

Acute phosphate nephropathy

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Current Opinion in Nephrology and Hypertension 2009, 18:513–518

Purpose of review

Acute phosphate nephropathy (APN) has been identified in renal biopsy specimens of patients exposed to oral sodium phosphate (OSP) bowel purgatives. Biopsy confirmed cases presented with bland urinary sediment, low-grade proteinuria, and varying degrees of creatinine elevation. Prospective identification of APN is difficult in that definitive diagnosis requires renal biopsy, and biopsy is rarely performed for patients with this clinical presentation.

Recent findings

Observational studies evaluating acute kidney injury after OSP exposure using interval changes in creatinine as a surrogate for APN have reported conflicting results. Although these studies have produced estimates of disease occurrence, they have been unable to definitively quantify the overall risk of APN with OSP as compared with alternative bowel-cleansing agents.

Summary

On the basis of association of APN and OSP, the US Food and Drug Administration issued a boxed warning and manufacturers have ceased production and distribution of some OSP products. As this is a temporary solution, more studies are needed to delineate the pathophysiology of this disease and to better identify the subset of the population at risk for APN.

Keywords

acute kidney injury, colonoscopy, nephrocalcinosis, phosphate nephropathy

Curr Opin Nephrol Hypertens 18:513–518
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1062-4821

