Respiratory Illness and Hypophosphatemia*

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We retrospectively reviewed the charts of 308 admissions to a pulmonary disease ward and 100 admissions to the general medical service over one year to find the prevalence, sequelae, and etiology of hypophosphatemia. The overall prevalence of low serum phosphate levels (<2.4 mg/dl) occurring at least once during hospitalization in chest patients was 17 percent, but was higher in patients with respiratory infections (28 percent). Moreover, the prevalence of hypophosphatemia on admission (before institution of intravenous fluid or drug therapy) was ten times higher in patients with respiratory infections than in patients with noninfectious respiratory illness or general medical patients (21 vs 2 percent, p < .001). Serum phosphate <2.0 mg/dl occurred in 4 percent of patients. Twenty-seven percent of the patients (including two with ventilatory failure) with abnormally low serum phosphate levels had symptoms or signs of uncertain etiology later explicable by the presence of hypophosphatemia. The most common additional laboratory finding associated with hypophosphatemia was elevation of muscle enzymes. Although mortality was no higher in hypophosphatemic patients, hospital stay was twice as long as that of patients with normal levels of serum phosphate. No correlation was found between simultaneous arterial blood gases and serum phosphate levels. Two patients given antacids had severe hypophosphatemia and worsened ventilatory function; phosphate-binding antacids should be used judiciously in patients with severe respiratory disease, since they may lead to the development or worsening of hypophosphatemia and diminished ventilatory function.

Hypophosphatemia is a not uncommon laboratory finding in hospitalized medical patients, with a prevalence of 2 to 3 percent. However, hypophosphatemia is more frequently found in patients withdrawing from alcohol (particularly during medical illness and treatment with intravenous [IV] dextrose), treatment of diabetic ketoacidosis, nutritional recovery (including surgery), and Gram-negative infections, where the prevalence of absolute hypophosphatemia (<2.5 mg/dl) ranges from 20 to 40 percent.

The pathogenesis of hypophosphatemia is thought to be multifactorial, with decreased intake, increased losses (renal and gastrointestinal [GI]), and transcellular shifts being the major mechanisms. Respiratory alkalosis has also been shown to be a potent stimulus for intracellular transport of phosphate; hence, patients with acute respiratory illness may be at risk for development of hypophosphatemia. In fact, one series of patients with Legionnaires' disease had a reported incidence of 51 percent of hypophosphatemia. Moreover, since hypophosphatemia has been associated with ventilatory failure, its presence in patients with respiratory illness may be of critical importance. Therefore, we retrospectively investigated the prevalence, determinants, and sequelae of hypophosphatemia in patients hospitalized with respiratory illness.

METHODS

Of a total of 556 admissions over one year to the Chest Service and Respiratory Intensive Care Unit of the Bronx Municipal Hospital Center (Van Etten Hospital), the charts of 328 admissions (274 patients) were chosen at random for review and were compared with charts of 100 admissions over the same period to the General Medical Service of the Bronx Municipal Hospital Center. Serum phosphate determinations were available for 308 chest service admissions and all general medical admissions, with 299 and 100 samples, respectively, drawn on the day of admission in the emergency room at the time of institution of IV fluid therapy. One hundred forty chest service patients had simultaneous serum phosphate and arterial blood gas determinations performed. Serum phosphate was analyzed with the SMA 12/60 Ethicon autoanalyzer (normal limits between 2.5 and 4.5 mg/dl). Hypophosphatemia was defined as one value equal to or less than 2.4 mg/dl and was subdivided into mild (2.0 to 2.4 mg/dl), moderate (1.6 to 1.9 mg/dl) and severe (<1.5 mg/dl). An admission with multiple episodes of hypophosphatemia was counted once. Patients who had hypophosphatemia on admission to the hospital and during their hospital course were counted as "admission" hypophosphatemia. For patients with multiple episodes of hypophosphatemia after day 1, the lowest phosphate level was recorded. Patients with uncontrolled diabetes mellitus (serum glucose >300 g/dl) were admitted to the general medical service. Patients suffering from alcohol withdrawal alone were not routinely admitted to the respiratory or general medical wards, but to a separate detoxification center. Patients were coded as "alcoholics" if there was a history of alcohol consumption ≥1 pint/day in the recent past.

The χ² and t tests were used to analyze the dichotomous and continuous variables, respectively. Data are presented as mean ± SEM.

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RESULTS

Prevalence, Onset, and Severity of Hypophosphatemia

The prevalence of hypophosphatemia was higher for patients admitted to the chest service than the general medical wards (17 vs 5 percent, p < 0.02), including hypophosphatemia on admission (10 vs 2 percent, p < 0.02) (Table 1). Thirty-one of the 52 hypophosphemic chest patients had a low serum phosphate level on admission vs two of five medical patients. The remainder had hypophosphatemia noted on subsequent hospital days.

