

A Rapid Intravenous Phosphate Replacement Protocol for Critically Ill Patients

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ABSTRACT

Objective: *There is a high incidence of hypophosphataemia in the critically ill. It is known that even moderate hypophosphataemia can produce a variety of adverse consequences. Many phosphate replacement regimens have been suggested, most are conservative and few validated in the critical care environment. We designed a study to determine the apparent volume of distribution of phosphate and quantify phosphate loss in critically ill patients following rapid phosphate infusion. With these data we sought to design a phosphate replacement protocol.*

Methods: *A prospective clinical study of an infusion of 14.5mmol of phosphate ions over 1 hour in seven patients with mild, moderate or severe hypophosphataemia was performed. Serum phosphate, total calcium, ionised calcium, urea, creatinine, urinary phosphate excretion and creatinine clearance were measured prior to phosphate administration. Urinary phosphate excretion and creatinine clearance and serum phosphate levels were followed for 24 hours.*

Results: *The median phosphate increment was 0.65 mmol/L (0.17 - 0.85). The median initial volume of distribution was 0.45 L/kg (0.21 - 0.87). There was no reduction in ionised calcium or creatinine clearance. The renal phosphate threshold was reduced in all patients.*

Conclusions: *The apparent volume of distribution of phosphate in this group of critically ill patients is large. Urinary phosphate losses contributed to the development of hypophosphataemia in these patients. In this patient cohort, there were no adverse effects from phosphate infusion of 14.5 mmol/hr. A rational protocol based on the estimated volume of distribution and estimated urinary losses can be developed to achieve the rapid and sustained correction of hypophosphataemia in such patients. (Critical Care and Resuscitation 2004; 6: 175-179)*

Key words: Hypophosphataemia, critically ill,

Hypophosphataemia is common in critically ill patients and its aetiology multifactorial.¹ Phosphate plays an important role in glycolysis and the production of high-energy compounds, such as adenosine triphosphate. Evidence of its depletion in critically ill patients may manifest itself as impairment in respiratory, cardiovascular, neuromuscular, and haematological function.² A number of phosphate replacement regimens have been suggested.³⁻⁶ Traditionally they are conservative, due to a perceived risk of hypocalcaemia and worsening renal function. Most were designed over 15 years ago and not specifically tailored to critical care. In order to design a physiologically rational phosphate replacement protocol,

we performed a prospective cohort study to determine the apparent volume of distribution of phosphate and mechanisms of phosphate loss in critically ill patients.

METHODS

Approval for the conduct of this study was obtained from the Local Institutional Ethics Committee. All patients admitted to intensive care demonstrated to have either moderate or severe hypophosphataemia were eligible for recruitment. Severe hypophosphataemia was defined as a serum phosphate concentration less than 0.32 mmol/L and moderate hypophosphataemia was defined as a serum phosphate concentration less than 0.8

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mmol/L but greater than 0.33 mmol/L.⁷ The following patient groups were excluded: patients requiring renal replacement therapy and patients with a serum potassium concentration greater than 5.0 mmol/L. Consent was obtained from the patient or the next of kin if the patient was unable to give consent.

An intravenous solution of 14.5 mmol of phosphate ions (David Bull Laboratories 1.83 g K₂PO₄, 0.54 g KHPO₄) were infused intravenously over a one-hour period. For each patient the following baseline data were collected: demographic data, diagnosis, serum phosphate, ionised calcium, magnesium, urea, creatinine, sodium, potassium, glucose and albumin concentrations together with a 2 hour urinary phosphate excretion and creatinine clearance.

Immediately post infusion, serum phosphate, ionised calcium, total calcium and albumin levels were measured. Urinary phosphate excretion and creatinine clearance were measured for 24 hours post infusion. Serum phosphate, ionised calcium, total calcium, glucose and renal function were measured at 6 and 24 hours post infusion. These data enabled the calculation of the apparent volume of distribution of phosphate and the ratio of the maximum tubular reabsorption rate of phosphate (T_m) and glomerular filtration rate (GFR) (T_m/GFR). This ratio removes the contribution of GFR to T_m. The phosphate T_m/GFR can discriminate between patients with different disease states. It can therefore be used to elucidate the cause of phosphate loss. The normal T_m/GFR is 0.8 - 1.35 mmol/L and can be derived from a nomogram.⁸ If hypophosphataemia (< 0.8 mmol/L) persisted after 6 hours, a further 14.5 mmol of phosphate ions were administered.