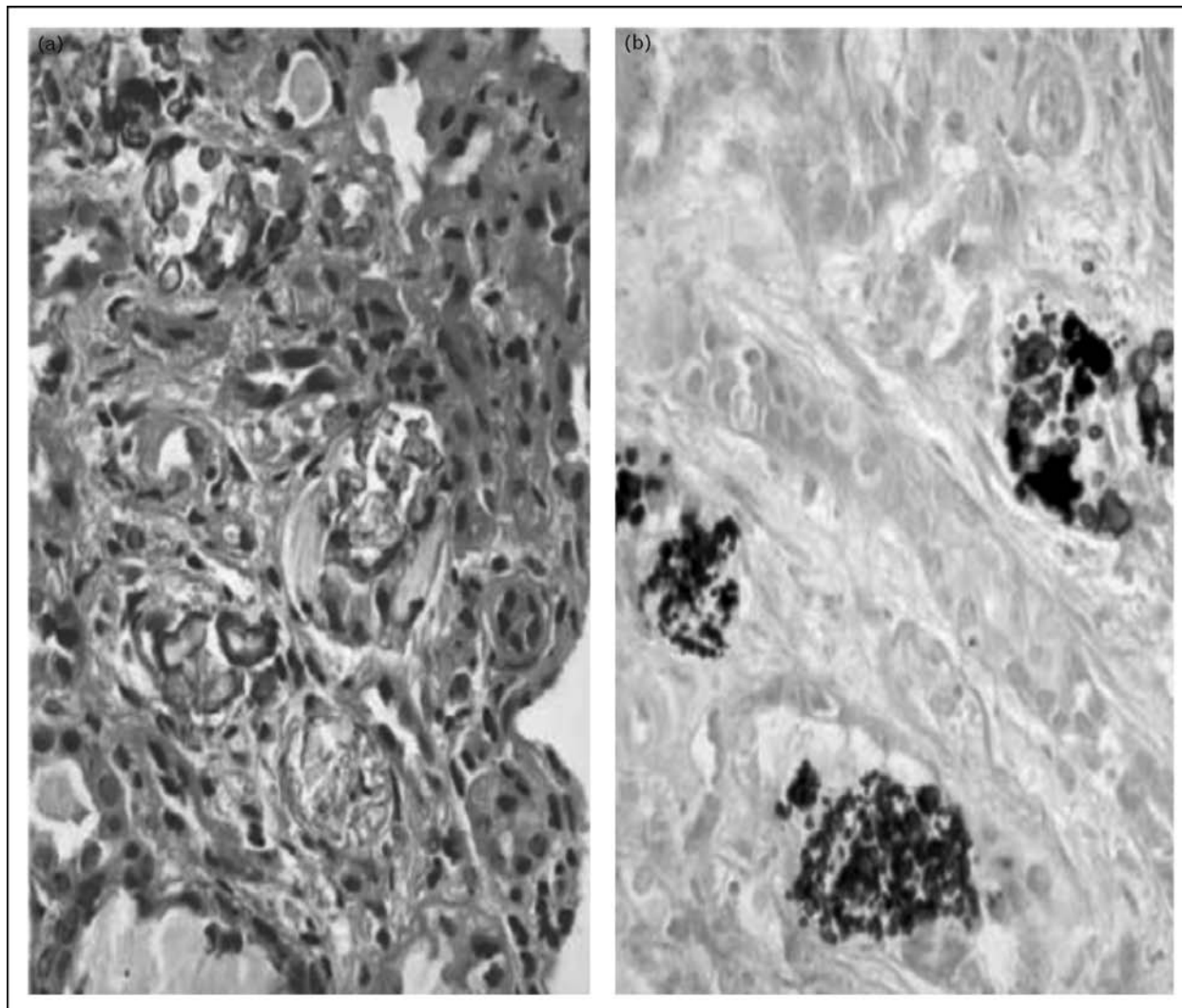
Introduction

Acute phosphate nephropathy (APN) was first described in 2003 in a 71-year-old female patient who developed acute kidney injury (AKI) after ingestion of oral sodium phosphate (OSP). She presented with nonspecific malaise 2 weeks after exposure to OSP with a serum creatinine of 4.5 mg/dl up from a prior baseline of 1.0 mg/dl. Renal biopsy showed numerous intratubular deposits containing calcium and phosphate ions assembled as hydroxyapatite crystals (Fig. 1). On the basis of appearance of the biopsy, the authors postulated that OSP ingestion led to obstructive calcium phosphate crystal-luria and intraluminal nephrocalcinosis. This insult resulted in chronic kidney disease (CKD) in that the patient's renal function did not return to prior baseline 1 year later (serum creatinine 1.7 mg/dl) [1].

Later, a large biopsy case series described more histopathologic cases of APN, strengthening the association of OSP ingestion to this pathologic finding. The authors reviewed biopsies over a 5-year period, searching for cases with the triad of unexplained AKI, OSP exposure, and nephrocalcinosis (with normal serum calcium). A

total of 21 cases met criteria out of 7349 biopsies (0.29%). The renal biopsy findings showed abundant calcium phosphate deposits in the distal tubules and collecting ducts often accompanied by tubular atrophy and interstitial fibrosis. Most patients had normal renal function prior to OSP exposure [mean baseline serum creatinine of 1.0 mg/dl (range 0.6–1.7 mg/dl)], though some patients had preexisting CKD. After a mean of 16.7 months of follow-up, no patient returned to baseline creatinine [mean 2.4 mg/dl (range 1.3–3.4)], and 19% were on permanent hemodialysis [2].

This study helped to confirm prior suspicions that APN may be an underrecognized cause of both AKI and CKD. With increased recognition of this disease and increasing numbers of reported cases, the US Food and Drug Administration (FDA) issued an alert in May 2006 describing APN as a rare but serious event associated with the use of OSP for bowel cleansing. Cases continued to surface, and several epidemiologic studies were published in an attempt to quantify the risk of AKI with the use of OSP. On 11 December 2008, the FDA issued a boxed warning on prescription OSP products and directed manufacturers to develop a risk evaluation

Figure 1 Histological features of acute phosphate nephropathy

(a) A light micrograph shows intratubular deposits (arrows) (hematoxylin and eosin). Signs of tubular necrosis and atrophy of the surrounding parenchyma are visible. (b) The micrograph shows black staining, which indicates that these deposits correspond to microcalcifications (von Kossa stain). Intratubular deposits were nonbirefringent under polarized light suggesting that the deposits represent calcium phosphate. Adapted with permission from [1].

strategy and to conduct postmarketing clinic trials to further assess the risk of AKI with OSP. After this announcement, the manufacturer of the over-the-counter OSP preparations ceased distribution and initiated a voluntary recall of their OSP products.

Diagnosis and clinical presentation

On the basis of the clinical presentation of APN cases with biopsy confirmation, it seems that this disease can present both acutely (shortly after exposure with symptoms related to uremia, hyperphosphatemia, or hypocalcemia) or subacutely with an incidentally discovered increase in serum creatinine from baseline [3]. If detected shortly after OSP exposure during the phosphorus reten-

tion phase, one could find an elevated serum phosphorus and low-to-normal serum calcium. However, this can be misleading with respect to diagnosis as it is not uncommon for patients (that do not develop AKI) to have hyperphosphatemia for several hours after bowel preparation with OSP [4,5]. Additionally, these are not uncommon laboratory findings in CKD secondary to phosphate retention and secondary hyperparathyroidism.

