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CASE REPORT

Renal failure due to acute phosphate nephropathy

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ABSTRACT

Case report of a 62-year-old woman who developed acute renal failure due to nephrocalcinosis, also called acute phosphate nephropathy, after large bowel cleansing in preparation for colonoscopy using oral sodium phosphate solution (Phosphoral, de Witt, Cheshire, UK). Subsequently her renal insufficiency resolved only partially resulting in stage 4 chronic kidney disease. In retrospect multiple risk factors for this condition (hypertension, diuretics, AT-II receptor blocker, female gender, advanced age and volume depleting due to vomiting and nausea) were identified. If these factors had been taken into consideration prior to prescribing this drug, acute and chronic renal failure would have been prevented. Future investigation of potential risk factors and the exact mechanism of this complication is necessary to identify those patients prone to develop this complication. In the meantime prescribing physicians should be made aware of this complication. On the basis of the current state of knowledge the evidence seems to be quite compelling not to prescribe these drugs in patients with one or more associated risk factors. It could even be argued that these drugs should not be prescribed at all.

KEYWORDS

Acute renal failure, nephrocalcinosis, oral sodium phosphate solution, phosphate nephropathy

INTRODUCTION

Acute renal failure due to nephrocalcinosis after large-bowel cleansing with sodium phosphate preparations prior to endoscopic procedures is a rare and easily overlooked diagnosis. The estimated risk of acute kidney failure after the use of oral sodium phosphate preparation is 1.14 to 2.35 (OR).[1,2] The main reasons for not diagnosing this condition are unfamiliarity with this complication, the time lag between the ingestion of the drug and the onset of renal failure and the fact that the acute as well as the chronic renal failure which results from this ingestion is not routinely checked for.

CASE REPORT

A 62-year-old woman was referred to our dialysis centre for acute renal failure of three days duration, which did not respond to conservative treatment and volume loading.
Her previous history was unremarkable with the exception of a hysterectomy and hypertension, which was managed with diuretics and an AT-II receptor blocker. She had undergone an ileocolonoscopy three days prior to presentation at our hospital for the analysis of abdominal pains of several months duration. Bowel cleansing for this procedure had been performed using 90 ml of oral sodium phosphate solution (OSPS, Phosphoral, de Witt, Cheshire, UK). This did not result in any complaints other than some nausea and several episodes of vomiting. Immediately after the endoscopy she developed atrial fibrillation with hypotension (85/45 mmHg), which resulted in admission for observation and treatment with volume loading and a bolus of digoxin. Within a few hours she converted back to sinus rhythm and her blood pressure normalised (150/80 mmHg). At admission, an increase of a pre-existent creatinine value taken three years earlier was noticed after colonoscopy: 73 to 175 µmol/l. In the following days, renal failure was progressive despite adequate volume loading and adequate blood pressure (day 3 creatinine 333 µmol/l). She was then referred to our centre for possible dialysis.
On physical examination a female patient in no obvious distress with a blood pressure of 145/75 was observed.

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There were no signs of either hypovolaemia, or volume overload, nor were there signs of pericarditis. Physical examination was completely unremarkable.

Laboratory test results showed elevated levels of creatinine and urea (325 µmol/l and 10.9 mmol/l). All other laboratory values where within the normal range including phosphorus and calcium (1.29 and 2.27 mmol/l). Urinalyses showed no sign of proteinuria or erythrocyturia and a urine sodium concentration of 24 mmol/l. The kidneys were normal on ultrasound examination. A kidney biopsy was performed on day 10 after colonoscopy (creatinine 390 µmol/l), demonstrating more than 10 glomeruli with a normal aspect. The immunofluorescence was negative for immunoglobulins as well as for complement factors. However, on light microscopy, the tubulointerstitium was abnormal with diffuse nonpolarising tubular deposits. These deposits were surrounded by degenerative changes of the epithelium and locally loss of a few cells combined with focal mitotic activity. The interstitium showed no deposits, nor was there any inflammatory infiltration. Von Kossa staining on the tubular deposits was positive, which established the diagnosis of acute nephrocalcinosis, also known as acute phosphate nephropathy (*figure 1*).

