Title
Preventing/treating Hypophosphatemia by Adding Phosphate to the Dialysate

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LETTER TO THE EDITOR

Preventing/treating hypophosphatemia by adding phosphate to the dialysate

Dear Editor,

Unlike potassium, calcium, magnesium, bicarbonate and chloride, there is normally no phosphorus in conventional hemodialysates. The reason is that not only are phosphates retained in renal failure, conventional therapy (3-4 hours of dialysis for each treatment, 3 treatments per week) is not efficient enough in removing phosphates from the body. It is well known that inorganic serum phosphates exist mainly in 2 moieties, namely, $H_2PO_4^{1-}$ (MW 97) and HPO_4^{2-} (MW 96) (1, 2). These entities are readily dialyzable, bringing about a reasonably low, immediate postdialysis serum phosphorus level. However, since (a) the total amount of phosphates present in the blood is small when compared to that in the total body store and (b) it takes a relatively long time for the intracellular phosphate store to liberate its kept phosphates, the amount of phosphates removed by conventional dialysis is not substantial enough to counterbalance the amount ingested. As a result, hyperphosphatemia is often a cardinal sign of patients maintained on conventional dialysis (3-7).

However, with vigorous dialysis or in the face of low body phosphate stores, dialysis-induced hypophosphatemia may develop in certain patients. These patients include daily dialysis patients, pregnant dialysis patients and patients who, in common with pregnant dialysis patients, also require aggressive dialysis treatments, such as those with hypercatabolism and those suffering from severe poisonings, e.g., due to ethylene glycol, methyl alcohol or lithium (8-14). At times, patients with preexisting hypophosphatemia may require dialysis treatments. Dialysis in these patients will certainly worsen the initial hypophosphatemia. Hypophosphatemia may lead to many untoward consequences. Phosphorus is crucial in the cell's energy metabolism and low phosphorus levels may in general lower acutely sick patients' ability to recover from critical illness (for example patients recovering from cardiac surgery). In addition hypophosphatemia has been shown to lead to rhabdomyolysis. In the past, the treatment of hypophosphatemia occurring in both dialysis and nondialysis patients, has mainly been centered on: (a) the ingestion of phosphorus-rich foods or (b) the administration of oral or intravenous phosphate preparations. The problem, with the above phosphate supplementation methods is the fact that undertreatments and overtreatments are hard to avoid (15). Undertreatment is not ideal. Overtreatment may lead to the myriad undesirable complications of hyperphosphatemia.

In patients who need hemodialysis treatments, in order to prevent or treat hypophosphatemia, we have previously used phosphorus-enriched dialysates on an acute, very short-term basis (10-14). Such dialysates were created by adding an amount of phosphorus (e.g., 4 mg/dL [1.3 mmol/L] in the final dialysate) in the form of Fleet® Enema or Phospho-soda buffered saline laxative preparations (C.B. Fleet Company) to a conventional dialysate. The problem with these special Fleet® product-containing dialysates is that they often contain ingredients other than phosphate salts in the form of preservatives. For example, proprietary phosphate preparations may contain preservatives such as bezalkonium chloride, disodium ethylene diamine tetra-acetic acid (EDTA), sodium benzoate or other products. It is conceivable that such preservatives might pose substantial problems since, for example, hypersensitivity reactions secondary to exposure to sodium benzoate have been described in other settings (5). With respect to the use of a phosphorus-enriched dialysate, it is of note that should the dialysate phosphorus level (e.g., 4 mg/dL [1.3 mmol/L]) be higher than the initial predialysis serum level (e.g., 1 mg/dL [0.32 mmol/L]), with other things being equal, the postdialysis serum level, will not be greater than the dialysate value (8-14).