Adding to the diagnostic difficulty, patients with APN have a bland urinary sediment with no cellular casts or crystals. Hematuria and pyuria have been intermittently observed, and there is typically low-grade proteinuria [2]. Taken together, the lack of unique clinical findings makes diagnosis difficult, if not impossible, without a

renal biopsy. However, patients with this clinical presentation (mild creatinine increase, minimal proteinuria, inactive urinary sediment) are rarely biopsied [2].

Another issue with diagnosis of APN involves how we define and label the outcome in question. In cases without pathologic correlation that present subacutely, the only available information is an interval increase in serum creatinine between two dates with an OSP exposure in between the dates. Some authors have referred to this as AKI, inferring that an acute event occurred between the lab dates leaving residual renal damage and the label itself ('acute' phosphate nephropathy) implies an abrupt change. However, the type of clinical presentation may just reflect the timing of the laboratory specimens. For example, if the case from Desmeules *et al.* [1] presented 1 year after colonoscopy, she would have an unexplained elevation of creatinine (1.7 mg/dl) and bland urinary sediment. Although this may seem to be unexplained CKD, it would actually represent irreversible renal damage from a prior episode of AKI. In addition to the primary insult, some authors have suggested a potential progressive decrease in renal function because of pro-inflammatory actions of tissue crystal depositions [6•].

Because APN is not always detected in the 'acute' stage, some authors have defined the outcome as incident CKD after OSP exposure [7,8]. The modification of diet in renal disease (MDRD)-estimated glomerular filtration rate (eGFR) prediction equation was designed to estimate GFR in CKD patients with stable renal function and should not be used during episodes of AKI [9]. However, it is unclear if this exception also applies to the more subacute 'interval creatinine increase' observed in suspected APN cases.

More sensitive markers of renal injury are being developed but have not transitioned into standard clinical practice. One of these markers, urinary *N*-acetyl-D-glucosamidase (NAG), was found to be elevated after exposure to OSP compared with a polyethylene glycol (PEG)-based purgative [10]. Neutrophil gelatinase-associated lipocalin (NGAL) is another marker for renal injury that may be more sensitive than serum creatinine [11], and there is a pilot study currently enrolling patients, which will evaluate the change in NGAL following OSP bowel preparation [12].

Frequency of occurrence

The exact frequency with which APN occurs in the national colonoscopy population is not known. APN is thought to be a relatively rare occurrence, and, as above, definitive diagnosis is difficult in that it requires an invasive procedure (renal biopsy). Retrospective reports have documented pathologic findings of APN in several

cases, but the denominator of exposed patients is not available for these studies. Presumably, cases that are biopsied represent the most severe cases, potentially missing patients with a subacute presentation or mild elevation in serum creatinine. There are several retrospective observational studies available that identify episodes of AKI (based on serial change in creatinine) among populations of patients exposed to OSP (Table 1) [8,13,14,15•,16•,17••], but few, if any, have biopsy confirmation. Although these studies help to estimate the frequency of APN occurrence, absence of biopsy confirmation limits the conclusions that can be drawn from these studies.

In the largest observational study to date, we identified 83 cases of AKI (defined as 50% increase in serum creatinine) out of 6342 patients (1.3%) exposed to OSP during the 3.5-year study period [13]. Using the same definition of AKI, Singal *et al.* [15•] identified seven cases out of 157 patients (4.5%), and Brunelli *et al.* [16•] found 14 cases out of 1432 patients (0.98%). When defining AKI as doubling of serum creatinine, we identified 15 cases out of 6342 (0.23%) [13], and Russmann *et al.* [8] found 11 cases out of 2083 patients (0.53%). Most of these studies did not assess long-term outcomes, and, without biopsy, it is possible that this injury may not represent histopathologic APN.

Unfortunately, because of differences in study design and varying definitions of AKI, it is difficult to combine the results to better understand the frequency of occurrence across centers. Previously, the incidence of serious adverse events was reported to be 1–5 per million 90 ml OSP treatments in the United States, though it has been suggested that these statistics may be at the lower end of what actually occurs [18]. If our cohort is representative of the general population, our data would suggest that the frequency of AKI with OSP is closer to 13 per 1000 patients (or 2 per 1000 patients with doubling of serum creatinine). As reported in our limitations, this figure could be an overestimate of risk in that the patients who had available serum creatinine values were older, had more medical comorbid disease, and were on more medications. However, it is also possible that this underestimates the risk in that patients without labs could have undetected AKI.