Supportive treatment was given and eventually the creatinine level decreased gradually over several weeks after reaching a creatinine peak of 438 µmol/l at day 11 after colonoscopy. On her visit to the outpatient clinic three months after admission, the renal failure had stabilised at a creatinine level of 160 µmol/l (chronic kidney disease stage 4, estimated creatinine clearance 25 ml/min by Cockcroft-Gault formula (female 62 years, 50 kg) and 28 ml/min by MDRD formula) (*figure 2*).

Figure 1. *Von Kossa staining showing tubular calcium deposit*

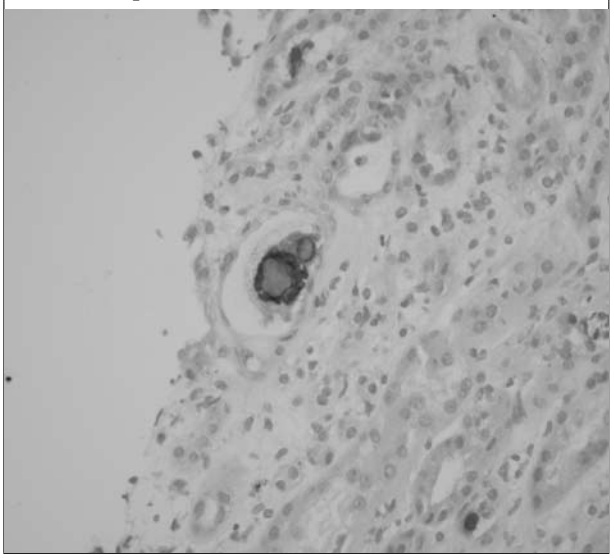
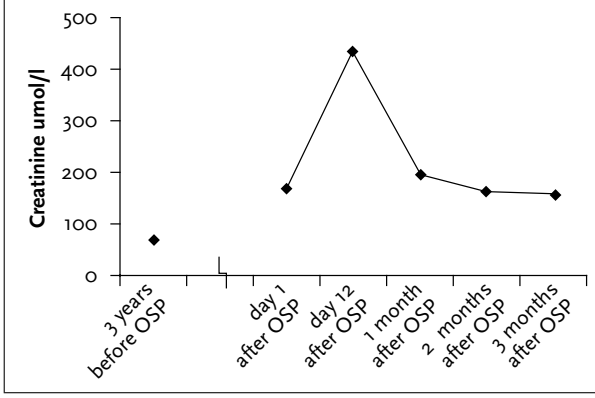


Figure 2. *Course of acute renal failure after oral sodium phosphate (OSP) preparation for colonoscopy*



DISCUSSION

In this case report a patient is presented who developed acute renal failure due to biopsy-proven nephrocalcinosis after the use of oral sodium phosphate during preparation for an elective colonoscopy. Chronic tubulointerstitial nephropathy due to nephrocalcinosis is a well-known histopathological entity associated with chronic hypercalcaemia. Acute nephrocalcinosis has also been described previously as a complication after the use of oral sodium phosphate solution (OSPS) or phosphorus-containing medications.[3-10] Acute phosphate nephropathy has been chosen as the term to describe this condition. A retrospective cohort study has identified 21 cases of acute phosphate nephropathy among 7349 kidney biopsies.[3] In this study the condition has proven to be partially reversible, but residual renal insufficiency persisted in all described cases. However, this might partially have been due to case selection.

The phosphorus concentration is regulated by the oral phosphorus load and renal excretion. Absorption in the gut takes place for up to 60% in the upper duodenum, jejunum and ileum by active (calcitriol dependent) and passive transport. Compared with a normal daily dietary phosphorus intake of 1.5 g, a 45 ml bottle of OSPS (as used in the Netherlands) contains 24.4 g of monobasic sodium phosphate and 10.8 g of dibasic sodium phosphate (two gifts of 45 ml are given in bowel preparation). These amounts of phosphorus lead to an almost 100% rise in serum phosphate concentration on the day after ingestion.[11] Hyperphosphataemia due to sodium phosphate enemas has been described in children but in adults this is a rare complication, although hypertonic sodium phosphate enemas can be absorbed and be life-threatening.[12] Martin[13] showed that normal doses of enema solution (containing 21 g sodium biphosphate and 7.9 g of sodium phosphate)

cause measurable changes in serum phosphorus level. In a pig model enema solutions at a dose of 20 to 30 ml/kg were uniformly fatal.[13]

