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Refeeding syndrome: effective and safe treatment with Phosphates Polyfusor

A. TERLEVICH*, S. D. HEARING*, W. W. WOLTERSDORF†, C. SMYTH*, D. REID*, E. MCCULLAGH*, A. DAY† & C. S. J. PROBERT*

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SUMMARY

Background: Severe hypophosphataemia associated with refeeding syndrome requires treatment with intravenous phosphate to prevent potentially life-threatening complications. However, evidence for replacement regimens is limited and current regimens are complex and replace phosphate inadequately.

Aim: To assess the effectiveness and safety of 50 mmol intravenous phosphate infusion, given as a 'Phosphates Polyfusor', for the treatment of severe hypophosphataemia in refeeding syndrome.

Methods: Patients with refeeding syndrome and normal renal function received a Phosphates Polyfusor infusion for the treatment of severe hypophosphataemia (< 0.50 mmol/L). The outcome measures were serial serum phosphate, creatinine and calcium concentra-

tions for 4 days following phosphate infusion and adverse events.

Results: Over 2 years, 30 patients were treated. Following treatment, 37% of cases had a normal serum phosphate concentration and 73% had a serum phosphate concentration of > 0.5 mmol/L within 24 h. Ten patients required more than one Phosphates Polyfusor infusion. Within 72 h, 93% of cases had achieved a serum phosphate concentration of ≥ 0.50 mmol/L. No patient developed renal failure. Three episodes of transient mild hyperphosphataemia were recorded. Four patients developed mild hypocalcaemia.

Conclusions: This is the largest published series of the use of intravenous phosphate for the treatment of severe hypophosphataemia (< 0.50 mmol/L), and is the most effective regimen described. All patients had refeeding syndrome and were managed on general wards.

INTRODUCTION

Refeeding syndrome was first described in Far East prisoners of war following World War II and in survivors of the Siege of Leningrad: the recommencement of food intake after a period of prolonged starvation seemed to precipitate cardiac failure.¹ The physiology of refeeding syndrome has now been established.² In starvation, insulin secretion is decreased in response to reduced carbohydrate intake. Instead, fat and protein stores are catabolized to produce energy.

This results in the intracellular loss of water and electrolytes, including phosphate. Thus, malnourished patients become total body phosphate depleted, although they often have normal or just below normal serum phosphate levels.³ Phosphate is required for the generation of adenosine triphosphate from adenosine diphosphate and adenosine monophosphate and for other crucial phosphorylation reactions. During refeeding, a sudden shift from fat to carbohydrate metabolism occurs and insulin secretion increases. This stimulates the cellular uptake of phosphate, in addition to glucose and other electrolytes, which can lead to profound hypophosphataemia.⁴ This phenomenon is usually most severe within 72 h of refeeding.⁵ Hypophosphataemia

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due to refeeding syndrome can be life threatening. Severe clinical manifestations are associated with serum phosphate levels of < 0.32 mmol/L. They include cardiac failure due to reduced myocardial contractility, hypotension, arrhythmias, respiratory failure requiring ventilation, seizures, coma and sudden death.^{6–11} However, in refeeding syndrome, a phosphate level of < 0.50 mmol/L has been shown to be clinically important. This level of hypophosphataemia is associated with important clinical features, such as rhabdomyolysis, erythrocyte haemolysis, leucocyte dysfunction and respiratory muscle weakness. Furthermore, in refeeding syndrome, phosphate levels often fall further and treatment should be initiated prior to the development of the life-threatening clinical features described. Thus, in refeeding syndrome, a level of phosphate of < 0.50 mmol/L is the threshold for treatment.¹² All the clinical features of hypophosphataemia resolve following phosphate correction.^{6–10} Cellular uptake of potassium and magnesium also occurs and can result in hypokalaemia and hypomagnesaemia.¹³ These electrolyte disturbances can occur whether patients are fed parenterally or enterally.^{1, 5, 12, 13} In current UK clinical practice, patients with anorexia nervosa, cancer or alcoholism and some post-operative patients are at the highest risk of developing refeeding syndrome.^{14–17}

