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Intravenous phosphate in the intensive care unit: More aggressive repletion regimens for moderate and severe hypophosphatemia

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Abstract *Objective:* To evaluate efficacy and safety of aggressive correction of hypophosphatemia with intravenous potassium phosphate in the ICU. *Design and setting:* Randomized interventional prospective study in the medical and surgical ICU of a tertiary university hospital. *Patients:* Critically ill patients with hypophosphatemia between June and November 1998. *Measurements and results:* Patients with moderate hypophosphatemia (<0.65 and >0.40 mmol/l; *n*=37) were randomized into two groups: group 1 received 30 mmol potassium phosphate intravenously in 50 ml saline over 2 h, and group 2 received 30 mmol potassium phosphate in 100 ml saline over 4 h. Patients with severe hypophosphatemia (<0.40 mmol/l; *n*=10) were also randomized into two groups: group 3 received 45 mmol potassium phosphate intravenously in 100 ml saline over 3 h, and group 4 received 45 mmol potassium phosphate in 100 ml saline over 6 h. Electrolytes, blood gas, renal function were monitored until day 3; urine was collected during and until 6 h after infusions. The overall efficacy of the protocols was 98% by the end of the infusion. There was no statistical difference in phosphate values between groups at the end of infusion or at 24 h. No adverse events were noted; one patient had an increase in serum potassium to 6.1 mmol/l. Phosphaturia in all groups was elevated as evidenced by fractional excretion above 20%. *Conclusions:* More rapid administration of large potassium phosphate boluses is effective and safe for correcting hypophosphatemia in ICU patients with preserved renal function if baseline serum potassium is below 4 mmol/l.

Keywords Phosphorus · Infusion · Critical illness · Phosphaturia · Treatment

Introduction

Hypophosphatemia is a common problem in the ICU, classified as moderate (0.32–0.65 mmol/l) or severe (<0.32 mmol/l). The incidence of moderate hypophosphatemia in hospitalized patients is 2.8% but is much higher in ICU patients, ranging between 8.8% and 80% [1, 2, 3, 4]. This probably reflects the fact that critically ill patients present several conditions predisposing to hypophosphatemia (e.g., malnutrition and refeeding, parenteral nutrition, catecholamines, insulin, β-adrenergic receptor agonists, diuretics, phosphate binders, alkalosis, diabetic ketoacidosis, sepsis) [5, 6]. Phosphate has many physiological functions vital to the cell [1, 5, 7]. Phosphate is the source of adenosine triphosphate which fuels cell functioning and controls the level of 2,3-diphosphoglycerate present in red blood cells. This is of particular relevance to ICU patients since depletion can lead to tissue dysfunction and hypoxia. Hypophosphatemia decreases the 2,3-diphosphoglycerate level in red blood cells, shifting to the left the oxygen dissociation curve and thereby increasing the affinity of hemoglobin for

oxygen and reducing oxygen delivery to tissue. Since early goal-directed therapy in sepsis seems to decrease mortality by improving tissue oxygenation [8], it appears logical to rapidly correct hypophosphatemia.

Clinical manifestations of hypophosphatemia reflect its importance in the body homeostasis: ventilatory muscle weakness, cardiac failure, arrhythmia, vasodilation, rhabdomyolysis, paresthesia, motor neuropathy, ataxia, hallucination, seizure, hemolysis, and insulin resistance [1, 5, 7, 9, 10, 11, 12, 13, 14, 15]. Correction of hypophosphatemia has been shown to reverse these alterations [1, 5, 13, 16, 17, 18].

Since Lentz et al. [19] first established the theoretical concept of phosphate repletion, many different intravenous protocols have been evaluated [20, 21, 22, 23, 24, 25, 26]. Because of fear of adverse reactions (hypocalcemia, hyperkalemia, arrhythmia, calcium deposition in tissues, renal insufficiency) such protocols typically use small amounts of phosphate and/or infuse them over long periods of time (from 4 to 12 h). More aggressive protocols have been used without adverse effects but the numbers of patients treated were small and the studies were not designed to evaluate safety and efficacy [13, 17]. Adverse reactions to treatment of hypophosphatemia have been reported mainly with overzealous repletion [27]. Faster repletion has the theoretical advantage of rapidly improving physiological disturbances (as discussed above) and from a practical point of view frees intravenous access to administer other drugs (since phosphate is incompatible with most of them).

