Acute phosphate nephropathy

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Acute phosphate nephropathy (APhN) is a clinical pathological entity characterized by acute and subsequent chronic renal failure following exposure to oral sodium phosphate (OSP) bowel purgatives. Renal biopsy findings include acute and chronic tubular injury with prominent tubular and interstitial calcium phosphate deposits. Risk factors for APhN include older age, female gender, hypertension, chronic kidney disease (CKD), and treatment with angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and diuretics. The pathomechanism of APhN involves hypovolemia-induced avid proximal salt and water reabsorption, delivery of a large phosphate load to the distal nephron, and precipitation of calcium phosphate in the distal tubule and collecting duct. To date, 37 cases of biopsy-proven APhN have been reported, and epidemiologic studies have produced inconsistent results regarding the incidence of acute kidney injury (AKI) following the use of OSP purgatives. OSP solution was withdrawn from the market in December of 2008, but OSP tablets, offered by prescription only, remain available. Prevention of APhN is best achieved by avoiding OSP in high-risk patients, aggressive hydration before, during, and after OSP administration, minimizing the dose of OSP, and maintaining a minimum of a 12 h interval between OSP administrations.

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Acute kidney injury (AKI) often results from drug toxicity, several types of which cause renal injury through intratubular crystal deposition.[1] In 2003, a newly described cause of drug-induced AKI, acute phosphate nephropathy (APhN), was reported following the use of an oral sodium phosphate (OSP) bowel purgative in an elderly woman.[2] Renal histopathology showed numerous tubular calcium phosphate deposits that formed crystals of hydroxyapatite. Subsequent observations confirmed this clinical pathological entity and noted acute and chronic tubular injury with prominent tubular and interstitial calcium phosphate deposits in patients exposed to OSP purgatives.[3]

PHOSPHATE HOMEOSTASIS

As phosphate exposure is critical to the occurrence of APhN, a brief review of phosphate homeostasis is undertaken. The majority of phosphorus in humans exists as the phosphate anion (PO_4^{3-}) and is present in bone, with smaller amounts present as inorganic phosphate in extracellular fluid and as organic phosphates within cells. In blood, phosphate exists mainly as HPO_4^{2-} and $H_2PO_4^{1-}$, with relative concentrations determined by serum pH. The average daily intake of phosphorus in the developed world is approximately 1000 mg.

Phosphate handling in the small intestine and renal tubules is mediated by sodium-dependent phosphate co-transporter proteins (NaPi), which are members of the SLC34 gene family.[4,5] The proximal tubular brush border contains NaPi-IIa (SLC34A1) and NaPi-IIc (SLC34A3), and their expression is downregulated by increases in serum phosphate or parathyroid hormone. These two factors rapidly reduce NaPi-IIa co-transporter expression in proximal tubular apical membrane through endosomal retrieval. NaPi-IIb (SLC34A2) is more broadly distributed and is present in the small intestinal brush border where levels increase in response to hypophosphatemia and vitamin D. In contrast to renal NaPi-IIa, intestinal NaPi-IIb expression requires days to respond to physiological changes.

Between 60 and 80% of dietary phosphate is absorbed in the small intestine, while net excretion occurs through glomerular filtration minus tubular reabsorption. The majority of phosphate is reabsorbed in the proximal tubule, with small amounts reabsorbed in the distal tubule and collecting duct.[6,7] Hyperphosphatemia occurs in the following settings: (1) excessive ingestion of phosphate over a short

time period; (2) massive release of intracellular phosphate (i.e., tumor lysis syndrome, rhabdomyolysis); (3) phosphate ingestion in the setting of impaired gastrointestinal motility (increased absorptive time); or (4) renal dysfunction leading to reduced excretion.