The dose of phosphate and the rate of infusion in these patients have previously been unclear.² The previously recommended dose of intravenous phosphate for the treatment of hypophosphataemia was 50 mmol over 12–24 h. However, in 1993, a case report of severe hyperphosphataemia and renal failure in a patient treated with this regimen led to the withdrawal of this dose recommendation from the *British National Formulary*.¹⁸ The patient described was post-operative and septic, in an intensive care unit and, importantly, did not appear to have refeeding syndrome. Current regimens for the treatment of hypophosphataemia have been mainly developed from experience in the treatment of small numbers of patients in intensive care settings with varying causes of hypophosphataemia. Few series have distinguished between severely unwell patients with hypophosphataemia and those with refeeding syndrome. Typically, regimens recommend multiple infusions guided by frequent repeat blood testing and are based on weight. Regimens involving 9 mmol over 12 h, 0.64 mmol/kg over 8–12 h and 30 mmol over 3 h have been effective in correcting severe hypophos-

phataemia in 20–50% of patients.^{12, 19, 20} However, these complex regimens may be impractical on general medical and surgical wards, and may be inadequate for patients with refeeding syndrome and normal renal function.¹³ Ideally, a treatment regimen for refeeding syndrome would not require blood test monitoring more frequently than daily, would provide an adequate dose of phosphate to correct severe hypophosphataemia in refeeding syndrome and would not require adjustment for weight.

In our unit, we have previously used aliquots of intravenous phosphate to correct hypophosphataemia due to refeeding syndrome. The initial administration of 5–10 mmol, repeated as required, was inadequate, and most patients ultimately required 50 mmol over 24 h with no adverse events. Thus, we now use 50 mmol of intravenous phosphate, infused over 24 h via a dedicated peripheral intravenous cannula, in all refeeding syndrome patients except those in renal failure. This can be conveniently given as a 'Phosphates Polyfusor' (PPF) (Fresenius Kabi Ltd., Warrington, UK). A Polyfusor is a sealed semi-rigid cylindrical polyethylene container, with a twist-off seal at one end and a ring tab at the other. A 500-mL PPF contains 50 mmol phosphate, 81 mmol sodium and 9.5 mmol potassium.

SUBJECTS AND METHODS

The Bristol Royal Infirmary is a university teaching hospital with a busy Accident and Emergency Department. The nutrition team consists of medical gastroenterologists, clinical biochemists, two nutrition nurses, two pharmacists and dieticians. Malnourished patients at risk of developing refeeding syndrome were identified by the dieticians and nutrition nurses. Information was given to the patient's medical team regarding refeeding syndrome and its treatment in the form of a printed sheet inserted into the notes. For those patients requiring artificial feeding (enteral or parenteral), this was commenced at a reduced calorific rate (50% of estimated requirements) in an attempt to reduce the risk of the development of refeeding syndrome. Serum phosphate, magnesium, calcium, potassium, urea and creatinine concentrations were measured prior to the start of feeding and were then repeated daily for 3 days after feeding had commenced. If the serum phosphate concentration fell to < 0.50 mmol/L and renal function was normal, a PPF was infused via a peripheral vein over 24 h. This level of hypophosphataemia has

previously been demonstrated to be clinically important in refeeding syndrome, and thus is our treatment threshold.¹² Other electrolyte abnormalities were also corrected. Feeding was not interrupted. If, after 24 h, the serum phosphate concentration remained at < 0.50 mmol/L or fell subsequently, further PPFs were administered over 24 h.

RESULTS

Over 2 years, 30 patients with severe hypophosphataemia due to refeeding syndrome have been treated with PPF. These included 16 males and 14 females with a mean age of 51.9 years and a mean weight of 60.0 kg. Refeeding was via oral (11), nasogastric (12) and parenteral (7) routes. Underlying causes for refeeding syndrome were alcoholism (12), malignancy (7), anorexia nervosa (4), Crohn's disease (3), recurrent small bowel obstruction (1), pneumonia (1), dysphagia due to pharyngeal pouch (1) and depression (1). All patients had a serum phosphate concentration of < 0.50 mmol/L at the diagnosis of refeeding syndrome (mean, 0.38 mmol/L). All patients were treated with at least one PPF. Following treatment with PPF, a normal serum phosphate concentration (0.85–1.4 mmol/L) was achieved in 37% (11) of cases, and 73% (22) had a serum phosphate concentration of $\geq$ 0.50 mmol/L within 24 h. Within 72 h, 93% (28) of cases had achieved a serum phosphate concentration of $\geq$ 0.50 mmol/L, although five patients required further PPFs as severe hypophosphataemia recurred following initial correction (Figure 1). Within 4 days, all patients had achieved a serum phosphate concentration of $\geq$ 0.50 mmol/L. Overall, eight patients required two

PPFs and two required three PPFs to maintain the serum phosphate concentration at > 0.50 mmol/L during refeeding. In addition to hypophosphataemia, seven patients required treatment for hypomagnesaemia and 18 for hypokalaemia.

