

Phosphate induced crystal acute kidney injury – an under-recognized cause of acute kidney injury potentially leading to chronic kidney disease: case report and review of the literature

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Abstract: Acute phosphate nephropathy or nephrocalcinosis is a tubulointerstitial nephropathy characterized by tubular calcium phosphate deposition – crystal nephropathy – and slowly progressive renal insufficiency during or following treatment with preparations containing sodium phosphate. We report a patient who developed nephrocalcinosis (crystal induced acute kidney injury) following the administration of a combination of oral and rectal sodium phosphate for treatment of postoperative constipation. A timely renal replacement therapy procedure may reverse the process of crystallization and the irreversible slope towards chronic dialysis.

Keywords: hemofiltration, acute phosphate nephropathy, hyperphosphatemia, crystal induced nephropathy, CRRT, worse prognosis, dialysis

Introduction

Crystal induced acute kidney injury (C-AKI) is a recent cause of acute kidney injury (AKI) in intensive care units (ICUs). Indeed, cholesterol embolism, oxalate, uric acid, phosphate, and many medications (sulfadiazine, acyclovir, indinavir, triamterene, methotrexate, orlistat, oral sodium phosphate preparation, and ciprofloxacin) can cause C-AKI.¹ Crystallization will vary for each individual condition as the urinary pH necessary for precipitation is extremely different from one condition to another and therefore urine alkalization may be very detrimental. For instance, for ciprofloxacin crystallization tends to occur at an alkaline pH in the tubules, therefore urine alkalization can surely not be recommended.³ Some intoxication, such as ethylene glycol poisoning, can also cause C-AKI.² C-AKI can also occur with myeloma.³

Sodium phosphate solutions are commonly used to cleanse the bowel in preparation for colonoscopy or surgical procedures and eventually for treatment of severe constipation. Though relatively safe, these drugs must be used with caution in the elderly and in patients with renal dysfunction, small intestinal disorders, or poor gut motility and are prohibited in bowel obstruction. Postoperative patients do represent a group at risk.

Acute phosphate nephropathy due to the use of agents containing sodium phosphate is a rare, but potentially life-threatening condition. Unfamiliarity with this complication in ICUs, the time gap between drug administration and onset of AKI, and the lack of monitoring of renal function during treatment all explain why this diagnosis is easily overlooked.

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Case report

A 71-year-old man was admitted to the ICU after heart surgery. His previous history was unremarkable except for adequately controlled arterial hypertension and dyslipidemia. The surgical procedure was complicated by a left atrium tear necessitating aggressive postoperative fluid loading and dobutamine infusion to maintain perfusion pressure.

After an initially uneventful evolution, the patient developed pneumonia, rapidly evolving to septic shock complicated by severe cardiac and respiratory failure. Mechanical ventilation was initiated under continuous analgesic sedation. Treatment with fluids, catecholamines, and antibiotics was started under invasive hemodynamic monitoring. At that time, renal function was normal. Hemodynamic stability was restored and the patient could be progressively weaned from ventilation and supportive medication. Since he passed no stools for more than a week, rectal enemas (Fleet Enema®; CB Fleet Company, Inc, Lynchburg, VA, USA) were repeatedly administered. They had only minimal effect and an oral laxative (Fleet Oros®; CB Fleet Company, Inc) was added 8 hours later. Less than 12 hours later, the patient suddenly developed an acute rise in creatinine and urea levels and became anuric. The patient was started on a small dose of angiotensin converting enzyme (ACE) inhibitors 7 days prior to the acute rise of phosphate. The patient did not receive diuretics, any other antihypertensive drugs, or angiotensin II (AT-II) receptor blockers during this period before the sudden rise in phosphate. Blood analysis revealed phosphorus and calcium levels of 21 mg/dL and 4.6 mg/dL, respectively.

Treatment procedure

Initially, the patient was put under high flow hemodialysis in order to quickly reduce the phosphate value and indeed, the phosphate went down from 21 mg/dL to 7.1 mg/dL.