In vitro experiments have shown that one can introduce powder phosphate salts to either the acid or the base concentrate of a dual concentrate, bicarbonate-based dialysate delivery system (16-18). It is possible to use either: (a) a combination of monosodium dihydrogen phosphate monohydrate and disodium monohydrogen phosphate heptahydrate (16) or (b) monosodium dihydrogen phosphate monohydrate or disodium monohydrogen phosphate heptahydrate alone for the dialysate enrichment (17, 18). After the introduction of the above powder phosphate salts, vigorous shaking of the modified final dialysate concentrate is required to dissolve the added salts.

Finally, one can use parenteral (necessarily pure) forms of phosphate salts (more likely to be sodium-based than potassium-based) to enrich a dialysate. Hussain et al described 2 pregnant patients who developed hypophosphatemia while receiving aggressive dialysis treatments (9). United States Pharmacopeial (USP)-grade sodium phosphate injections (Abbott Laboratories) were used for the phosphate addition to a bicarbonate dialysate concentrate. Both patients were able to maintain normal serum phosphorus concentrations after using the phosphorus-enriched dialysate throughout their pregnancies.

In recent years both Gambro and Fresenius have developed phosphorus-containing dialysates and replacement fluid products for continuous renal replacement therapy (CRRT) (19). Clearly these products are ideal for preventing hypophosphatemia in the critically ill patients undergoing CRRT in the intensive care unit. The phosphorus concentration of these products is 3.6 mg/dL (1.2 mmol/L). At this time these products are not widely available, at least not in the United States. Also, as far as we know, there is no premade phosphorus-containing dialysates for use in intermittent hemodialysis.

We discourage the use of impure proprietary phosphate-containing products that contain undesirable preservatives and/or other substances for the purpose of preparing phosphorus-enriched dialysates. Ideally, one should use pure phosphate products that are geared specifically for the purpose of dialysate enrichment and are free from harmful additives. However, such nonparenteral phosphate preparations are not commercially available at present. In the mean time, in order to prevent or treat hypophosphatemia occurring during dialysis, the following options are available:

1. Increase phosphate intake (in the form of phosphate salt medications and/or phosphate-rich foods): hard to regulate serum phosphorus level with precision; overtreatment or undertreatment common.

2. Enrich dialysate yourself with pure USP-grade powder sodium phosphate salts: this is challenging but it can be done.
3. Enrich dialysate with parenteral preparations of sodium phosphate salts: this is the best approach for the present; the only disadvantage is the expense of the preparations involved.

The following example illustrates the calculations used in enriching a dialysate with phosphorus. For instance, if a final dialysate phosphorus concentration of 2 mg/dL (0.65 mmol/L) is desired, then 36.7 mL of the above-described (Abbott Laboratories) parenteral sodium phosphate preparation will be needed for addition to a gallon of a 45X acid concentrate (i.e., the acid concentrate employed in a bicarbonate-based dialysate generating system using the ratio of "acid concentrate: bicarbonate concentrate : water = 1 : 1.72 : 42.28") (20). One gallon (3.79 L) would generate 170.6 L of final dialysate (3.79L × 45 = 170.6 L). For a final dialysate phosphorus concentration of 2 mg/dL (20 mg/L), one would need to add 3,411 mg of phosphorus (170.6 × 20 mg = 3,411 mg). Since each milliliter of the parenteral phosphate preparation contains 93 mg of elemental phosphorus, dividing 3,411 mg by 93 mg will give us 36.7 mL of the preparation that would be necessary to add to a gallon of the above acid concentrate.

Under certain clinical circumstances, there is indeed a need for a nephrologist to employ a phosphorus-enriched dialysate. In the mean time, it is fervently hoped that some dialysis product manufacturers will take up the challenge of making pure, high-grade phosphorus-enriched dialysates that are free from harmful extraneous substances.

In conclusion, we would like to caution against adding phosphorus to the dialysate using impure proprietary phosphate preparations as they might contain undesirable ingredients which may have adverse consequences. Rather we would like to encourage using pure powder phosphate formulations or injectable forms for dialysate phosphate enrichment.

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