Adverse events

Three patients developed transient, mild hyperphosphataemia (highest, 1.57 mmol/L; reference range, 0.85–1.4 mmol/L) without complication. Four patients developed asymptomatic hypocalcaemia. One patient's corrected calcium concentration fell from 2.53 to around 2.00 mmol/L (reference range, 2.25–2.70 mmol/L), although this was associated with a fall in albumin during rehydration from 22 to < 10 g/L (at which level calcium correction is inaccurate). The other three episodes involved a fall in calcium concentration from 2.43 to 2.20 mmol/L, 2.28 to 2.08 mmol/L and 2.32 to 2.19 mmol/L. None of these episodes was associated with hyperphosphataemia, renal dysfunction or clinical evidence of hypocalcaemia. One patient had a minor episode of phlebitis. No patient developed renal failure following phosphate infusion. Five patients died during admission due to their underlying disease process.

DISCUSSION

This is the largest published experience of the use of intravenous phosphate for the treatment of severe hypophosphataemia due to refeeding syndrome. Importantly, all patients were managed on general medical/surgical wards. Our study demonstrates that 50 mmol phosphate, given as a PPF over 24 h, is an effective treatment for refeeding syndrome, with 93% (28) of cases achieving a serum phosphate concentration of > 0.50 mmol/L within 72 h. Some patients with persistently low serum phosphate, or recurring hypophosphataemia, required multiple PPF infusions over longer periods of time. Indeed, 33% (10) of patients required more than one PPF, emphasizing that patients with refeeding syndrome have severe total body phosphate depletion despite normal serum phosphate levels prior to feeding. Furthermore, the treatment of refeeding syndrome by this method appears to be safe: in our series of 30 patients, only three patients developed transient, mild hyperphosphataemia and no patient developed symptomatic hypocalcaemia or renal

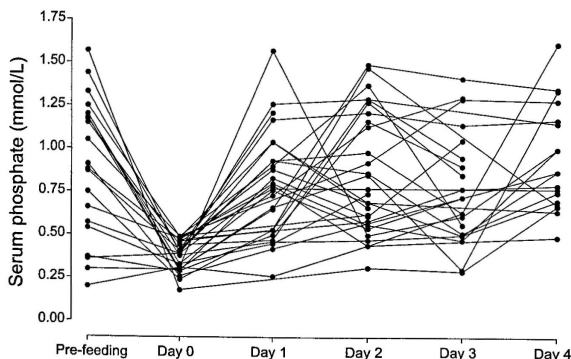


Figure 1. Correction of hypophosphataemia.

failure. *British National Formulary* recommendations for the treatment of all causes of hypophosphataemia previously advised 50 mmol phosphate over 12–24 h. However, following one case report of severe hypophosphataemia (5.59 mmol/L) and subsequent renal failure, requiring temporary dialysis, in a septic patient,¹⁸ the recommendations were altered to a regimen of 9 mmol over 12 h. This dose of phosphate is inadequate for patients with refeeding syndrome. Previously published data have shown that oral phosphate does not prevent the worsening of hypophosphataemia in refeeding syndrome.²¹ This was seen in one of our patients with anorexia nervosa, being fed enterally via a nasogastric tube, who developed severe hypophosphataemia despite receiving oral phosphate supplements. Several of our patients required potassium and magnesium supplementation as expected in refeeding syndrome, and these were given concurrently with no complications. Although our study is uncontrolled, it provides the best current evidence for the treatment of refeeding syndrome. However, future studies of the treatment of refeeding syndrome could involve a randomized controlled trial of this regimen: a PPF repeated as required after daily monitoring of serum phosphate vs. a previously described phosphate replacement regimen (multiple infusions guided by frequent repeat blood testing). Regardless of the exact regimen used, the most important aspect of the treatment of refeeding syndrome is the correction of severe hypophosphataemia by the administration of an adequate dose of intravenous phosphate, repeated as required, guided by the monitoring of serum phosphate.

The identification of patients at risk of the development of refeeding syndrome and the understanding of its pathophysiology are poor on general medical and surgical wards. Importantly, many patients at risk of refeeding syndrome are cared for on general wards as opposed to intensive care units or specialist nutrition units. However, nutrition teams can assist in this process. In addition, when patients are identified to be at risk of the development of refeeding syndrome, information regarding electrolyte monitoring and treatment, with a regimen which can be easily implemented on general wards, is required. We have shown that, for patients being cared for on general medical and surgical wards, this can be achieved by written advice from a nutrition team, daily blood monitoring for 3 days in

at-risk patients and treatment with a PPF containing 50 mmol of phosphate over 24 h.

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