Because of the hemodynamic instability, the patient was switched over to continuous venovenous hemofiltration at 35 mL/kg/hour in order to avoid a rebound of hyperphosphatemia and ensure hemodynamic stability while continuing extrarenal blood purification of the hyperphosphatemia. After correction of electrolyte imbalance, the patient left the ICU in good condition, though still needing intermittent renal replacement therapy for persisting anuria.

After a follow-up at 6 months, we should be able to confirm his chronic kidney disease (CKD) status in regards to dialysis.

Discussion

The amount of phosphorus in the blood is determined by oral intake and renal excretion. Approximately 60% to 65%

of dietary phosphate is absorbed in the upper duodenum, jejunum, and ileum either passively or by active transport mediated by vitamin D. Renal elimination of phosphorus depends on the filtered load and the renal threshold. Even a slight increase of phosphatemia in response to an increased phosphate load results in a reduction of proximal tubular phosphate reabsorption. Excess phosphate induces hypocalcemia by precipitating calcium, decreasing calcium absorption from the gastrointestinal tract and lowering of 1,25-dehydroxycholecalciferol synthesis, and produces sodium phosphate complex formation in the serum. The decline in ionized calcium serum concentration triggers the release of parathyroid hormone (PTH) which further reduces phosphate renal reabsorption.⁴ The cathartic action of sodium phosphate, a small volume laxative, results essentially from its osmotic properties, drawing plasma water into the gastrointestinal tract. Sodium phosphate-based enemas are commonly used for bowel cleansing or treatment of “stubborn” constipation. Sodium phosphate mainly induces a marked and transient increase in serum phosphorus, sodium, and chloride levels whilst simultaneously decreasing serum calcium and potassium concentrations. Hyperphosphatemia associated with administration of preparations containing phosphate may result from excessive and/or repeated doses, increased intestinal absorption, or impaired renal excretion. Intestinal absorption is facilitated by impaired gut peristalsis prolonging retention of these substances in the gut lumen.⁵ When the urine is oversaturated and buffering factors such as pH, citrate, and pyrophosphate are overwhelmed, renal phosphorus excretion becomes compromised and crystallization will occur. Tubular damage produced by the release of reactive oxygen species when calcium phosphate crystals bind to tubular epithelial cells is the presumed main pathway leading to impaired renal excretion.⁶ Risk factors for developing C-AKI include female gender, CKD, dehydration, diuretic treatment, colitis, and, to a lesser extent, diabetes mellitus and the use of specific drugs such as nonsteroidal anti-inflammatory agents, ACE inhibitors, and AT-II receptor blockers. Urine alkalization may also be a trigger in some specific conditions such as ciproxin induced C-AKI.¹

Elderly patients are at particular risk for phosphate intoxication. They are more sedentary, have lower fluid intake, have intrinsically less bowel movements, often take medications that decrease or influence gut motility, and suffer more underlying systemic and gastrointestinal diseases that incapacitate intestinal function. Moreover, an age-related decline in renal function is frequently present.⁷

Many concomitant factors played a role in the development of acute hyperphosphatemia in our patient. First, an already inefficient gut peristalsis in this elderly patient became more impaired during a turbulent postoperative phase characterized by severe hemodynamic, respiratory, and metabolic derangement. Elderly age in association with concurrent medication known to diminish gastrointestinal tract motility (sedation, analgesics, and catecholamines), resulted in colonic retention and subsequent increased absorption of phosphorus. Second, the pharmacological efforts to combat constipation obviously culminated in a too excessive phosphate load. Indeed, normal daily dietary phosphorus intake is approximately 1.5 g whereas one Fleet enema contains 8.533 g. Such high amounts will produce an almost 100% rise in serum phosphate concentration.⁸ Finally, renal dysfunction that may have been induced or worsened by phosphate intoxication in se, prevented excretion of redundant phosphate. The diagnosis is pending on excluding other causes, but also on the urine microscopy that can identify crystallization. Unfortunately, in our case, the patient did not pass more urine in order to do this microscopy. Nevertheless, the extreme hyperphosphatemia in the absence of other causes of AKI did confirm the diagnosis.