However, there are no solid published data on the exact amount of intestinal phosphate absorption after OSPS. Only a letter describing five healthy volunteers showed an average intestinal uptake of 43% of the ingested dose of phosphorus.[14] The kidneys play an important role in the regulation of plasma phosphorus leading to high urinary phosphate excretion.[11] When the urine gets supersaturated and inhibiting factors such as pH, citrate and pyrophosphate concentrations are low, crystallisation will take place. The calcium phosphate crystals bind to the tubular epithelial cells causing reactive oxygen damage.[15] This is the supposed main pathway which leads to the renal impairment.

In phosphate nephropathy nonpolarising tubular calcium phosphate deposits are typically found on histological examination. The von Kossa staining, accentuating the phosphate component, is positive. This is combined with normal glomeruli, mildly to none affected interstitium and tubular epithelial cells showing signs of degenerative changes.[3,5,7,9] All of these histological findings were present in our case.

Patients who are volume depleted are more prone to develop acute phosphate nephropathy when using OSPS. For this reason ulcerative colitis and diarrhoea are relative contraindications for the use of OSPS. Medications contributing to renal hypoperfusion such as diuretics, ACE inhibitors and AT-II receptor blockers could also predispose to this disorder. Other risk factors which have been suggested are advanced age, diabetes, renal impairment and female gender.[1,2,16] A retrospective analysis of a single-centre database (n=286) showed an absolute decline in glomerular filtration rate of up to 6 ml/min over a period of six months in the OSPS group compared with 1% in the control group, who did not undergo colonoscopy, over a period of one year.[17] These groups where equally matched for gender, age, race, comorbidity and the use of several medications (ACE inhibitors, AT-II receptor blockers and diuretics). Furthermore these groups had creatinine levels which where in the normal range (<130 µmol/l) at baseline. Linear regression analysis marked ACE inhibitors, AT-II receptor blockers and diabetes as significant determinants of glomerular filtration loss. *Table 1* shows the combined risk factors as described in six studies with a total of 488 cases of renal failure secondary to OSPS.

On the basis of these data, our 62-year-old female patient with mild hypertension managed with diuretics and an AT-II receptor blocker and possible volume depletion due to vomiting had a high risk for developing this complication.

We consider prospective studies to formally assess the risk for developing this partially irreversible complication and to formally define relevant risk factors unethical since multiple safe alternative agents are available. It is therefore considered relevant to report individual cases to national and/or international pharmacovigilance databases. In the meantime, physicians prescribing these drugs should be aware of the associated risks. As mentioned by others, oral sodium phosphate purgatives should not be used in patients with chronic kidney disease stage 3-5.[17,18] With the growing numbers of studies reporting about this complication in patients with stage 1-3 chronic kidney disease and even with normal renal function, there seems to be compelling evidence not to use this kind of purgative in patients with known risk factors.

Table 1. *Risk factors for acute phosphate nephropathy as found in 6 studies with 488 cases of renal impairment*

Study	N° of cases	RI due to OSP	Risk factors	Odds ratio
J Am Soc Nephrol, Hurst et al, 2007	9799	83	Age, HT, DM, ACVD, CHF, ACE, ARB, diuretics	2.35
J Am Soc Nephrol, Markowitz et al, 2005	7349	21	Volume depletion, female gender, ACE ARB, diuretics, HT, age, CKD	NA
Am J Gastroenterol, Russmann et al, 2007	2083	79	CKD, age, African American race, HT, ACE, ARB, diuretics	1.14
Arch Intern Med, Khurana et al, 2008	286	286	DM, ACE, ARB, age	NA
Arch Pathol Lab Med, Gonlusen et al, 2006	19	19	HT, ACE, ARB, diuretics	NA
Am J Gastroenterol, Sica et al, 2007	NA	NA	Age, female gender, CKD, ACE, ARB, volume depletion, diuretics	NA

RI = renal impairment; OSP = oral sodium phosphate; HT = hypertension; DM = diabetes mellitus; ACVD = atherosclerotic cardiovascular disease; CHF = chronic heart failure; ACE = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CKD = chronic kidney disease; NA = not available.

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