Many of the observational studies have compared patients who received OSP preparations to those who received PEG-based preparations in order to have an equivalent control population that also undergoes purging in an attempt to minimize confounding. However, we found that the population of patients who receive PEG for colonoscopy is not equivalent in that it is an older population with more comorbidities, more medications, and more frequent lab monitoring. Other

Table 1 Summary of observational studies reporting acute kidney injury events in oral sodium phosphate-exposed patients

Reference	Study design	CSPs performed	SCr available	Percentage with SCr	OSP exposed	Percentage with OSP	OSP events	Percentage with event	Event definition
Hurst <i>et al.</i> [13]	RC	16 826	9799	58.24	6432	65.64	83	1.29	50% rise in SCr
Hurst <i>et al.</i> [13]	RC	16 826	9799	58.24	6432	65.64	15	0.23	100% rise in SCr
Abaskharoun <i>et al.</i> [14]	RC	Unknown	767	Unknown	618	80.57	42	6.80	Abnormal SCr (or CrCl) ^a
Russmann <i>et al.</i> [8]	RC	7897	3969	50.26	2083	52.48	79	3.79	Post-CSP GFR < 60 ml/min ^b
Russmann <i>et al.</i> [8]	RC	7897	3969	50.26	2083	52.48	11	0.53	100% rise in SCr ^c
Singal <i>et al.</i> [15 [•]]	RC	Unknown	311	Unknown	157	50.48	7	4.46	50% rise in SCr
Singal <i>et al.</i> [15 [•]]	RC	Unknown	311	Unknown	157	50.48	32	20.38	25% rise in SCr
Brunelli <i>et al.</i> [16 [•]] ^a	CC	8218	2237 ^d	27.22	1432	64.01	14	0.98	50% rise in SCr
Brunelli <i>et al.</i> [16 [•]] ^a	CC	8218	2237 ^d	27.22	1432	64.01	11	0.77	50% rise in SCr, earliest post-CSP
Brunelli <i>et al.</i> [16 [•]] ^a	CC	8218	2237 ^d	27.22	1432	64.01	56	3.91	25% rise in SCr, earliest post-CSP
Brunelli <i>et al.</i> [16 [•]] ^a	CC	8218	2237 ^d	27.22	1432	64.01	6	0.42	50% rise in SCr, age > 50 years
Brunelli <i>et al.</i> [16 [•]] ^a	CC	8218	2237 ^d	27.22	1432	64.01	32	2.23	25% rise in SCr, age > 50 years
Khurana <i>et al.</i> [17 ^{••}]	CC	>3000	286	9.53	Unknown	Unknown	Unknown	Unknown	Mean difference in SCr and eGFR

CC, case-control; CrCl, creatinine clearance; CSP, colonoscopy; eGFR, estimated glomerular filtration rate; OSP, oral sodium phosphate; RC, retrospective cohort; SCr, serum creatinine.

^a Abnormal SCr (or CrCl) in patient with previously normal SCr (or CrCl).

^b Post-CSP GFR < 60 ml/min and decrease of ≥ 10 ml/min.

^c Data obtained directly from authors.

^d Estimated 2237 patients with creatinine data available based on 64% exposed to OSP (Case-control study so exact number exposed not known).

authors have reported similar differences in bowel purgative selection in the 'as-treated' population [8,14,15[•]].

Because of the above differences in patient populations, unadjusted comparisons of outcomes between OSP and alternative agents must be interpreted with caution. Even when comparing the adjusted rates of AKI between these two treatment groups, there have been conflicting results. In our analysis, we found that OSP use conferred a two-fold to three-fold increased risk of AKI (depending on multivariate model used) when compared with patients who received PEG-based purgatives. Of note, we could not account for dose of purgative received, volume status of patients, or fluid intake around the time of purgative use.

Brunelli *et al.* [7] demonstrated an association between OSP and AKI, but only in patients who were taking angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). Singal *et al.* [15[•]] showed a significant association with OSP and AKI (defined as 25% increase in serum creatinine), but this seemed to be reversible in that all creatinine values returned to baseline after 6 months of follow-up. Khurana *et al.* [17^{••}] noted a significant increase in serum creatinine and significant decrease in MDRD eGFR from baseline at 6 and 12 months after OSP exposure. Other studies have found no association between OSP and AKI when compared with PEG [8,14]. The limitations of these studies are beyond the scope of this review. In an attempt to pool results from these studies, a recent systematic review and meta-analysis was performed.

However, the author concluded that it is impossible to discern an association between OSP and AKI based on the heterogeneity of existing data [19^{••}].

