Pharmacokinetic interaction of Phosphorus on the treatment of sputum positive pulmonary tuberculosis patients

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Abstract

Tuberculosis (TB) in children is a neglected aspect of the TB epidemic despite it constituting 20% or more of all TB cases in many countries with high TB incidence. Tuberculosis constitutes a serious global health problem with nearly 10 million new cases of tuberculosis (2011) and 1.4 million deaths every year. In pharmacokinetic studies, co-administration of various inhibitors of this enzyme (e.g., erythromycin, antifungal substances, protease inhibitors, and grapefruit juice) raised plasma phosphate concentrations by up to 500%.

Materials and Methods: The study was conducted in Chennai tuberculosis hospital from January 2012 through July 2015 in seven target groups, with consecutive recruitment. The first group consisted of otherwise deselected patients who are presented with suspected tuberculosis to the tuberculosis hospital in Chennai. Blood samples were collected from the subjects of tuberculosis Hospital at Chennai. To non-treatment and treatment variations, fasting blood samples were collected from 8 AM - 9 AM. Experiments were carried out as soon as possible. Whenever there was a delay in experiments, samples were stored at -10° to -15°C for a maximum of 1 day. Blood samples thus collected using standard sampling techniques were centrifuged to get the serum that was analysed phosphorus levels by Phosphomolybdate method. The study protocol was approved by the Institutional ethics committee and was carried out in accordance with the principle of the declaration of Helsinki.

Results: In the study, mean serum phosphorus level in newly diagnosed patients was 13 ± 3.30 mg/dl, after first month treatment to sixth month treatment the level was 13 ± 3.60 mg/dl, 11 ± 3.30 mg/dl, 10.50 ± 3.30 mg/dl, 11 ± 3.30 mg/dl, 11.20 ± 2.80 mg/dl and 10.20 ± 2.80 mg/dl respectively. Six-month treatment 20 patients were get the hyperphosphatemia for include female 9 patients. One study suggests that Estrogen may act directly to suppress sodium-dependent phosphate absorption in the renal proximal tubules inducing phosphaturia and decreased serum phosphate; women who are post-menopausal and Estrogen deficient would be at increased risk for hyperphosphatemia Low serum phosphate levels are associated with reduced cardiac output and also with risk for arrhythmia.

Conclusion: Our findings offer the possibility that early intervention will help achieve calcium and phosphorus conversion and ultimately a successful treatment outcome. In order for us to update guidelines and optimize patient care, some gaps in the evidence base need to be addressed. Although available data demonstrate the association between hyperphosphatemia and increased risk of mortality, it remains a challenge in the clinic to achieve and maintain recommended serum phosphorus concentrations.

Keywords: Hyperphosphatemia, Phosphomolybdate Method, Pulmonary Tuberculosis.

Introduction

Tuberculosis (TB) is caused by infection with *Mycobacterium tuberculosis*, which is transmitted through aerosolized droplets. Tuberculosis constitutes a serious global health problem with nearly 10 million new cases of tuberculosis (2011) and 1.4 million deaths every year.[1,2] TB infection can either be acute and short-lived or chronic and long term. The identification and spread of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis pose a serious threat to the world.[3,4] Several studies have been conducted to assess the bioavailability, acceptability, or microbiological efficacy of rifampicin and isoniazid with or without Pyrazinamide administered in a fixed combination for daily or intermittent use. 2-5. These studies have shown that 2- and 3-drug FDCs are generally well tolerated, with proportions of adverse effects similar to those for separate formulations and no difference in acquiring drug resistance. Efforts in the past decade to control tuberculosis by the consistent application of existing strategies have met with only limited success, slowing the rate of increase but failing to make substantial progress toward the goal of tuberculosis elimination. Shortened therapy and most importantly biomarker discovery regimens will be needed to realize the goal of global tuberculosis elimination or control.[6,7] Before the advent of effective chemotherapy, many studies on the biochemistry of tuberculosis were carried out in the hope of finding some metabolic anomaly or defect whose rectification would lead to a cure.