Statistical analyses

Statistical analysis was performed using Analyse it for Excel (Analyse it Software, Leeds UK). Data was tested for normality. Non-normally distributed-paired data were analysed using the Wilcoxon rank sign test. Median values plus range are presented. A p value of

less than 0.05 was considered significant

RESULTS

Seven patients were enrolled in this study. No patient enrolled received an aluminium containing antacid or sucralfate during the study period. All seven patients received enteral nutrition during the study period. All patients had a serum phosphate level of less than 0.7 mmol/L. The serum phosphate concentrations and the apparent volumes of distribution for phosphate (initial and 6 hours) are presented in Table 1. The median increase in phosphate concentration was 0.65 mmol/L. The median initial volume of distribution was 0.45 L/kg (0.21 - 0.87 L/kg). No adverse events were noted following phosphate infusion. There was no change in post infusion ionised calcium levels (p = 0.58) or creatinine clearance, (p = 0.69) (Figure 1). One patient received an additional dose of phosphate (patient 2) at 6 hours. The ratios of the maximal rate of renal tubular reabsorption of phosphate to GFR, (T_m/GFR) for the seven patients are presented in Figure 2.

All patients had a reduced ratio (< 0.8) indicating a reduction in the renal phosphate threshold leading to inappropriate phosphate loss. In 5 of seven patients, the six hour T_m/GFR was further reduced from baseline.

DISCUSSION

The daily determination of serum phosphate concentration is commonplace in critically patients. Hypophosphataemia is common with an incidence of between 17 and 28%.^{3,9,10} There is increasing evidence as to the potentially harmful effects of hypophosphataemia.^{11,12} The physiological functions of phosphate have been well described previously.² They include its role in high-energy compounds such as ATP, cellular integrity, intracellular communication, multiple enzyme pathways and the immune system.

Hypophosphataemia in the critically ill patients is due to one or a combination of three recognised causes. These are inadequate intake, intracellular redistribution

Table 1. Changes in phosphate concentration in study patients

Patient	Age	Mass (kg)	Diagnosis	Phosphate concentration (mmol/L)				Vd (L/kg)
				pre	post	6 hour	24 hours	
1	43	55	Hepatic failure	0.54	1.21	0.72	0.49	0.39
2	48	98	Encephalitis	0.07	0.24	0.12	0.46	0.87
3	65	50	Post cardiac arrest	0.55	0.89	0.91	0.95	0.85
4	55	43	Spinal Cord Injury	0.67	1.52	0.98	1.04	0.40
5	63	55	Exacerbation COPD	0.48	1.07	1.15	0.85	0.45
6	57	44	Pneumonia	0.58	1.8	0.91	0.84	0.26
7	55	65	Post respiratory arrest	0.58	1.8	1.16	1.12	0.21

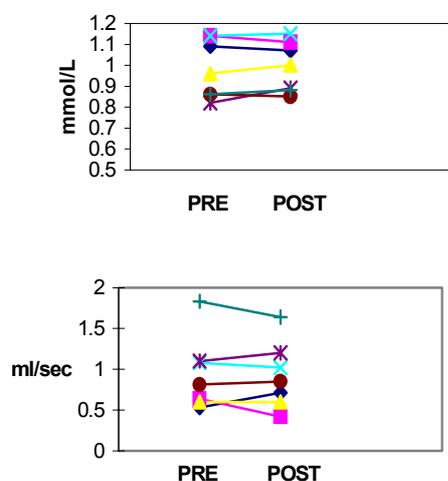


Figure 1. Changes in serum ionised calcium (upper diagram) and creatinine clearance (lower diagram) 6 hours after phosphate administration

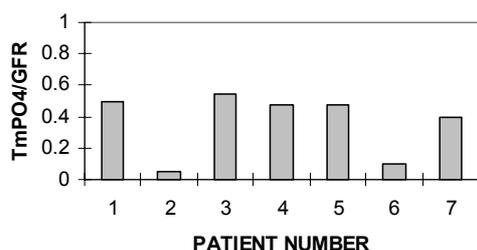


Figure 2 Phosphate Tm/GFR following phosphate infusion. All seven patients had a reduced renal phosphate threshold (<0.8)

of phosphate or phosphate losses. All patients in this study were enterally fed and prescribed an appropriate daily phosphate intake. Impaired phosphate absorption has been described with sucralfate or aluminium containing antacids. In our patient cohort, none received either sucralfate or aluminium containing antacids. Inadequate intake is therefore unlikely to have been a significant cause of hypophosphataemia in this patient group.

Intracellular redistribution is associated with the administration of parenteral nutrition, β adrenergic agonists and disease states including trauma and burns.² Alkalosis also has been reported to cause hypophosphataemia.¹ Two of our patients were receiving β adrenergic agonists. In critically ill neonates internal redistribution of phosphate has been demonstrated by measuring red cell adenosine triphosphate and 2,3-

diphosphoglycerate levels.¹³ Critically ill adults patients with severe plasma hypophosphataemia have low erythrocyte phosphate and ATP concentrations.¹⁴ This suggests that redistribution may not be as significant as phosphate loss in critically ill adults. In our study, we did not determine these concentrations and therefore cannot exclude redistribution as a cause of hypophosphataemia in this group of patients.