It has been routine practice in our ICUs to infuse phosphate rapidly, and we have encountered no adverse effects. We therefore wanted to standardize our protocol and formally evaluate its efficacy and safety. Furthermore, to understand the pharmacokinetics of phosphate after rapid administration we measured the rate of excretion of phosphate in urine.

Materials and methods

Between June 1998 and November 1998, 47 critically ill patients admitted to the medical and surgical ICU presenting hypophosphatemia on daily laboratory tests were randomized into four groups of intravenous phosphate repletion. Diagnoses at admission included neurological disorders including meningitis, ischemic events, subarachnoid hemorrhage, hematoma, seizure, Guillain-Barré syndrome, and myasthenia gravis (n=18), respiratory failure from chronic obstructive pulmonary disease or pneumonia (n=9), digestive including upper gastrointestinal bleeding, pancreatitis, peritonitis, and abdominal surgery (n=9), aortic aneurysmal repair (n=4), sepsis (n=2), trauma (n=1), diabetic ketoacidosis (n=1), bone marrow transplant (n=1), acute leucemia (n=1) and cardiogenic shock (n=1). Patients were categorized according to the severity of hypophosphatemia: moderate (<0.65 mmol/l) or severe (<0.40 mmol/l). The normal values of phosphatemia at our institution range from 0.8 to 1.6 mmol/l (to convert millimoles/liter to milligrams/deciliter, divide by 0.323). This prospective clinical trial was approved by our institutional review board, and the need for informed consent was waived. Patients were excluded if they had significant renal insufficiency either acute or chronic (defined by serum creatinine >200 μmol/l), massive cellular lysis with potential release of phosphate and potassium (tumor lysis syndrome, severe rhabdomyolysis, intravascular hemolysis), hypercalcemia (total calcium corrected for albumin >2.6 mmol/l), hypocalcemia (corrected value of <1.9 mmol/l), a phosphocalcic product higher than 4.5 $mmol^2/l^2$ (>55 mg^2/dl^2), or a serum potassium above 4.5 mmol/l. None of the patients had a condition that could cause excess phosphate excretion (amyloidosis, cystinosis, Fanconi's syndrome, multiple myeloma, hyperparathyroidism, Wilson's disease, lead or cadmiun intoxication). Note that our surgical ICU does not admit cardiac surgery patients. During the study period six patients were excluded (four because of renal insufficiency and two because of potassium above 4.5 mmol/l).

Patients with moderate hypophosphatemia (<0.65 mmol/l) were subdivided into two groups. Group 1 (n=19) received intravenously 30 mmol potassium phosphate (containing 3 mmol/ml phosphate and 4.4 mmol/ml potassium; Sabex, Boucherville, Canada) in 50 ml NaCl 0.9% over 2 h. Group 2 (n=18) received intravenously 30 mmol potassium phosphate in 100 ml NaCl 0.9% over 4 h. Patients with severe hypophosphatemia (<0.4 mmol/l) were also subdivided into two groups. Group 3 (n=5) received intravenously 45 mmol potassium phosphate in 100 ml NaCl 0.9% over 3 h. Group 4 (n=5) received intravenously 45 mmol potassium phosphate in 100 ml NaCl 0.9% over 6 h. Phosphate was preferentially administered through a central line but this was not mandatory. Additional supplementation of phosphate was not included in the protocol and was left at the discretion of the caring physician. It was not administered during the first 24 h and usually consisted either of a repeated protocol dose depending on serum phosphate concentration or of oral Phosphosoda (C.B. Fleet, Lynchburg, Va., USA).

Major modifications in drug administration or nutrition were avoided during infusions and for a period of time extending from 6 h before and after infusions. No diuretics were administered during this period. Nutritional support was prescribed by the attending physician and contained a standard amount of phosphate (10–15 mmol/l for parenteral nutrition and 20–25 mmol/l for enteral nutrition); this support was instituted as soon as the medical condition would allow it, as in routine care.