Phosphorus is the most important macro minerals required for the body's growth of bones and its function. Phosphorus abnormality has been variably reported in studies carried out on the subject. Phosphate plays a critical role in regulating various essential biological functions, and phosphorus-containing

compounds are components of cellular membranes, energy metabolism, intracellular signalling, and bone and tooth mineralization.[8,9] Nucleic acids, and nucleoproteins that act as acid-base homeostasis regulators, play important roles in post-receptor signalling and energy transfer through phosphorylation or ATP generation.[10,13] Phosphate homeostasis is maintained by the combination of intestinal phosphate absorption, phosphate influx and efflux to and from bone and intracellular stores, and renal excretion of phosphate.[14] However, hyperphosphatemia, defined as having an excessive phosphatelevel (≥ 4.5 mg/dL), has emerged as a risk factor for diseases such as chronic kidney disease (CKD) and cardiovascular diseases.[15,21] In the general hospital population, the prevalence of moderate hypophosphatemia ranges between 2.2 and 3.1%[22,23] and the prevalence of severe hypophosphatemia is reported to be 0.2 to 0.4%.[24,25] Therefore, hypophosphatemia can result in dysregulation of respiratory, cardiac, hematologic, musculoskeletal, renal, and central nervous system functions, thereby causing considerable morbidity and increased mortality.[11,13] Hypophosphatemia has a higher incidence in certain patient groups, such as patients with diabetic ketoacidosis, sepsis, and postoperative patients.

This study here is to prepare a preliminary report about abnormal spectrum of phosphorus presentation on the routine biochemical laboratory investigation.

Material and Methods
Study Patients and Setting

The study was conducted in Chennai tuberculosis hospital from January 2012 through July 2015 in seven target groups, with consecutive recruitment. The first group consisted of otherwise deselected patients who are presented with suspected tuberculosis to the tuberculosis hospital in Chennai. The second to seventh group consisted of patients who are presented with suspected tuberculosis to the tuberculosis hospital and who were at high risk for tuberculosis with chemotherapy. Inclusion in this group required the presence of one or more constitutional symptoms (fever, weight loss, night sweats, and sputum positive), or patients with risk factor for tuberculosis with chemotherapy treatment.

Inclusion criteria: For enrolment were an age of 18 years or older, history of TB or family history of TB, symptoms of respiratory tract and other body parts for TB The examination such as X-ray chest radiograph and Sputum positive TB confirmed, Physical condition: No obvious heart, liver, kidney, gastrointestinal tract, nervous system, mental disorder and metabolic abnormalities and other medical history, Smoking and non-smoking, alcoholic and non-alcoholic for drinking beverages during the study, Negative HIV infection and no previous receipt of chemotherapy treatment patients.

Sampling: Patients with newly diagnosed smear-positive pulmonary tuberculosis who had provided written information consent were randomly assigned to receive either a test or control regimen. The test Fixed-dose combinations (FDC) regimen consisted of a first intensive chemotherapy phase of 8 weeks of daily rifampicin, isoniazid, pyrazinamide, and ethambutol in tablets followed by 18 weeks of rifampicin and isoniazid FDC tablets 3 times weekly. Patients were required to attend the treatment facility daily during the first intensive phase (first 8 weeks) of chemotherapy and then 3 times weekly during the continuation phase. Every treatment dose was to be taken under supervision of a member of the medical staff (i.e., as directly observed therapy). The blood samples of these suspected patients were collected from seven groups and those collected from sputum positive pulmonary tuberculosis patients were stained for mycobacterium visualization (Ziehl–Neelsen staining). Blood samples were collected from the subjects of tuberculosis Hospital at Chennai. To non-treatment and treatment variations, fasting blood samples were collected from 8 AM - 9 AM. Experiments were carried out as soon as possible. Whenever there was a delay in experiments, samples were stored at -10° to -15°C for a maximum of 1 day. Blood samples thus collected using standard sampling techniques were centrifuged to get the serum that was analysed phosphorus levels by phosphomolybdate method.[16] The study protocol was approved by the Institutional ethics committee and was carried out in accordance with the principle of the declaration of Helsinki.

Results

Enrolment started in June 2012 and was completed in December 2015, after inclusion of 162 patients. Results were expressed as Mean ± S.D for each measure. There were significant differences between treatment months. In the study, mean serum phosphorus level in newly diagnosed patients was 13 ± 3.30 mg/dl, after first month treatment to sixth month treatment the level was 13 ± 3.60 mg/dl, 11 ± 3.30 mg/dl, 10.50 ± 3.30 mg/dl, 11 ± 3.30 mg/dl, 11.20 ± 2.80 mg/dl and 10.20 ± 2.80 mg/dl respectively. Patients with an adverse outcome contributed to observation of phosphorus to the midpoint of a 30-day interval. Phosphorus TB incidence of the patients before and after six-months was found to be on the low levels 1.08 to 1.25 mg/dl, medium levels 2.0 to 4.0 mg/dl and then high levels 7.5 to 12.84 mg/dl and follow-up are shown in the graph.
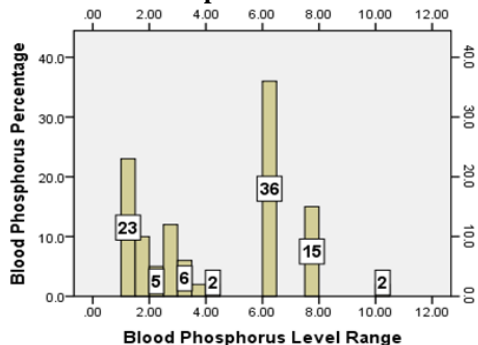
Discussion
Phosphorus levels for Tuberculosis