Serum phosphate for the hypophosphemic admissions was 2.1 ± 0.4 mg/dl vs 3.6 ± .05 mg/dl for the nonhypophosphatemic patients (p < 0.001). Thirty-five of the chest patients had mild hypophosphatemia (73 percent), nine moderate (19 percent), and four severe (8 percent). Serum phosphate <2.0 mg/dl occurred in 4.0 percent of patients admitted with respiratory illness. Two such patients had severe hypophosphatemia on admission (pneumonia, ventilatory failure), and two during hospitalization (pneumonia, ventilatory failure). Two patients admitted to the medical ward had moderate hypophosphatemia (treatment of diabetes mellitus, Gram-negative urinary tract infection) during their hospitalization. The three remaining medical patients had mild hypophosphatemia.

Etiology of Hypophosphatemia

Although the total prevalence of hypophosphatemia was similar for patients with acute infections and ventilatory illness compared with the other chest patients (21 vs 8 percent, NS), the prevalence of hypophosphatemia on admission was higher in patients with more acute respiratory illness (13 vs 4 percent, p < 0.05). More specifically, the total and admission prevalence of hypophosphatemia was highest among patients with pulmonary infections (pneumonia, acute bronchitis, tuberculosis, and lung abscess) compared with the other chest patients (total, 28 vs 11 percent; admission, 21 vs 2 percent; both, p < 0.001).

Of the 73 admissions with pneumonia, 16 were associated with hypophosphatemia (22 percent). Eleven of 51 radiologically single-lobe pneumonias (22 percent) and 5 of 17 multilobe pneumonias (29 percent, NS) were associated with hypophosphatemia. Although four of nine patients with Gram-negative pneumonia had hypophosphatemia, the prevalence was not higher than that of patients with pneumococcal

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Table 1—Prevalence of Hypophosphatemia

<table>
<thead>
<tr>
<th>Etiology</th>
<th>No. of Admissions</th>
<th>Total No. Hypophosphatemic (%)</th>
<th>Admission Hypophosphatemia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHEST SERVICE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute infectious/ventilatory illness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>85</td>
<td>9 (11)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>73</td>
<td>16 (22)</td>
<td>15 (21)</td>
</tr>
<tr>
<td>Ventilatory failure</td>
<td>39</td>
<td>11 (28)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Acute bronchitis</td>
<td>14</td>
<td>8 (57)</td>
<td>4 (29)</td>
</tr>
<tr>
<td></td>
<td>211</td>
<td>44 (21)</td>
<td>27 (13)</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung cancer</td>
<td>29</td>
<td>1 (3)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>12</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>12</td>
<td>5 (42)</td>
<td>3 (25)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>7</td>
<td>1 (14)</td>
<td></td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>7</td>
<td>1 (14)</td>
<td></td>
</tr>
<tr>
<td>Lung abscess</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Interstitial lung disease</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Sarcoïdosis</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>? Pulmonary embolus</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Solitary pulmonary nodule</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>14</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>97</td>
<td>8 (9)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Total (Chest Service)</td>
<td>308</td>
<td>82 (27)</td>
<td>31 (10)</td>
</tr>
<tr>
<td>MEDICAL SERVICE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td>28</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Infection (other than lung)</td>
<td>19</td>
<td>1 (5)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14</td>
<td>2 (14)</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>11</td>
<td>1 (9)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Miscellaneous (renal failure,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hyperthermia, drug intoxication, jaundice,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>acute arthritis, acute leukemia)</td>
<td>28</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Total (Medical Service)</td>
<td>100</td>
<td>5 (5)</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>
(5/22) or Mycoplasma pneumonia (1/8) or patients in whom a causative agent for pneumonia was not established (6/34).

One hundred forty chest patients had simultaneous serum phosphate and arterial blood gases drawn. There were no differences in arterial pH (7.43 ± 0.1 vs 7.40 ± 0.1, NS), Pco2 (35.8 ± 1.9 vs 34.1 ± 1.0 mm Hg, NS), or Po2 (64.0 ± 2.9 vs 66.7 ± 1.9 mm Hg, NS) in the hypophosphatemic (n = 44) vs normophosphatemic patients (n = 96), respectively. In addition, there was no correlation between arterial pH and serum phosphate in the hypophosphatemic admissions (r = -0.26, NS).