ORAL SODIUM PHOSPHATE BOWEL PURGATIVES

Colonoscopy is critically dependent on adequate pre-procedural bowel cleansing. In 1990, OSP solution (OSPS) began to gain acceptance as a purgative for colonoscopy.[8] The small volume of OSPS was associated with improved patient compliance, less discomfort, and superior colonic cleansing compared with polyethylene glycol (PEG)-based lavage solution. The price for a better bowel preparation was transient hyperphosphatemia (mean increase in serum phosphate of 4.1 mg/dl) that resolved within 24 h and was not associated with hypocalcemia.[8] Subsequent studies confirmed that OSPS was better tolerated and was associated with improved bowel cleansing compared with PEG-based purgatives.[9–11] A meta-analysis of randomized, controlled trials published from 1990 to 2005 found that OSPS was more efficacious than PEG in nine studies, inferior in one study, and equivalent in six studies.[11]

For many years, the commonly recommended regimen of OSP solution (Fleet Phosphosoda; C.B. Fleet, Lynchburg, VA, USA) consisted of two 45-ml doses taken 10–12 h apart, the evening before and the morning of colonoscopy. Each 45-ml dose contained 21.6 g of monobasic sodium phosphate (NaH_2PO_4) and 8.1 g of dibasic sodium phosphate (Na_2HPO_4), which is equivalent to 5.8 g of elemental phosphorus. The 5.8 g of phosphorus was diluted into a single eight ounce glass and administered twice in a 12−24 h period, far exceeding the usual dietary intake of 1 g/day. Following increasing reports of APhN, the more commonly recommended regimen became 45 ml followed by 30 ml of OSP, and requirements for hydration were increased to 36 ounces of clear fluid with each administration. On 11 December 2008, following continuing reports of APhN, the United States Food and Drug Administration issued an alert stating that over-the-counter OSP products should no longer be used for bowel cleansing, and that the use of these products should only occur pursuant to a prescription from a health-care provider. (http://www.fda.gov/cder/drug/infopage/OSP_solution/default.htm). Shortly thereafter, Fleet Phosphosoda was voluntarily withdrawn from the US market.

Oral sodium phosphate remains available by prescription in a tablet form under the brand names Visicol and Osmoprep (Salix Pharmaceuticals, Morrisville, NC, USA). These agents are given in two separate administrations separated by 12 h. A regimen of 20 tablets of Visicol, administered as three tablets with at least eight ounces of clear fluid every 15 min until completion, has a cumulative sodium phosphate content that is near identical to a 45-ml dose of OSPS. Osmoprep has largely replaced Visicol, and current recommendations are for the second administration to consist of 12 rather than 20 tablets. The main distinctions between OSP solution and OSP tablets is that the latter is tasteless, is consumed over a longer time period, mandates greater fluid consumption, and has always been available by prescription only.

Prior to its withdrawal, OSP was contraindicated in patients with congestive heart failure (CHF), clinically significant kidney failure, ascites, gastrointestinal obstruction, or active inflammatory bowel disease. It was not recommended for use in children under the age of 18 years, and should have been used with caution in patients who were elderly, debilitated, pregnant or nursing, had underlying heart disease, had increased risk of renal impairment, and had increased risk for or pre-existing electrolyte disturbances (www.phosphosoda.com). For Osmoprep, the product label states that 'considerable caution should be advised before use' in patients with creatinine clearance <30 ml/min, CHF, ascites, unstable angina, gastric retention, ileus, acute bowel obstruction, pseudo-obstruction of the bowel, severe chronic constipation, bowel perforation, acute colitis, toxic megacolon, gastric bypass, or hypomotility syndrome (www.osmoprep.com). Recently, a 'black box warning' was added to the labels for Visicol and Osmoprep that addresses the risk of APhN.

ACUTE PHOSPHATE NEPHROPATHY

Clinical findings

In 2004, a series of five cases of APhN was reported in patients with a history of hypertension (HTN), a mean age of 69.2 years, and normal serum calcium levels.[3] The patients developed AKI shortly after colonoscopy preceded by bowel cleansing with OSPS. The changes were referred to as 'acute nephrocalcinosis' to emphasize the rapidity of onset compared with the more commonly described forms of nephrocalcinosis seen with hypercalcemia related to hyperparathyroidism, malignancy, sarcoidosis, and milk alkali syndrome.