Graph 1: Before treatment for Tuberculosis Patients
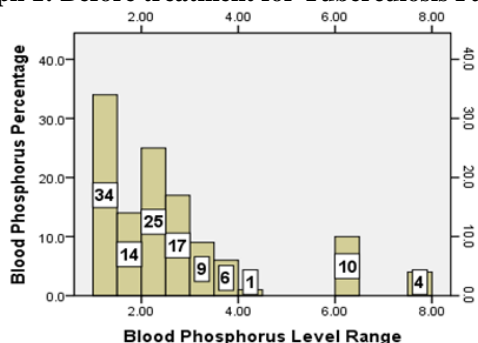
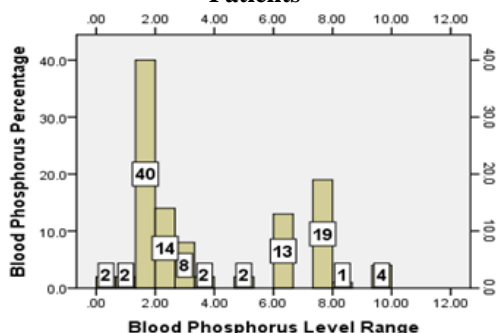**Graph 2: One month treatment for tuberculosis patients**

The frequency of select before and after treatment for each of the keyword groups presented in the figure, the following variations of the blood normal phosphorus levels.
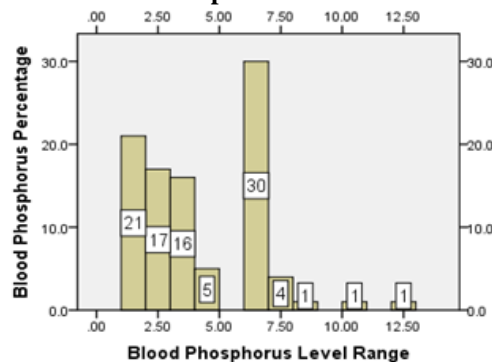
Before Treatment: 0 to 2 level bars are hypophosphatemia (48 patients), 2 to 4 level bars are normal values (57 patients), and 4 to 8 level bars are hyperphosphatemia (15 patients).

One month Treatment: 0 to 2 level bars are hypophosphatemia (23 patients), 2 to 4 level bars are normal values (11 patients), and 4 to 12 level bars are hyperphosphatemia (55 patients).

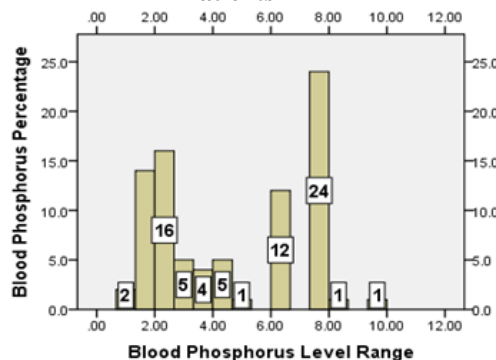**Graph 3: Two months treatment for tuberculosis Patients**

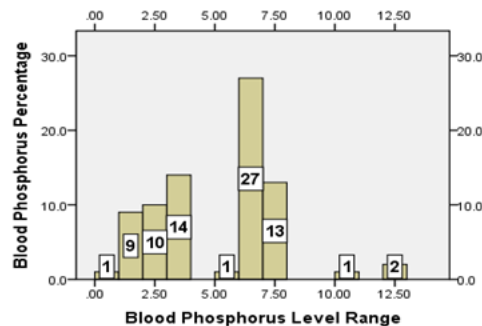**Graph 4: Three month treatment for tuberculosis patients**

Two months Treatment: 0 to 2 level bars are hypophosphatemia (4 patients), 2 to 4 level bars are normal values (64 patients), and 4 to 12 level bars are hyperphosphatemia (39 patients). Three-month Treatment: 0 to 2 level bars are nil hypophosphatemia (0 patients), 2 to 4 level bars are normal values (54 patients), and 4 to 12.5 level bars are hyperphosphatemia (55 patients).