A small randomized control trial of 411 patients reported no significant increase in serum creatinine after OSP bowel preparation and reported no serious adverse events [20]. Another small randomized trial (completed and previously published as an abstract) with results presented at the 2005 American College of Gastroenterology meeting enrolled 207 patients with normal renal function, who received OPS for elective colonoscopy and followed renal function for 3 months after procedure. They divided patients into two groups based on presence ($n = 98$) or absence ($n = 109$) of implicated medications [ACEI, ARB, nonsteroidal anti-inflammatory drugs (NSAIDs)]. There was no significant change in GFR from baseline or between groups [21].

Clearly, large prospective randomized controlled studies are needed. Because this is presumably a rare outcome somewhere in the range of 1–5 per million to 2–13 per 1000 (in our study), a rather large number of patients would be required to demonstrate differences in risk or safety among populations. Also complicating matters is which population to study. Presumably, studying a lower risk population will require more patients to demonstrate outcomes, and there are potential ethical issues with administration of OSP to thousands of higher risk patients. Other issues are whether or not to hold potentially offending medications (ACEI, ARB, and NSAIDs)

and whether patients should be sequestered to ensure adequate hydration. This situation highlights the need for better tools to detect and evaluate rare outcomes. Although prospective randomized controlled trials are ideal, they may not be feasible with uncommon adverse events such that we must rely on other methods (observational studies, meta-analysis, etc.).

It is important to note that APN has not been reported in prior randomized controlled trials designed to assess bowel cleansing. This could be because not enough patients are studied for this rare outcome but could also represent differences between the trial populations and the general population. OSP dose and fluid intake instructions may differ or patients may be less likely to comply in the 'as-treated' population. It is also possible that cautions are not as enforced in the 'as-treated' population [8]. Alternatively, some patients may have increased susceptibility to APN as many become hyperphosphatemic and hyperphosphaturic but do not develop APN. This could be related to duration of exposure or absolute threshold of calcium phosphate product. However, arguing against this is the lack of calcium phosphate deposition in the postmortem specimen of a patient with a peak phosphorus of 47 mg/dl, suggesting that not all patients may be susceptible to the APN lesion [22].

We also must not ignore that OSP was also used as a purgative prior to colorectal or gynecologic surgery, although without renal biopsy it is even more difficult to establish an association in these populations as surgical intervention induces other potential confounding factors (general anesthesia, intraoperative hypotension, ureteral injury, etc.).

Prevention

While we do not know the exact frequency at which this disease occurs, actions have been taken to minimize future cases. Initially, additional cautions were added to product labels and fluid intake recommendations were increased. Recommended OSP dose was reduced from 90 to 75 ml, and newer-generation OSP products with less phosphorus were introduced. However, after the recent FDA warning, many OSP products were discontinued and removed from distribution. Although avoidance is one option to prevent future cases of APN, we may be eliminating the more tolerated bowel purgative options for the lower risk population. However, with increased fluid intake recommendations, OSP may no longer be the 'low-volume' preparation it once was, and newer tolerability studies may not favor OSP over PEG.

Although the use of OSP solution as a bowel purgative is currently on hold, prescription OSP products are still available studies are being performed with alternative

agents. A recent study reports the use of a sulfate-based osmotic purgative that was found to be less likely to produce calcium salt deposition in tubules when compared with lower dose OSP and was an equally effective cathartic when compared with PEG [23**]. In addition to substitution of phosphorus for other osmotic agents, future investigation should focus on preventing the absorption of phosphorus, which would eliminate the hyperphosphatemia/hyperphosphaturia thought to cause APN and increase cathartic action as the osmotically active substances would remain in the bowel.

Conclusion

Bowel preparation is an essential part of colorectal cancer screening, and OSP was once the dominant bowel purgative in the United States because of patient tolerability and improved colonic visualization [24]. However, because of the potential risk of APN, manufacturers have ceased production and distribution of some OSP bowel-cleansing products. On the basis of biopsy studies, there is an association of OSP and APN, but observational studies to date have been unable to definitively quantify the risk of APN with OSP. Although the current risk reduction strategy may prevent future cases of APN, it may also result in missed cases of colorectal cancer. Further studies are needed to delineate the pathophysiology of this disease and to better identify the subset of the population at risk for APN.

Acknowledgements

We would like to thank Dr David Balaban and his coauthors for providing an update on the unpublished results of their randomized trial, which is currently only published in abstract form. We would also like to thank Dr Stefan Russmann and his coauthors for providing additional data from their study.

The views expressed in this article are those of the authors and do not reflect the official policy of the Department of Army, the Department of Defense, or the United States government.

There was no conflict of interests.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 556).

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