Phosphate loss occurs principally via the urine. This loss is due to either an increased phosphate excretion or a change in the renal phosphate threshold concentration. Carbonic anhydrase inhibitors have a potent phosphaturic effect.² In contrast, loop diuretics such as frusemide do not produce significant phosphaturia because they lack carbonic anhydrase activity.¹⁵ A number of drugs including theophylline and glucocorticoids reduce phosphate uptake in the proximal tubule. At the time of study one patient was receiving intravenous glucocorticoids. No patient received carbonic anhydrase inhibitors or theophylline. However, we demonstrated abnormal renal phosphate thresholds in all seven patients. All patients studied had low phosphate Tm/GFRs. These data suggest that inappropriate renal phosphate handling is a major contributor to hypophosphataemia in critically ill patients irrespective of the underlying diagnosis. In critically neonates with sepsis high urinary losses of phosphate have also been observed suggesting that the hypophosphataemia is partly due to inappropriate urinary loss.¹³

The adverse effects of hypophosphataemia are well known.^{1,2} Hypophosphataemia has been implicated in diaphragmatic dysfunction and failure to wean from mechanical ventilation. It also produces a left shift of the oxygen dissociation curve. Its effects on the cardiovascular system include reversible myocardial dysfunction, impaired responsiveness to vasopressor agents and ventricular tacharrhythmias. In addition to the effects on the respiratory and cardiovascular systems, hypophosphataemia has been associated with neuropathy, myopathy, and increased red cell fragility.^{9,16-18} A strong case exists for the rapid correction of serum phosphate concentrations in critically ill patients with diminished physiological reserve.

The potential adverse effects of high dose rapid phosphate repletion include hypotension, hypocalcaemia and renal failure.² In general, however, reports describing these adverse effects involve high infusion rates (greater than 50 mmol/hr).^{19,20} Due to these concerns, phosphate replacement regimens have traditionally been conservative.

The most widely quoted was that proposed by Vannatta *et al.*⁵ This regimen involved the administration of 0.32 mmol/kg over a 12-hour period.

For a 70 kg patient the infusion rate is less than 2 mmol/hr. Rosen *et al*,⁶ developed a more rapid protocol. In this study, 15 mmol of sodium phosphate was infused over 2 hours. In the eleven patients studied, no adverse events were reported. However, these investigators were unable to determine ionised calcium levels, relying on total calcium corrected for serum albumin, clinical signs of hypocalcaemia or ECG changes. Perreault *et al*,²¹ described the safety and efficacy of a three hour infusion of 15 - 30 mmol of phosphate. No serious adverse events were reported, but again ionised calcium was not reported. In our patient cohort we demonstrate that phosphate repletion at a rate of 14.5 mmol/hr was not associated with a reduction in ionised calcium concentration or creatinine clearance. Accordingly, we designed a phosphate replacement protocol for critically ill adult patients (Table 2) with a minimum infusion rate of 15 mmol/hr. The dose was calculated according to the median volume of distribution observed and a target serum phosphate concentration of 1 mmol/L.

Table 2. Phosphate infusion regimen

Serum phosphate concentration (mmol/L)	Dose
< 0.35	25 mmol
≥0.35 & < 0.5	20 mmol
≥0.5 & < 0.7	15 mmol

This rapid phosphate replacement protocol presented is complementary to, not a substitute for, the provision of maintenance phosphate either enterally or parenterally Charron *et al*,²² recently reported a series of 47 critically patients who received up to 15 mmol/hr of intravenous potassium phosphate. No adverse events were noted, in particular no reduction in ionised calcium was observed. In keeping with our study, phosphaturia was observed. Renal phosphate threshold concentrations were not evaluated.

Our study does have limitations. The small sample size reduces the generalisability of the data. Nevertheless, all patients in this heterogeneous group had a reduced renal phosphate threshold and high urinary phosphate losses. No complications of rapid phosphate replacement were observed. For example, hypocalcaemia, the complication most feared with rapid replacement protocols, was not demonstrated in any subject and no deterioration in renal function was observed. Clearly in only seven subjects the safety of this technique is not established. However, these preliminary data together with Charron's²² support the further evaluation of rapid phosphate replacement therapy.

Conclusion

We demonstrated that increased urinary phosphate loss secondary to a reduced renal phosphate threshold, as indicated by a reduced TMP/GFR, occurred in all patients regardless of the underlying pathology. Phosphate supplementation is therefore required to offset this loss. Our study suggests that in critically ill patients with hypophosphataemia, where excessive urinary losses of phosphate are a major contributing factor, the Vd of phosphate is approximately 0.5 L/kg. Phosphate ion infusions can be administered to critically ill patients at rates higher than previously recommended. This information provides a rational basis for rapid correction and subsequent prevention of hypophosphataemia in such patients

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