Graph 5: Four month treatment for tuberculosis Patients

Graph 6: Five month treatment for tuberculosis Patients

Four months Treatment: 0 to 2 level bars are hypophosphatemia (2 patients), 2 to 4 level bars are normal values (27 patients), and 4 to 12 level bars are hyperphosphatemia (44 patients). Five-month Treatment: 0 to 2 level bars are hypophosphatemia (1 patients), 2 to 4 level bars are normal values (33

patients), and 4 to 12.5 level bars are hyperphosphatemia (44 patients).

Graph 7: Six Month Treatment for Tuberculosis Patients
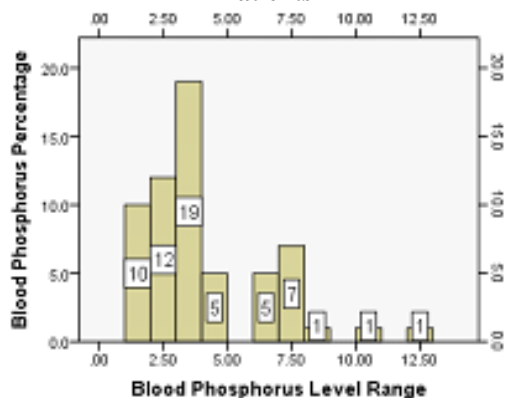
Six-month Treatment: 0 to 2 level bars are Nil hypophosphatemia (0 patients), 2 to 4 level bars are normal values (41 patients), and 4 to 12.5 level bars are hyperphosphatemia (20 patients).

The statistically significant difference in the serum phosphorus was found among culture-positive patients. According to the results of blood test at admission, Serum phosphorus levels had increased during the continuation phase. The mean value for serum phosphorus levels in PTB-7 group was statistically extremely significant ($p > 0.05$). Phosphorus concentrations of above 6.4 mg/dL were associated with an increased risk of all-cause mortality.[25] While these results suggest some known factors associated with hyperphosphatemia including an association with increasing calcium levels, we also found increased risk with anemia, as indicated by low hemoglobin levels, as well as an association with lower BMI, and some time it will caused by mineral and bone disorders (CKD-MBD) may result in a direct suppressive effect on erythropoiesis, resulting in anemia, including low vitamin D, calcium and increased serum parathyroid hormone levels. Other known my fund result was risk factors for hyperphosphatemia include female gender. Six month treatment 20 patients were get the hyperphosphatemia for include female 9 patients. One study suggests that estrogen may act directly to suppress sodium-dependent phosphate absorption in the renal proximal tubules inducing phosphaturia and decreased serum phosphate; women who are post-menopausal and estrogen deficient would be at increased risk for hyperphosphatemia.[20,21] Low serum phosphate levels are associated with reduced cardiac output and also with risk for arrhythmia.[28] Tuberculosis patient were loose the weight for before treatment to three month treatment, so those time we were found result in a hyperphosphatemia. Low serum phosphate level limits phosphorylation of carbohydrate

intermediates in glycolysis and glycogenesis and chronic hypophosphatemia inhibits glucose transport potentially resulting in diabetes mellitus and hypertension.[29] Hypophosphatemia can cause life-threatening consequences, and severe hypophosphatemia is reportedly associated with a fourfold increase in mortality.[29] Hypophosphatemia is not uncommon and is observed in 1-5% of the general medication population. Hypophosphatemia can lead to the onset of haemolysis, leukocyte dysfunction, respiratory failure, impaired myocardial performance, and impaired central nervous system function. But our studies was five case only hypophostemia for before treatment than after treatment reduced. The liver demonstrates significant early uptake of serum phosphorus, which peaks during the first few days posthepatectomy, corresponding to the period of maximum liver regeneration and correlating with the decrease in free serum phosphorus levels commonly observed.[23,24] Our studied was result of four to six-month treatment patients for billrubin and creatinine highly increase but low level phosphorus. The maximum metabolic demand on the regenerating liver typically occurs during the first 72 h, with the decrease in serum phosphorus levels post hepatectomy mirroring this pattern.[30]

Conclusion

In the present study serum phosphorous level was much decreased and increased in newly diagnosed patients as compared to the PTB 7 group which came to normal levels after the anti-tubercular therapy but here end stage 20 hyperphosphatemia patients. Studies can be carried out on the prospects of use early markers of hypocalcaemia, hyperphosphatemia, and hypophosphatemia as for before and after TB treatment. Our findings offer the possibility that early intervention will help achieve calcium and phosphorus conversion and ultimately a successful treatment outcome. In order for us to update guidelines and optimize patient care, some gaps in the evidence base need to be addressed. Although available data demonstrate the association between hyperphosphatemia and increased risk of mortality, it remains a challenge in the clinic to achieve and maintain recommended serum phosphorus concentrations.

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