The same investigators subsequently reported a larger series of patients with AKI following the use of OSP bowel purgatives[12] and adapted the term APhN[1] to emphasize the central pathogenical role of exogenous phosphate administration. The archives of the Columbia University Renal Pathology Laboratory from 2000–2004 were reviewed to identify additional cases of APhN. Diagnostic criteria included the following: (1) AKI; (2) recent exposure to OSP bowel purgatives; (3) renal biopsy findings of acute and chronic tubular injury with abundant calcium phosphate deposits; (4) no evidence of hypercalcemia or conditions associated with hypercalcemia; and (5) no other significant pattern of renal injury. Overall, 7349 native renal biopsies were processed over this period, of which 31 met the above-noted criteria of acute and chronic tubular injury with abundant calcium phosphate deposits. Twenty-one patients met all five criteria for the diagnosis of APhN, including the single case associated with OSP tablets which had been previously reported.[13]

The cohort consisted of predominantly Caucasian women with a mean age of 64.0 years. Sixteen patients had a history

Table 1 | Cases of renal biopsy-proven acute phosphate nephropathy

Study (reference)	N	Age/gender	Baseline sCr (μmol/l)	Final sCr (μmol/l)	Medications/drugs	Co-morbidities
Desmueles *et al.*[2]	1	71/F	88.4	76	NA	NA
Markowitz *et al.*[12]	21	39–82/F=17, M=4	53–150.3	132–299 ESRD=4	ACE-I or ARB=14, diuretics=4, NSAIDs=3	Hypertension=15, CKD=4, diabetes=4
Gonlusen *et al.*[14]	1	56/F	70	141		
Manley *et al.*[15]	1	85/F	NA	200	ACE-I, diuretic	Hypertension
Aasebo *et al.*[16]	1	69/F	62	114	ARB, diuretic	Hypertension
Beyea *et al.*[17]	1	69/F	70	229		Hypertension
Steinman *et al.*[18]	1	64/M	123	256		Hypertension
Connor *et al.*[19]	1	76/F	98	271		Hypertension, CKD
Ori *et al.*[20]	5	56–73/F=4, M=1	62–106	115–274	ACE-I/ARB=1	Hypertension=5, CKD=3
Kim *et al.*[21]	1	66/F	88.4	115	Diuretic	Hypertension
Rocuts *et al.*[22]	1	60/F	80	168	ACE-I, diuretic, NSAID	Diabetes, hypertension
Demoulin *et al.*[23]	1	50/M	97.2	141.4	ARB	Hypertension
Slee *et al.*[24]	1	62/F	73	160	ARB, diuretic	Hypertension
Total	37	39–85/>60 yo: *n*=26 F=30, M=7	sCr range: 53–150.3 sCr ⩾106: 6/35	sCr range: 76–299 ESRD=4	ACE-I or ARB=20, diuretics=9, NSAIDs=4	Hypertension=29, diabetes=5, CKD=8 (defined as eGFR<60 ml/min per 173 m^2)

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; F, female; NA, not available; NSAID, non-steroidal anti-inflammatory drugs; sCr, serum creatinine concentration. To convert μmol/l to mg/dl, divide by 88.4.

of HTN, including 14 who were treated with an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin-receptor blocker (ARB). The mean baseline serum creatinine was 88.4 μmol/l (1.0 mg/dl). Patients presented with AKI and a mean creatinine of 3.9 mg/dl at a median of <1 month following OSPS use. The mean 24-h urine protein was 256 mg, and microscopic evaluation of the urine revealed either a bland sediment or rare red or white blood cells. The mean duration of post-colonoscopy follow-up was 16.7 months. During this time, four patients progressed to end-stage renal disease. Sixteen of the remaining 17 patients had a decline in serum creatinine to a mean of 2.4 mg/dl. Only four patients reached a creatinine <176.8 μmol/l (2.0 mg/dl), and no patient returned to baseline.

Additional reports of biopsy-proven APhN (Table 1) have followed.[14–24] Similar to the cases previously described, patients appear to have taken OSPS for bowel cleansing, possess many of the same co-morbidities, and have developed permanent kidney damage.

Pathological findings

Renal biopsy findings in APhN primarily involve the tubules and are dependent on the time interval between OSP use and renal biopsy. When biopsy is performed within 3 weeks of OSP exposure, acute tubular degenerative changes predominate and resemble findings seen in acute tubular necrosis.[3,12] The acute tubular injury is accompanied by interstitial edema and involves all tubular segments. In contrast, renal biopsies performed more than 3 weeks following OSPS exposure exhibit evidence of chronicity in the form of tubular atrophy and interstitial fibrosis. As the interval from OSP exposure to renal biopsy increases, the acute tubular degenerative changes become less severe. This pattern of renal injury may be described as an acute and chronic tubulointerstitial nephropathy and is reminiscent of changes seen in repeat renal biopsies from patients with non-resolving acute tubular necrosis. Mild-to-moderate interstitial inflammation is often seen in APhN but is not associated with significant tubulitis. Vascular disease is a frequent finding, correlating with the high incidence of HTN and the fact that APhN is most commonly encountered in older patients.