Data on demographics, need for mechanical ventilation, and survival were recorded. Table 1 shows baseline characteristics for patients in the four groups. There is no statistical difference at baseline between groups except for ionized calcium (lower in group 1 than in group 2 and lower in group 4 than in 3). Also, patients in group 4 tended to be smaller than those in the other groups (lower body mass index) and to receive fewer steroids. The Acute Physiology and Chronic Health Evaluation II score was calculated. Baseline (i.e., immediately before infusion) phosphate, calcium, albumin, potassium, urea, creatinine, and glucose serum concentration were measured hourly during potassium phosphate administration and daily for 3 days thereafter. Blood gas were drawn at time zero and daily afterward. Urine was collected for analysis (urea, creatinine, phosphate, and volume) from the beginning of infusion until 6 h after it was completed. Excretion fraction of phosphate ($FePO_4$, in percentage) was calculated as follows: $FePO_4$=(urinary PO_4/serum PO_4)/(urinary creatinine/serum creatinine). Patients were monitored for adverse reactions with standard ICU equipment and nursing surveillance particularly during and shortly after infusion. The overall mortality rate was 27%: 37% in group 1, 17% in group 2, 60% in group 3, and 0% in group 4.

Data are presented as mean ±SD. Comparison of baseline characteristics was performed using an unpaired Student's t test. Serological data before and after administration were compared using Student's paired t test. A p value less than 0.05 was considered significant.

Table 1 Patients baseline characteristics (*APACHE II* Acute Physiology and Chronic Health Evaluation II)

	Group 1	Group 2	Group 3	Group 4
Number	19	18	5	5
Age (years)	64±15	60±10	54±25	49±13
Sex: M/F	13/6	9/9	2/3	2/3
APACHE II	19.6±11.2	18.3±9.7	19±6.6	11±6.3
Weight (kg)	66.7±11.4	71.3±18.4	73.2±15.9	60±22.7
Height (cm)	163.4±8.0	167.4±6.5	163.2±9.4	163.8±7.8
Body mass index	24.2±3.7	25.4±6.5	28±8.8	22.4±8.5
Nutrition (yes/no)	15/4	14/4	4/1	4/1
Mechanical ventilation (%)	58	78	60	80
Steroid (% of patients)	42	44	40	20
Insulin (% of patients)	16	39	40	40
Baseline values				
pH	7.42±0.07	7.43±0.04	7.39±0.11	7.44±0.08
pCO_2	40.4±11.7	38.6±9.8	39.0±14.6	32.5±3.5
HCO_3^- (mmol/l)	25.4±5.7	25.0±4.4	22.6±5.7	22.9±6.4
Glucose (mmol/l)	9.0±2.7	8.6±2.7	8.2±1.8	8.1±4.4
Serum creatine (µmol/l)[a]	89±44	90±46	88±20	63±24
PO_4(mmol/l)[b]	0.58±0.13	0.56±0.12	0.38±0.03	0.31±0.10
K (mmol/l)	3.8±0.5	3.8±0.4	3.9±1.2	3.6±0.4
Total Ca (mmol/l)[c]	1.89±0.19	2.00±0.17	2.01±0.11	1.84±0.14
Ca^{2+}(mmol/l)	1.23±0.09	1.28±0.05	1.26±0.08	1.20±0.14
$PO_4 \times Ca$ ($mmol^2/l^2$)	1.08±0.21	1.12±0.25	0.76±0.08	0.56±0.17

[a] Normal creatinine level <120 µmol/l
[b] To convert phosphate from millimoles/liter to milligrams/deciliter divide by 0.323
[c] Corrected for albumin; to convert calcium from millimoles/liter to milligrams/deciliter divide by 0.25

Table 2 Electrolyte concentrations (mmol/l) during potassium phosphate infusion in the four study groups

