may be associated with coma in critically ill patients, and that, when found, hypophosphatemia should be recognized as an easily correctable cause of metabolic coma. Correction with intravenous phosphate therapy is safe and potentially life-saving, although hyperphosphatemia and its attendant complications should be avoided by monitoring the serum phosphate concentration. Thorough investigation is, of course, essential in all cases of coma since the underlying factors are diverse and many are treatable.

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Zyloprim* (allopurinol)

Indications: ZYLOPRIM is intended for the treatment of gout as well as primary and secondary hyperuricaemia. ZYLOPRIM is indicated in the treatment of primary or secondary uric acid nephropathy. ZYLOPRIM is especially useful in patients with gouty nephropathy, in those who form renal urate stones, and those with unusually severe disease. ZYLOPRIM is effective in preventing the occurrence and recurrence of uric acid stones and gravel. ZYLOPRIM is useful in the therapy and prophylaxis of tissue urate deposition, renal calculi and of acute urate nephropathy in patients with neoplastic disease who are particularly susceptible to hyperuricaemia and uric acid stone formation, especially after radiation therapy or the use of antineoplastic drugs.

Contraindications: Zyloprim should not be given to patients who are hypersensitive or who have had a severe reaction to this drug.

Precautions and Warnings: Acute gouty attacks may be precipitated at the start of treatment with Zyloprim in new patients, and these may continue even after serum uric acid levels begin to fall. Prophylactic administration of colchicine and a low dosage of Zyloprim are advisable, particularly in new patients and in those where the previous attack rate has been high. Zyloprim is not recommended for use during pregnancy or in women of child-bearing potential unless in the judgement of the physician, the potential benefits outweigh the possible risks to the fetus. Zyloprim should not be given to children except those with hyperuricaemia secondary to malignancy or with Lesch-Nyhan syndrome. Patients with impaired renal or hepatic functions should be carefully observed during the early stages of Zyloprim administration and the drug withdrawn if increased abnormalities in hepatic or renal functions appear.

Uricosurics and Zyloprim: Combined therapy of Zyloprim and uricosurics will result often in a reduction in dosage of both agents.

Purinethol or Imuran with Zyloprim: In patients receiving PURINETHOL* (mercaptapurine) or IMURAN* (azathioprine), the concomitant administration of 300-600 mg of ZYLOPRIM per day will require a reduction in dose to approximately 1/2 to 1/4 of the usual dose of mercaptopurine or azathioprine. Subsequent adjustment of doses of PURINETHOL or IMURAN should be based on therapeutic response and any toxic effects.

Chlorpropamide with Zyloprim: In the presence of allopurinol, there may be competition in the renal tubule for the excretion of chlorpropamide. When renal function is poor, the recognised risk of prolonged hypoglycaemic activity of chlorpropamide may be increased if ZYLOPRIM is given concomitantly.

Coumarin anticoagulants with Zyloprim: It has been reported that under experimental conditions allopurinol prolongs the half-life of the anticoagulant, dicumarol. The clinical significance of this has not been established, but this interaction should be kept in mind when allopurinol is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.

Adverse reactions: Skin reactions associated with exfoliation, fever, chills, nausea and vomiting, lymphadenopathy, arthralgia and/or eosinophilia are the most common and may occur at any time during treatment. Gastrointestinal disorders were reported but may diminish if Zyloprim is taken after meals.

Symptoms and treatment of overdose: Overdosage of allopurinol is usually manifested by nausea and vomiting. No treatment is normally required, provided the drug is withdrawn and adequate hydration is maintained to facilitate excretion of the drug. If, however, other forms of acute distress are observed, gastric lavage should be considered, otherwise the treatment is symptomatic.

Pharmacology: When taken orally, allopurinol is rapidly metabolized. The main metabolite is oxypurinol, which is itself a xanthine oxidase inhibitor. Allopurinol and its metabolites are excreted by the kidney, but the renal handling is such that allopurinol has a plasma half-life of about one hour, whereas that of oxypurinol exceeds 18 hours. Thus, the therapeutic effect can be achieved by a once-a-day dosage of ZYLOPRIM in patients taking 300 mg or less per day.

Dosage and administration: ZYLOPRIM, administered orally should be divided into 1 to 3 daily doses. Daily doses up to and including 300 mg may be taken once daily after a meal. Divided doses should not exceed 300 mg. The minimum effective dose is 100 to 200 mg. The average is 200 to 300 mg/day for patients with mild gout, 400 to 600 mg/day for moderately severe tophaceous gout, and 700 to 800 mg/day in severe conditions. The maximal recommended dose is 800 mg per day in patients with normal renal function.

Treatment with 600 to 800 mg daily for two or three days prior to chemotherapy or x-irradiation is advisable to prevent uric acid nephropathy. Treatment should be continued at a dosage adjusted to the serum uric acid level until there is no longer a threat of hyperuricaemia and hyperuricosuria. It is essential that a daily urinary output of two litres or more be maintained during ZYLOPRIM therapy, and neutral or alkaline urine is desirable.

Children: For the treatment of secondary hyperuricaemia associated with malignancies and in the Lesch-Nyhan syndrome, ZYLOPRIM should be given in doses of 10 mg/kg/day. The response should be evaluated after approximately 48 hours by monitoring serum uric acid and/or urinary uric acid levels and adjusting the dose if necessary.

Presentation: ZYLOPRIM 100 mg scored white tablets. Bottles of 100 and 500 tablets; Code: Wellcome U4A. ZYLOPRIM 300 mg scored peach coloured tablets. Bottles of 100 tablets. Code: Wellcome C9B.

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