Regardless of the degree of acuity or chronicity, the hallmark of APhN is abundant tubular and less prominent interstitial calcium phosphate deposits (Figure 1a). The extent of tubular calcification is dependent on adequacy of tissue sampling but in biopsies with 10 or more glomeruli, >30 calcifications are typically encountered and >100 calcifications can be seen.[3,12] The calcifications form

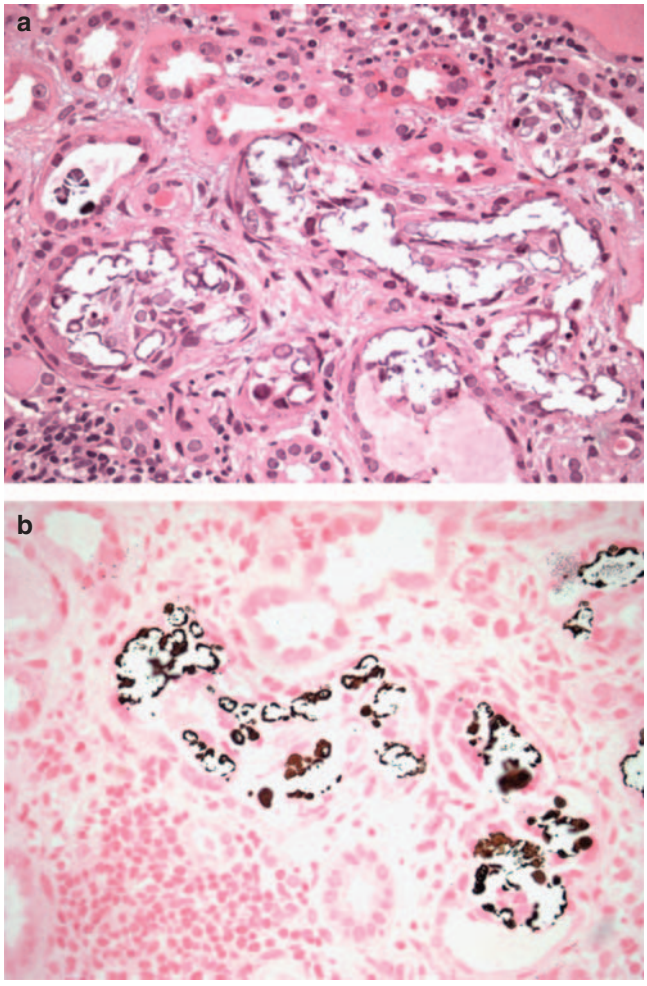

Figure 1 | Renal biopsy findings in acute phosphate nephropathy. (**a**) Case of acute phosphate nephropathy with abundant intraluminal and intracellular calcifications in distal tubules. (Hematoxylin and eosin, original magnification $\times 400$.) (**b**) A positive histochemical reaction with the von Kossa stain confirms that the tubular concretions are composed of calcium phosphate (original magnification $\times 400$).

basophilic rounded concretions, are mainly confined to distal tubules and collecting duct,[3] and are more prominent in the renal cortex than medulla. The calcifications do not polarize and have a strong histochemical reaction with the von Kossa stain, indicating that they are composed of calcium phosphate (Figure 1b).