	0 h	1 h	2 h	3 h	4 h	5 h	6 h	24 h[d]	48 h	72 h
Phosphate[a]										
Group 1	0.58±0.13	0.9±0.26	1.28±0.33[e]	–	–	–	–	0.86±0.22	0.93±0.28	1.19±0.45
Group 2	0.56±0.12	0.76±0.17	0.97±0.19*	1.09±0.25	1.20±0.32[e]	–	–	0.89±0.24	0.80±0.22	0.95±0.31
Group 3	0.38±0.03	0.79±0.49	1.27±0.39	1.32±0.32[e]	–	–	–	0.83±0.24	0.79±0.27	0.91±0.25
Group 4	0.31±0.10	0.44±0.27	0.61±0.27**	0.77±0.34**	0.97±0.39	1.07±0.35	1.07±0.2[e]	0.61±0.22	0.72±0.31	0.86±0.31
Potassium[b]										
Group 1	3.85±0.53	4.18±0.51	4.56±0.61[e]	–	–	–	–	4.00±0.59	3.94±0.62	4.23±0.89
Group 2	3.83±0.40	4.03±0.45	4.15±0.45*	4.23±1.12	4.39±0.32[e]	–	–	3.94±0.50	4.02±0.58	4.06±0.47
Group 3	3.92±1.16	4.18±1.31	4.78±1.31	4.88±1.12[e]	–	–	–	4.40±0.64	4.28±0.75	4.45±1.04
Group 4	3.58±0.38	3.68±0.51	3.68±0.28	3.78±0.11	3.90±0.20	3.96±0.29	4.05±0.26[e]	3.84±0.51	3.96±0.92	3.90±0.73
Ionized Ca[c]										
Group 1	1.23±0.09	1.22±0.10	1.20±0.09[e]	–	–	–	–			
Group 2	1.28±0.05	1.26±0.06	1.25±0.06	1.26±0.06	1.26±0.06[e]	–	–			
Group 3	1.26±0.07	1.24±0.05	1.22±0.03	1.21±0.04[e]	–	–	–			
Group 4	1.20±0.14	120±0.09	1.21±0.09	1.20±0.08	1.18±0.07	1.18±0.05	1.19±0.06[e]			

*$p \leq 0.05$ vs. group 1, **$p \leq 0.05$ vs. group 3
[a] Normal range: 0.8–1.6 mmol/l
[b] Normal range: 3.5–5.0 mmol/l
[c] Normal range: 1.15–1.37 mmol/l
[d] No statistical difference between end of infusion and at 24 h or between groups 1 and 2 or between groups 3 and 4 at 24 h
[e] No statistical difference at end of infusion between groups 1 and 2 or between groups 3 and 4

Results

Table 2 shows phosphate, potassium, and ionized calcium values throughout the study period. By the end of infusion every patient except one (in group 2) had a phosphate value above 0.65 mmol/l (98% efficacy by the end of the infusion). There was no statistical difference between groups at the end of infusions. Groups 1 and 3 had faster repletion than groups 2 and 4, respectively. Phosphate levels had decreased in every group at 24 h, but the differences were not statistically significant and remained in the normal range except in group 4. At 24 h ten patients (21%) required additional phosphate repletion since their phosphate levels were below

Table 3 Urinary elimination of phosphate ($FePO_4$ fractional excretion of phosphate)

	Group 1	Group 2	Group 3	Group 4
PO_4, urinary (mmol/vol)	11.26±6.51	12.47±7.50	18.62±1.46	6.89±4.29*
PO_4, urinary (mmol/l)	17.70±17.65	12.03±8.38	24.07±9.37	4.68±3.79*
$FePO_4$ (%)	46±18	36±29	54±31	22±26

*$p<0.01$ vs. group 3

0.65 mmol/l. Over the entire study period 13 patients (28%) required additional phosphate supplementation (mean 41 mmol, range 30–90 mmol). Theses patients were distributed among the four different groups. A delay between time of randomization (daily laboratory value) and baseline blood tests was sometimes observed; by the beginning of infusion five patients in group 1, three in group 2, one in group 3, and one in group 4 (21%) had phosphate levels above 0.65 mmol/l or 0.4 mmol/l at the beginning of infusion. Potassium increased in each group by the end of infusion (no statistically significant difference) as we administered potassium phosphate (44 and 66 mEq of potassium in groups 1 and 2 and groups 3 and 4, respectively); potassium serum concentration was also diminished by 24 h. There was no significant variation in serum ionized calcium during infusion. At 24, 48, and 72 h only total calcium was measured; no hypocalcemia was ever noted.