There were no differences in age (56.7 ± 2.4 vs 57.1 ± 3.1 years, NS) or sex (24 men, 24 women vs 124 men, 136 women, NS) between hypophosphatemic and normophosphatemic respiratory admissions. There were no differences in the seasonal prevalence of hypophosphatemia (autumn, 19 percent; winter, 12 percent; spring, 16 percent; summer, 16 percent, NS). In 17 of the 52 hypophosphatemic admissions, causative factors for low serum phosphate levels other than respiratory illness were present (five IV glucose therapy, five antacid therapy, four nutritional recovery, two Gram-negative urinary tract infection, and one alcohol withdrawal). No patient had insulin-requiring diabetes mellitus or underwent hyperalimentation.

Associated electrolyte abnormalities were unusual. Hypokalemia (<3.5 mg/dl) occurred in 11 of the 308 chest admissions with concomitant hypophosphatemia in three patients. Only two patients had serum potassium <3.0 mg/dl. One patient had transient hypercalcemia (>10.5 mg/dl), which normalized during hospitalization with fluid repletion. One patient with tuberculosis and hypophosphatemia had hyponatremia (Na <130 mEq/L). Serum magnesium levels were not routinely measured.

Sequela Associated With Hypophosphatemia

Symptoms and Signs: Fourteen of the 52 hypophosphatemic admissions (27 percent) had clinical findings attributable to hypophosphatemia, including elevated muscle enzymes (eight), worsening mental status (four), worsening ventilatory function (two), worsening congestive heart failure (two), and anemia (one).

Clinical Vignettes: An 81-year-old man admitted with pneumonia and acute deterioration of mental status had used antacids for chronic duodenal ulcer disease. His serum phosphate level on admission was 1.6 mg/dl and decreased to 1.4 mg/dl on the third hospital day after intubation for ventilatory failure. He was given antacids via a nasogastric tube; his phosphorus level was 1.2 mg/dl on the seventh hospital day. He subsequently had anemia and rhabdomyolysis (CPK = 748 IU, MB band negative) of unknown cause and died seven weeks after admission after several unsuccessful attempts at extubation.

A 74-year-old woman was admitted with ventilatory failure and upper GI bleeding, which was aggressively treated with antacids. The patient subsequently had worsened ventilatory failure, congestive heart failure, declining mental status, and ileus associated with the new onset of hypophosphatemia (1.4 mg/dl). Her physicians treated her with IV potassium phosphate, and her ventilatory function improved. She was subsequently extubated and discharged from the hospital.

Unexplained Enzyme Elevation: Muscle enzymes were elevated in 8 of 52 hypophosphatemic patients (vs 2/260 normophosphatemic patients, p <0.001) in whom other explanations (myocardial infarction, alcohol use, hypotension, or crush injury) were not apparent. The CPK was 1,926 ± 635 IU (normal <100 IU), LDH 441 ± 150 (normal <225 units), and SGOT 302 ± 237 (normal <40 units).

Mortality and Morbidity: The mortality for the hypophosphatemic and normophosphatemic chest patients was similar (4.2 vs 5.0 percent, respectively, NS). However, the hospitalization was longer in the hypophosphatemic patients (24.0 ± 4.0 vs 11.3 ± 10 days, p <0.005).

DISCUSSION

We have found that reduced serum phosphate is frequent in patients with respiratory illness (17 percent), specifically, in patients with respiratory infections (28 percent). However, the true prevalence of in-hospital hypophosphatemia in patients with respiratory illness is unknown, since this study was retrospective, and all patients did not have daily serum phosphate measurements performed. Serum phosphate <2.0 mg/dl occurred in 4.0 percent of patients. Severe hypophosphatemia (<1.5 mg/dl) was uncommon (1 percent), but when present was often related to concomitant use of antacids (two of four patients).

The overall prevalence of hypophosphatemia in chest patients on admission to the hospital was 10 percent, but was ten times higher in patients with respiratory infections compared with other chest and general medical patients (21 vs 2 percent) in this and other studies. Since the most important causes of hypophosphatemia were not present in these patients on admission (IV dextrose, diabetes mellitus, alcohol withdrawal), these data indicate that patients with infectious respiratory illness have a high prevalence of hypophosphatemia, similar to that of patients with Legionnaires’ disease, and should be considered a high risk population for hypophosphatemia, as are patients with alcohol withdrawal, nutritional recovery, treatment of diabetic ketoacidosis, and Gram negative infections.