Pathogenesis

Both the massive phosphate intake and the consequent diarrhea-induced hypovolemia appear to be critical factors in the development of APhN. Phosphate absorption in the small intestine is loosely controlled and therefore cannot be rapidly altered following OSP ingestion.[4–5] In contrast, proximal tubular phosphate reabsorption is modulated within minutes of ingestion, leading to decreased proximal tubular reabsorption and a rapid increase in delivery to the distal tubule. This is particularly true following the second dose of OSPS, where proximal tubular phosphate reabsorption is likely to be fully inhibited. Although this response is beneficial in most situations, it appears to be harmful in the setting of profound volume depletion that often follows OSP-induced diarrhea. Hypovolemia leads to avid salt and water reabsorption in both the proximal tubule and descending limb of Henle's loop, which is relatively impermeable to calcium and phosphate.[25] The net effect is decreased phosphate reabsorption in proximal segments of the nephron, leading to a marked increase in calcium–phosphorus product within the lumen of the distal tubule. This mechanism is strongly supported by the observation that calcium phosphate precipitates in APhN occur predominantly in the distal tubule and collecting duct.[3] Hypovolemia-associated tubular injury may also precondition the distal tubular epithelium, leading to the surface expression of hyaluronan and osteopontin, which in turn creates a ripe environment for calcium phosphate crystal adherence.[26] The magnitude and duration of the elevation of the distal tubular calcium–phosphorus product are likely to be critical factors in the development of APhN.

Epidemiological studies

The recognition of APhN as a clinical pathological entity associated with acute and chronic renal failure has led to population-based studies that more broadly examine risk factors and attempt to determine the incidence of this condition. These studies, which are limited by the absence of confirmatory renal biopsy and thus unable to diagnose APhN, have attempted to determine the incidence of AKI or CKD following OSP use (Table 2).

An observational cohort analysis of 9799 Department of Defense beneficiaries in the US national capital area, the largest study to date, was undertaken to examine the incidence of APhN.[27] Patients were identified through an electronic medical record that has the unique feature of tracking over the counter medication use, such as OSPS. The study excluded patients under the age of 50 years (due to the high incidence of inflammatory bowel disease) and defined AKI as a $\geqslant 50\%$ increase in serum creatinine from baseline over 1 year post-colonoscopy. In this study, 114 patients (1.16%) developed AKI, including 1.29% of the 6432 patients who received OSPS and 0.92% of the 3367 patients who received PEG. The PEG group included patients who were significantly older and had a higher incidence of diabetes mellitus, HTN, CHF, CKD, diuretic use, and ACE-I or ARB use (all $P<0.05$). When multiple logistic regression models were applied to adjust for covariates and suspected risk factors, OSPS was found to be the strongest risk factor for the development of AKI following colonoscopy (odds ratio 2.35; $P<0.001$). When AKI was redefined more strictly as doubling of serum creatinine, an even stronger association between OSPS and AKI was found (odds ratio 3.52; $P=0.03$). Most worrisome was that the number needed to harm was calculated to be 81 (that is, 1 case of AKI for every 81 OSPS-exposed patients).[27]

Table 2 | Retrospective studies on risk factors for AKI following colonoscopy

Study (reference)	Number of patients	Renal function inclusion	Renal end point	Study results: (OSP versus PEG or control)	Risk factors
Hurst *et al.*[27]	OSP: 6432, PEG: 3367	sCr before and within 1 year of colonoscopy	>50% increase in sCr	AKI rate: 1.29 vs 0.92% end point RR: 2.35 ($P<0.001$)	Old age, CHF, HTN, ACE-I/ARB, diuretics, DM, OSPS
Brunelli *et al.*[28]	OSP: 296, PEG: 156	sCr (<133 μmol/l) before and within 6 months of colonoscopy	>25% or >44.2 μmol/l increase in sCr	AKI rate: 4.6 vs 6.0% end point RR: 0.7 (*P*=NS)	Female gender, CHF, diuretics
Russmann *et al.*[29]	OSP: 2083, PEG: 269	SCr (<133 μmol/l) before and within 6 months of colonoscopy	GFR<60 ml/min and >10 ml/min Δ; or >100% increase in sCr	AKI rate: 3.8 vs 3.3% end point RR: 1.14 (*P*=NS)	Old Age, CKD, HTN, diuretics, ACE-I/ARB
Khurana *et al.*[31]	OSP: 286, Controls: 125	sCr (<133 μmol/l) before and at 6 and 12 months after colonoscopy	GFR at 6 and 12 months	GFR loss (ml/min) 6 months: 6.0 vs 0 12 months: 8.0 vs 1.3	CKD, DM, ACE-I/ARB, OSPS
Singal *et al.*[32]	OSP: 157, PEG: 154	sCr (<133 μmol/l) before and within 1 year of colonoscopy	>25% or >50% increase in sCr	AKI rate: 5 vs 3% end point RR: 1.37 (*P*=NS)	CKD, NSAIDs, OSPS (did not assess age, HTN, ACE-I/ARB, diuretics, gender)
Russmann *et al.*[30]	OSP: 126, PEG: 191	Estimated GFR <60 ml/min	>44.2 μmol/l increase in sCr	AKI rate: 6.3% vs 0.5% end point RR: 12.6 (CI: 1.5–106.5)	CKD, OSPS