No adverse reaction was observed during infusion although phosphate and potassium values above normal limits were encountered. Two patients in group 1, two in group 2, and one in group 3 had phosphate values above 1.6 mmol/l during treatment (2.1, 1.8, 1.96, 1.67, 1.71 mmol/l, respectively). Patients in groups 1 and 2 had normal values by 24 h and by the end of infusion; the level in the group 3 patient was back to normal. Four patients in group 1, one in group 2, and three in group 3 had transient potassium values above 5.0 mmol/l but below 5.4 mmol/l during infusion. Six of these had a baseline potassium level higher than 4.0 mmol/l. The single maximum potassium value recorded was 6.1 mmol/l (group 3). One value was corrected by the end of infusion (group 3), six were normal at 24 h, and one remained marginally elevated until the end of the observation period (group 1).

Duration of urine collection varied according to the group of randomization as defined by protocol: 8, 10, 9, and 12 h in groups 1–4, respectively. Phosphaturia was observed in every group albeit to a lesser degree in group 4 (Table 3). Fractional excretion of phosphate ($FePO_4$ in %) was elevated above 20% in each group. Although there is no statistical difference between groups, there is a trend toward an increase $FePO_4$ in the groups with shorter infusion time (groups 1 and 3). $FePO_4$ was below 20% in one patient in group 1, five in group 2, and one in group 3.

Discussion

This study shows that intravenous potassium phosphate administered rapidly (30 mmol in 2 or 4 h or 45 mmol in 3 or 6 h) to ICU patients with diverse pathological conditions and no significant renal insufficiency (creatinine <200 μmol/l) is a safe and effective treatment for correcting moderate and severe hypophosphatemia. Protocols used in this study have a 98% efficacy in correcting hypophosphatemia by the end of infusion. Furthermore, an inappropriate phosphaturia for the level of hypophosphatemia was found in our ICU patients, at least during and shortly after the infusion of phosphate.

There are theoretical and practical advantages to rapidly correct hypophosphatemia in ICU patients. Respiratory muscle strength, cardiac index, peripheral resistance, oxygen delivery to tissues, and insulin resistance are all improved with phosphate repletion [1, 5, 13, 16, 17, 18]. In ICU patients in whom tissue damage and hypoxia are the rule, reestablishing a normal physiology as soon as possible is probably desirable [8] and phosphate is a major component of normal cell functioning [1, 5, 7]. Various protocols for phosphate repletion have been studied since the late 1970s, and there is an obvious trend towards the use of larger and faster boluses of phosphate because of high failure of repletion (20–70%) and need for additional phosphate administration [19, 20, 21, 22, 23, 24, 25, 26]. Usually 15–30 mmol phosphate is infused over 3–12 h. A bolus larger than 30 mmol is infused over 8–12 h. Authors usually agree that larger amounts of phosphate are needed to correct total body deficit [19, 23, 24, 26], but their fear of adverse reactions has prompted a prudent attitude. Recent studies on ICU patients have used substantial boluses (20 mmol in 1 h, 0.8 mmol/kg in 30 min) without adverse reaction and suggest that ICU patients tolerate well such repletion [13, 17]. Unfortunately, these studies were not designed to assess safety and efficacy of phosphate repletion. Our results confirm that relatively rapid infusion of potassium phosphate is safe if baseline serum potassium is below 4.0 or even 4.5 mmol/l and ensures adequate correction of hypophosphatemia. Phosphatemia was corrected 98% of the time by the end of infusion, and the need for resupplementation over the entire study period was 28%, a rate lower than previously reported [20, 21, 24].

The amount of phosphate required to correct total body deficit is quite variable depending on the cause of hypophosphatemia and the chronicity of the process [5,

7, 19]. Malnourished alcoholic patients have a larger deficit due to long-standing negative phosphate balance. In ICU patients many physiological derangements may explain the need for larger amounts required for repletion. A state of malnutrition sufficient to induce a refeeding syndrome has been described after only 48 h of fasting in the ICU [6]. The volume of distribution of phosphate might be increased [19], while insulin, carbohydrate, and catecholamine administration act to decrease serum phosphate concentration [1, 5, 6, 7].

