Scientific Research Publishing

Health, 2023, 15, 810-813
https://www.scirp.org/journal/health
ISSN Online: 1949-5005
ISSN Print: 1949-4998

Uniphyline-Induced Hypophosphatemia: A Rare Etiology of Severe Respiratory Failure

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How to cite this paper: Mohammed, H.M.I., Ahmad, F., Abdalrahman, M. and Mohamed, G. (2023) Uniphyline-Induced Hypophosphatemia: A Rare Etiology of Severe Respiratory Failure. *Health*, **15**, 810-813.
https://doi.org/10.4236/health.2023.157052

Received: June 26, 2023
Accepted: July 24, 2023
Published: July 27, 2023

Abstract

Hypophosphataemia is defined as low level of phosphate in the blood (normal range 0.8 - 1.4 mmol/l), which can be drug-induced such as uniphyline. We present a case of elderly female patient with known chronic obstructive pulmonary disease, admitted with acute respiratory failure and low serum phosphate level, her clinical signs and serum phosphate level did not improve with conventional therapy and intravenous phosphate replacement, until her recently commenced uniphyline was discontinued. This highlights the importance of awareness amongst the clinicians about this rare but potential side effect of uniphyline. We suggest monitoring phosphate levels in patients admitted with acute respiratory failure especially those on extended bronchodilator therapy.

Keywords

Hypophosphatemia, Acute Respiratory Failure, Chronic Obstructive Pulmonary Disease, Uniphyline, Theophyline, Bronchodilator Therapy

1. Introduction

Hypophosphatemia [1] is further classified in to mild (0.4 - 0.8 mmol/l), moderate (0.3 - 0.8 mmol/l) and severe (<0.3 mmol/l). Most patients with hypophosphatemia are asymptomatic. Those with mild hypophosphatemia may complain of generalized non-specific mild to moderate weakness. The history of presenting illness will rarely indicate possible hypophosphatemia. For this reason, a clinician should have high index of suspicion for phosphate abnormalities

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whenever an etiology associated with hypophosphatemia is present.

Conditions to consider possible hypophosphatemia include: poor nutritional status, symptoms or history of intestinal malabsorption, history of unusual fractures, history of or suspicion for multiple myeloma, parenteral nutrition supplementation (re-feeding syndrome), medication-induced [2] including chronic glucocorticoids, antacid, cisplatin or pamidronate, current treatment for diabetic ketoacidosis [3], and any hospitalization requiring an Intensive care unit setting. Mild hypophosphatemia will not be clinically apparent. Severe hypophosphatemia may have the clinical presence of altered mental status, neurological instability including seizures, generalized muscular weakness which can subsequently result in or worsening acute respiratory failure [4].

2. Case Presentation

A 76-year-old woman was admitted in June 2022 to the hospital with worsening dyspnoea and cough productive of greenish phlegm for the three days duration. Her medical history was significant for chronic obstructive pulmonary disease [4], hypertension and osteoporosis. Socially she was moderately frail patient, lived alone with cares in place. Her medications list included; Carbocistine, Aspirin, omeprazole, salbutamol, Adcal-D3 and Seretide inhaler. Uniphyline (slow-release thyophyline [2]) was commenced one month prior to admission to the Hospital. On initial assessment, she had tachycardia with heart rate of 113 per minute (pm), tachypnoea with respiratory rate 24 per minute(pm) and blood pressure of 123/82 mmhg. Her chest examination revealed bilateral widespread polyphonic wheezes associated with decreased breath sounds; chest x-ray showed hyper inflated lungs without consolidation and blood gas analysis showed type 2 respiratory failures. Her initial blood test results showed raised inflammatory markers and very low serum phosphate level of 0.23 mmol/l in comparison to normal range of (0.8 - 1.4 mmol/l).

The patient was commenced on conventional treatment for infective exacerbation of chronic obstructive pulmonary disease along-with intravenous phosphate infusion for severe hypophosphatemia. Despite 5 days of intravenous phosphate infusion, there was no clinical improvement of the condition or the serum phosphate level low remained between 0.3 mmol/l and 0.44 mmol/l. However, her serum phosphate levels returned to normal with corresponding improvement in the patient's clinical signs and symptoms after only two days of cessation of uniphyline (slow-release thyophyline).

3. Discussion

Phosphate [5] is one of the most important molecular elements for the normal cellular function within the body. Phosphorus-containing compound have important role in cell structure (cell membrane and nucleic acids), cell metabolism (generation of adenosine-triphosphate), regulation of sub cellular process (phospharylation of key enzyme) and maintainence of acid-base homeostasis

(urinary buffering). In average adult, total body content is 700 g, of which 85% is in the bone and teeth, 14% in soft tissue while only 1% is found in the extracellular fluid. On average, approximately 800 - 1400 g of phosphorus is taken daily, while the serum concentration of it is 0.8 - 1.4 mmol/l. Its homeostasis is regulated by various actions including reabsorption by the kidneys, out of which 80% occurs in proximal tubule and is mediated by sodium-phosphate co-transporter (NaPi-II [6]) where parathyroid hormone is the main regulator via the series of intracellular signaling cascades leading to NaPi-II internalization and down regulation.

To describe the prevalence and mechanism of hypophosphatemia as a reversible cause of respiratory muscle hypo-contractility and reduced tissue oxygen extraction in a patient with chronic obstructive lung disease and asthma, a study of phosphate homeostasis was conducted in 22 patients with chronic asthma/chronic obstructive pulmonary disease who had been hospitalized for acute exacerbation. Serum phosphate concentration was normal in all patients on presentation, and fell after the initiation of bronchodilator therapy [4]. Twelve patients (54%) developed hypophosphatemia (serum phosphate, less than 0.8 mmol/L). Urinary phosphate level falls in parallel. A negative correlation was observed between serum phosphate and serum theophylline concentrations, and a positive correlation between serum and urinary phosphate concentrations. These data indicate that hypophosphatemia is a common metabolic abnormality during the emergency treatment [7] of asthma/chronic obstructive pulmonary disease. The underlying mechanism appears to be drug-induced phosphate influx from the extra-cellular to the intracellular space, a situation which necessitates the physicians to be fully aware when dealing with critically hospitalized ill patients, the debate that need to be approved by larger number of studies.

4. Conclusion

This case illustrates severe respiratory failure triggered by uniphyline-induced hypophosphatemia in our patient with background chronic obstructive pulmonary disease, with newly added bronchodilator therapy. Physicians must be more alert and aware about this rare but potentially life-threatening adverse effect of uniphyline induced hypophosphatemia, as it is a widely used drug in chronic obstructive airway disease. It is also suggested that serum phosphate level be monitored in patients undergoing emergency treatment of bronchospasm, particularly if prolonged period of bronchodilator therapy is required and there is persistent hypophosphatemia despite optimum treatment. Severe hypophosphatemia (<0.3 mg/dl) can induce or worsen acute respiratory failure, cause delay in weaning-off from mechanical ventilator and increase the duration of intensive care stay, hospitalization and death.

Disclosures

Human subject: consent was obtained and waived by all participants in this

study.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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