ACE-I, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin-receptor blocker; CHF, congestive heart failure; CI, confidence interval; CKD, chronic kidney disease; DM, diabetes mellitus; GFR, glomerular filtration rate; HTN, hypertension; NSAIDs, non-steroidal anti-inflammatory drugs; OSP, oral sodium phosphate; OSPS oral sodium phosphate solution; PEG, polyethylene glycol; RR, relative risk; sCr, serum creatinine concentration. To convert μmol/l to mg/dl, divide by 88.4.

A retrospective case–control study by Brunelli *et al.*[28] evaluated 2237 patients undergoing outpatient colonoscopy. AKI, defined as a 25% or a 0.5 mg/dl increase in serum creatinine over 6 months post-colonoscopy, was identified in 141 patients (6.3%). Female gender, CHF, and diuretic use were identified as risk factors for AKI. An association between OSP and AKI was only identified in patients who were receiving an ACE-I or ARB. The small sample size and permissive definition of AKI limit this study, as the mean increase in creatinine in patients with AKI was only 36.2 μmol/l (0.41 mg/dl). Thus, patients with pre-renal glomerular filtration rate (GFR) changes, likely to occur in both groups due to bowel prep-induced hypovolemia, would be identified. A stricter definition of AKI (serum creatinine increase >88.4 μmol/l (1.0 mg/dl)) resulted in a decline in the number of AKI cases from 116 to 3.[28]

A retrospective cohort study by Russmann *et al.*[29] included 2352 patients with a baseline GFR >60 ml/min and compared AKI in OSPS versus PEG-exposed patients. The utility of this study is significantly hampered by the unusual AKI definition, which required a decline in GFR to <60 ml/min with an interval change of at least 10 ml/min or doubling of baseline serum creatinine. Unbalanced baseline characteristics were present in the groups, as patients who received PEG were older and had a higher prevalence of CHF, HTN, diabetes mellitus, and diuretic and ARB use (*P*-values not provided). On univariate analysis, AKI was associated with age ⩾65 years, HTN, lower baseline GFR, African–American race, and the use of ACE-I, ARB, or thiazide diuretics, but was not specifically associated with the use of OSPS or PEG.[29] This study is significantly limited by the bias toward the inclusion of healthier patients in the OSPS group. In addition, the unusual definition of AKI further complicates the results as a 15% decline in GFR from 68 to 58 ml/min would meet criteria for AKI but a 33% decline in GFR from 90 to 60 ml/min would not qualify.

Russmann *et al.*[30] subsequently carried out a similar retrospective analysis on 317 patients with a baseline GFR <60 ml/min in an effort to specifically address the risk of APhN in patients with moderate CKD. AKI, defined as an otherwise unexplained increase in serum creatinine >44.2 μmol/l (0.5 mg/dl) within 14 days of colonoscopy, was present in 8 of the 126 patients who used OSPS (6.3%) versus only 1 of the 191 patients who received PEG (0.5%). The unadjusted and adjusted relative risk of AKI for OSPS-exposed patients as compared with PEG users was 12.1 (95% confidence interval, 1.5–95.8) and 12.6 (95% confidence interval, 1.5–106.5), respectively. The researchers concluded that OSPS should not be used in patients with moderate or severe renal impairment and recommend assessment of renal function before the use of OSPS in patients who are at risk for CKD.[30]

A case–control study examined changes in estimated GFR (abbreviated MDRD formula) over a 12-month period in 286 patients who underwent colonoscopy following OSPS and compared them with an age- and risk factor-matched cohort of 125 patients who had not undergone colonoscopy.[31] Mean GFR in the study group was 79.33 ml/min per 1.73 m^2 at baseline, declining to 73.31 and 71.33 ml/min per 1.73 m^2 at 6 and 12 months post-colonoscopy, respectively. The 7.6 and 10.1% decline in GFR at 6 and 12 months in the OSPS group was significantly greater than the

1.7% decline in GFR at 12 months in the control group. Study significance is limited by the use of a control group that did not undergo colonoscopy and, more importantly, inclusion of only OSP-exposed patients who had serum creatinine determinations at 6 and 12 months post-colonoscopy (favoring inclusion of sicker patients). As only 10% of the study participants met these criteria, significant selection bias is likely.