Phosphaturia is increased by mechanical ventilation [3], corticosteroid administration [1], alkalosis [28], hypoxia [29], excessive diuresis [30], and renal dysfunction [31], all of which can be encountered at the same time in a single ICU patient. Our study confirms that renal phosphate excretion is enhanced, as demonstrated by the high $FePO_4$ and the amount of phosphate present in the urine (6.89–18.62 mmol). Renal phosphate reabsorbtion is normally rapidly increased during hypophosphatemia by activation of the sodium/phosphate cotransporter at the proximal tubule level so that phosphate excretion is virtually zero [31, 32]. In addition to the causes of phosphaturia mentioned above, normal renal excretion of a rapid and large amount of infused phosphate cannot by ruled out in our study population since collection of urine was carried out during and immediately after the administration of phosphate. Such an enhanced phosphaturia has been observed by others [20, 25, 30, 33]. Phosphaturia in group 4 was significantly lower than that in the other groups ($FePO_4$=22%). This may be due to the fact that pCO_2 was lower in that group, that they received less steroid (which decreases renal reabsorbtion), and that serum phosphate was relatively lower than in the other groups during urine collection (not statistically significant). This being said, $FePO_4$ in group 4 was also abnormally elevated. Thus ICU patients with preserved renal function seem to be protected against a phosphate overload by an enhanced renal loss.

In fact only five patients (10%) had elevated serum phosphate during or at the end of infusion. The levels were marginally elevated without physiological consequences (arrhythmia, hypocalcemia, renal insufficiency). Furthermore, by 24 h phosphatemia was back to normal in every patient, emphasizing the contribution of redistribution, phosphate deficit, and/or phosphaturia to phosphate homeostasis in the ICU. The other major concern about potassium phosphate infusion is potassium overload. We observed mild hyperkalemia in eight patients (17%) without detrimental consequences. This complication can easily be avoided by administering sodium phosphate or restricting potassium phosphate to patients with normal renal function, good diuresis, and serum potassium below 4 mmol/l. Potassium phosphate was used in this study because of hospital policy and cost. Phosphate was normalized in ten patients even before the beginning of infusion. This stresses the fact that phosphate measurement is subject to variation during the day, and that redistribution plays an important role in the regulation of phosphatemia. Nevertheless, the physician caring for an ICU patient with hypophosphatemia must decide about treatment without having to routinely control an abnormal laboratory value. This would be time consuming and lead to delay in treatment and excessive cost. The fact that no adverse reaction happened even with supplementation of normal phosphate values is reassuring about the safety of protocols used in the present study.

This study is limited by the fact that the population was highly heterogeneous, relatively small, and reflective of a single center, and that treatment, medication administered, and general care were not standardized. We nonetheless believe that our protocol could be used in a wide variety of patients. Results about urinary excretion of phosphate must be placed in perspective since urine collection was limited in time, and since baseline value of phosphaturia was not measured. Phosphaturia could have been influenced by concomitant infusion of phosphate. Our study was not designed to assess patients' morbidity, mortality, or length of stay in the ICU, and no conclusions in that regard can be drawn.

In summary, ICU patients are prone to hypophosphatemia which can lead to several physiological alterations in cell function. These potential deleterious effects are reversed by phosphate supplementation. Rapid correction of phosphate deficit, as demonstrated here, appears safe. To prevent additional insult to tissues from phosphate deficit and because phosphate infusion is incompatible with many other medications we suggest infusing phosphate in the following manner: 30 mmol potassium phosphate over 2 h or 45 mmol over 3 h in patients with a baseline serum potassium below 4.0 mmol/l and creatinine below 200 μmol/l. Slower protocols (i.e., 30 mmol potassium phosphate over 4 h or 45 mmol over 6 h) or sodium phosphate (which is more expensive) are as efficacious and should be favored if kalemia is a concern.

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