Regarding further insights concerning pathophysiology,^{6,9-11} the kidneys play an important role in the regulation of plasma phosphorus leading to high urinary phosphate excretion. When the urine gets supersaturated and inhibiting factors such as pH, citrate, and pyrophosphate concentrations are low, crystallization will take place.

Regarding the role of PTH,^{6,11} it is well known that an acute phosphate load (although most of the time small in amount) will uniformly lower both ionized and total calcium and produce a compensatory PTH response in the presence of intact parathyroid glands. An increase in PTH will lead to an increased load in urinary calcium and will accelerate the precipitation process.^{6,11}

In our case, PTH was already elevated at admission without increased phosphate and did not increase further after the extreme hyperphosphatemia, but PTH was analyzed too late after the sudden increase in phosphate in order to detect a sudden increase in PTH that could have induced an increase in urinary excretion of calcium leading to more potential precipitation (see Table 1).

As important guidelines for bedside intensivists,^{10,11} we suggest to consider as contraindications for the use of oral and rectal phosphate containing purgatives, patients under the following conditions. Patients who are volume depleted are more prone to develop C-AKI. Patients under medications contributing to renal hypoperfusion, such as diuretics, ACE inhibitors, and AT-II receptor blockers should be seen as patients at risk. Other risk factors which have been suggested are advanced age, diabetes, and stage 1–3 CKD, all of which should be seen as potential contraindications.

As stated earlier, our patient was on small doses of ACE inhibitors for 7 days prior to the acute rise of phosphate and was not on diuretics, other antihypertensive drugs, or AT-II receptor blockers. Therefore, we believe that hyperphosphatemia remains the main mechanism of AKI in our patient,

Table 1 The most important biological values for acute phosphate nephropathy

	Pre-operative	POD 0	POD 10	POD 11	POD 12	ICU discharge
BP S (mmHg)		133	130	86	107	118
BP D (mmHg)		84	53	48	53	63
BP mean (mmHg)		100	78	60	71	81
HR (bpm)		91	97	128	102	118
CVP (mmHg)		19	13	16	23	15
Diuresis (mL/24 hours)		1240	1090	20	20	10
Urea (mg/dL)	39	31	83	35	40	74
Creatinine (mg/dL)	0.81	0.76	2.1	1.59	1.03	1.9
GFR (mL/min/ 1.73 m ²)	60	60	32	44	60	36
Na (meq/dL)	142	139	148	138	135	140
K (meq/dL)	3.3	3.7	3.6	4.2	3.7	4.2
Cl (meq/dL)	101	108	104	104	105	104
Bicarbonate (mmol/dL)	30	28	21	18	19	29
Anion Gap mEq/L	14	7	27	20	15	11
P (mg/dL)	3	3.1	21.2	7.1	3.1	2.2
Ca (mg/dL)	9.7	7.8	5.6	8.3	7.6	8.6
PTH (ng/L)	116.3					85

Note: Sudden rise in phosphate occurred on Day 10.

Abbreviations: BP S, systolic blood pressure; BP D, diastolic blood pressure; BP mean, mean blood pressure; CVP, central venous pressure; GFR, glomerular filtration rate; HR, heart rate; ICU, intensive care unit; POD, post-operative day; PTH, parathyroid hormone.

even though we do not have a biopsy to definitively confirm this diagnosis. As also stated earlier, septic shock may have played a role as a trigger.

In summary, we have described a critically ill patient who developed severe hyperphosphatemia, hypocalcemia, and unexpected C-AKI after receiving oral and rectal phosphate containing purgatives. This case highlights the importance of using these drugs with caution in patients at risk and explains why the diagnosis is frequently overlooked.⁹ The presence of any known risk factor should impose the use of alternative preparations. Early detection of this complication could potentially prevent the irreversible slippery slope towards CKD and chronic dialysis.

Disclosure

The authors report no conflicts of interest in this work.

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