Two additional studies are worth mentioning. A retrospective chart review on 311 patients (98% male) who received OSPS or PEG found a greater incidence of AKI with OSPS when AKI was defined as a 25% increase in creatinine, but not when AKI was defined as a 50% increase in creatinine.[32] A randomized controlled study that enrolled 481 patients and compared OSP tablets (32 tablet Osmoprep) to PEG reported no cases of AKI.[33]

Meta-analysis of epidemiological studies

Although case reports and case series provide strong support for an etiological relationship between OSP and the development of APhN (Table 1), epidemiological studies have produced less consistent results (Table 2). Recently, Brunelli[34] undertook a systematic review and meta-analysis in an attempt to determine the strength of association between OSP exposure and AKI. Ninety-two potential studies were evaluated and seven met inclusion criteria of providing data on renal function outcomes and having a control group. The seven studies analyzed,[27–29,31–33,35] which had varied baseline kidney function and used different AKI definitions, did not support an association between OSP and AKI. Using random effects models, the estimated pooled odds ratios for OSP versus control were 1.22 (95% confidence interval, 0.77–1.92) and 1.08 (95% confidence interval, 0.71–1.62) when higher and lower estimates for two studies[30,31] were used. The author concluded that it was not possible to discern whether an association between OSP and kidney injury exists. However, a number of limitations of the study should be considered. Of primary concern is the significant heterogeneity that exists among the studies as they relate to choice of bowel preparation, patient populations, baseline kidney function, AKI definitions, renal outcomes, and control groups. Second, it is unclear whether the studies were appropriately weighted, as the most thorough study[27] that showed the strong association between OSP and AKI had twice as many patients as did the other six studies combined. Third, multiple studies used inappropriate definitions for AKI[29,35] including one that considered follow-up serum creatinine values as late as 9 years post-OSP exposure.[35] In our opinion, at least one of these studies[35] should have been excluded from the analysis.

Risk factors for APhN

Case reports, case series, and epidemiologic studies (Tables 1 and 2) have facilitated the identification of risk factors for the development of APhN. These factors in turn provide insight into the pathogenesis of this condition and may help to establish safe guidelines for the use of OSP. Some of the risk factors, including CKD, advanced age, and HTN, can be broadly viewed as risk factors for AKI in numerous clinical settings.

Advanced age appears to be an important risk factor for the development of APhN, as the majority of reported cases (Table 1) have involved individuals who are 60 years of age or older (26/37, 70.3%). Advanced age has also been identified in epidemiological studies as a risk factor for AKI following the use of OSP[27,29] (Table 2). Of note, OSPS exposure is associated with more severe hyperphosphatemia in the elderly,[36–37] which may relate to both age-related decline in GFR and increases in intestinal transit time.

Chronic kidney disease is a risk factor for APhN. Before its withdrawal, 'clinically significant renal failure' was listed as a contraindication to the use of OSPS, although this term was not specifically defined in terms of GFR. In addition to the fact that CKD is a general risk factor for all forms of AKI, a low GFR limits renal phosphate excretion and exposes the fewer functioning nephrons to a higher concentration of phosphate. Despite the warning in the product label, 8 of the 37 cases of APhN in Table 1 had a baseline creatinine $\geqslant 105\,\mu mol/l$ (1.2 mg/dl) or estimated GFR <60 ml/min per $1.73 m^2$ (CKD stage III or higher). CKD was identified as a risk factor for AKI following the use of OSP in four of the six studies in Table 2. Most importantly, the study by Russmann *et al.*[30] suggests that OSP should not be used in patients with stage III CKD (that is, GFR <60 ml/min).