We found no relationship between age, sex, season of hospital admission, and the development of hypophosphatemia. Moreover, there was no correlation between arterial blood gas findings and hypophosphatemia. Respiratory alkalosis has been shown to lower serum phosphate levels acutely via transcellular shifts; metabolic acidosis may lead to renal phosphate losses. Hence, a mixed metabolic disturbance...
may account for the development of hypophosphatemia which might be invident by assessment of arterial pH alone. We did not examine serum bicarbonate levels in relationship to arterial blood gases and to serum phosphate in this retrospective study. Therefore, we cannot make a definitive statement as to the relationship between arterial blood gases and the development of hypophosphatemia in patients with respiratory illness. However, our data suggest that the hypophosphatemia in these patients is not purely related to respiratory alkalosis due to hyperventilation. Moreover, in patients with pneumonia, the radiologic severity and the etiologic agent were unrelated to the development of hypophosphatemia. In addition, hypophosphatemia was common in patients with acute bronchitis (8/14, 57 percent).

Twenty-seven percent of patients with hypophosphatemia had otherwise inexplicable symptoms or signs, including worsening ventilatory function, rhabdomyolysis, worsening congestive heart failure, diminished mental status, and anemia. Of note is that the muscle enzyme elevation associated with Legionnaires’ disease may be related to the frequent development of hypophosphatemia in patients with infectious respiratory illness, and hence may reflect a more generalized pathogenetic mechanism rather than a specific clinical feature of Legionnaires’ disease. However, in contrast to patients with Legionnaires’ disease, associated electrolyte abnormalities in our hypophosphatemic patients were unusual. Moreover, the development of asymptomatic rhabdomyolysis in patients with respiratory illness and hypophosphatemia is also unusual. Clinically mild or asymptomatic rhabdomyolysis with hypophosphatemia occurs most commonly in patients with alcoholic withdrawal (especially with IV dextrose), and less frequently in patients with hyperalimentation or diabetic ketoacidosis. Knochel claims that such patients invariably demonstrate severe deficiency of muscle phosphate. Such assays were not performed in our patients. However, an alternative explanation for the development of rhabdomyolysis in these patients with respiratory illness is tissue hypoxia. The combination of hypophosphatemia with resultant reduced red blood cell 2,3-DPG and ATP concentration and increased hemoglobin-oxygen affinity (hence, reduced tissue oxygen release in patients with hypoxemia) may well result in acute tissue hypoxia with resultant rhabdomyolysis.

Although hypophosphatemia was not associated with increased mortality, hospital stay was twice as long as in those patients with normal serum phosphate levels. Hypophosphatemia may be the cause of prolonged illness due to its adverse effects on multiple organ systems. For example, the course of an infectious illness may be prolonged by phagocytic dysfunction secondary to hypophosphatemia. Alternatively, chronically ill patients who have hypophosphatemia may be more likely to have infection, or it may be that the more ill patients are more likely to have hypophosphatemia. Further investigation is needed into the mechanism underlying the association of hypophosphatemia with respiratory infection.

We found severe hypophosphatemia associated with worsened ventilatory function in two patients given phosphate-binding antacids; one patient recovered when IV phosphate was administered. Antacids should be used prudently in patients with respiratory illness because they can deplete body phosphate stores and predispose to the development of symptomatic hypophosphatemia. However, the development of hypophosphatemia in these severely ill patients is most likely multifactorial, with renal and GI losses and transcellular shifts playing roles in the genesis of the low serum phosphate levels. Dextrose infusion may lead to lowered serum phosphate, and hyperalimentation of the nutritionally deprived may lead to severe hypophosphatemia due to transcellular fluxes; hence, the development of respiratory failure shortly after initiation of total parenteral nutrition may be related to acute, severe hypophosphatemia.

We conclude that respiratory illnesses, particularly infectious, should be added to the list of disorders frequently associated with hypophosphatemia, and that careful attention should be paid to the use of phosphate-binding antacids in these patients. The finding of otherwise unexplained serum skeletal muscle enzyme elevation in these patients should prompt consideration of hypophosphatemia.

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13th Annual Symposium, Fleischner Society
The Fleischner Society will hold its 13th Annual Symposium on Chest Disease, May 27-29, at the Grand Hyatt, New York City. For information, contact the conference coordinator, Fleischner Society, 3770 Tansey, San Diego 92121 (714:433-6222).

Pulmonary Mechanics and Chest Physiotherapy
This one-day meeting will be held at and by the Hospital Universitaire Saint-Pierre, Brussels, Belgium, May 29. For information, contact Dr. A. DeCoste, Departement des voies respiratoires, Hopital Universitaire Saint-Pierre, rue Haute 322, 1000 Brussels, Belgium.

First International Congress on Cyclosporine
The University of Texas Health Science Center at Houston will sponsor this program at the Westin Galleria Hotel, Houston, May 16-19. For information, contact Ms. Sherry Smith, University of Texas Medical School at Houston, Office of Continuing Education, 6431 Fannin, Houston 77030 (713:792-5346).