Hypertension. The majority of cases of APhN have occurred in patients with a history of HTN, including 29 of the 36 (80.5%) biopsy-proven cases (Table 1). The effect of HTN may relate to its effect on renal function and the associated vascular scarring, which can impair physiological adjustments to hypovolemia. Epidemiological studies support the association between HTN and AKI following colonoscopy[27,29] (Table 2).

Angiotensin-converting enzyme inhibitors, ARBs, and diuretics are known to exacerbate the pre-renal state, a condition that commonly results from OSP-induced diarrhea and volume depletion. ACE-I and ARB were used in 20 of the 36 cases (55.5%) of biopsy-proven APhN in Table 1, and were identified as risk factors for OSP-induced AKI in three of five epidemiological studies in Table 2. An additional, less critical factor may be that ACE-I and ARB decrease angiotensin-II-dependent bicarbonate reabsorption in the proximal tubule, inducing bicarbonaturia[38] and promoting calcium phosphate precipitation in the distal tubule.[39] The rapid reduction in GFR in volume-depleted patients exposed to ACE-I and ARB also decreases phosphorus disposal, further promoting intra-luminal calcium phosphate precipitation. Loop or thiazide-type diuretics were administered to 9 of the 36 patients with APhN (25%) in Table 1 and also have been recognized in epidemiological studies as a risk factor for AKI following colonoscopy[27,29] (Table 2). Diuretics limit the kidneys' ability to retain salt and water in the setting of hypovolemia.

Table 3 | Risk factors for acute phosphate nephropathy

Risk factors (*n*)	Number of patients (*n*)
6 Risk factors	2
5 Risk factors	7
4 Risk factors	8
3 Risk factors	7
2 Risk factors	10
1 Risk factor	3
0 Risk factors	0
	Total = 37

Risk factors: age > 60 years, female gender, GFR < 60 ml/min, hypertension, angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, diuretics.

Female gender. As seen in Table 1, the majority of reported cases of biopsy-proven APhN have occurred in women (30 of the 37 cases; 81%). Experimental studies have shown that female rats are more susceptible to developing nephrocalcinosis following exogenous phosphate administration.[40] Risk is likely to be estrogen dependent, as it diminishes in female rats following oophorectomy and is acquired in male rats following gonadectomy and estrogen therapy.[40] Given that the majority of women with APhN are post-menopausal, the critical factor may be that female subjects typically are smaller than males, as a recent study has shown that body weight is a critical determinant of the degree of hyperphosphatemia following the use of OSP.[41] These findings raise the issue of whether OSP dosing should be adjusted for gender and body weight.

Additional factors which may predispose to the development of APhN include diabetes mellitus[27,31] and the use of non-steroidal anti-inflammatory drugs.[32] Non-steroidal anti-inflammatory drug use and diabetes mellitus were only reported in four (11.1%) and five (13.9%) patients in Table 1, respectively. As such, firm conclusions about the independent effect of these risk factors cannot be drawn. Although the studies in Tables 1 and 2 did not specifically address these issues, phosphate dose, interval between OSP dosing, and adequacy of hydration also are undoubtedly critical factors in determining the risk for the development of APhN.

One might predict that the risk of APhN would increase in parallel with the number of risk factors. Table 3 lists the number of risk factors present in each of the 37 patients in Table 1 with biopsy-proven APhN. All had at least one risk factor, and 24 of the 36 patients (66 %) had three or more risk factors. Careful consideration of these risk factors is likely to lead to more informed, individualized decisions regarding selection of bowel preparation for patients undergoing colonoscopy.

CONCLUSIONS

Acute phosphate nephropathy is a clinical pathological entity characterized by acute and subsequent chronic renal failure following the use of OSP bowel purgatives. Risk factors for the development of APhN include CKD (i.e., GFR <60ml/min), older age (i.e., >60 years), HTN, female gender, treatment with certain antihypertensive agents (ACE-I, ARB, and diuretics), excess phosphate dosing, inadequate hydration, and a short interval between OSP administrations (i.e., <12 h). In December 2008, OSP solution was withdrawn from the market following the recommendation of the US Food and Drug Administration. OSP tablets remain available by prescription. Removal of over the counter OSP, awareness of the risk factors for APhN, and careful individualized selection of bowel purgatives should continue to lead to a marked decline in the incidence of APhN.

DISCLOSURE

GSM is a consultant to Salix Pharmaceuticals.

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