

# Food and Drug Administration Science Background Paper: Acute Phosphate Nephropathy and Renal Failure Associated With the Use of Oral Sodium Phosphate Bowel Cleansing Products

Healthcare professionals should be aware that acute phosphate nephropathy, a type of acute renal failure, is a rare, but serious adverse event associated with the use of oral sodium phosphate (OSP) products for bowel cleansing. Documented cases of acute phosphate nephropathy include 21 patients who used an OSP solution (such as Fleet Phospho-soda and Fleet ACCU-PREP) and one patient who used OSP tablets (Visicol). The bowel cleansing doses of OSP solutions (two 45 mL doses taken 10-12 hours apart) and Visicol (40 tablets) provide nearly identical amounts of sodium phosphate: about 60 grams of sodium phosphate per dose. No cases of acute phosphate nephropathy have been associated with OsmoPrep, an OSP tablet bowel preparation (containing 48 grams of sodium phosphate), approved in March 2006.

## Summary

- Acute phosphate nephropathy, a type of acute renal failure, is a rare, but serious adverse event associated with oral sodium phosphate bowel cleansing.
- When acute phosphate nephropathy occurs, renal impairment is often permanent and may require chronic dialysis.
- Individuals at increased risk include: those of advanced age, those with decreased intravascular volume or kidney disease, and those using medicines that affect renal perfusion or function [diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and possibly nonsteroidal anti-inflammatory drugs (NSAIDs)].

## Recommendations

Healthcare professionals should consider the following when choosing a bowel cleanser for their patients:

- Avoid the use of OSP in patients with kidney disease, impaired renal function or perfusion, dehydration, or uncorrected electrolyte abnormalities.
- Avoid exceeding the recommended OSP doses and avoid concomitant use of laxatives containing sodium phosphate.
- Use OSP with caution in patients taking diuretics, ACE inhibitors, ARBs, and NSAIDs.

- Encourage patients to take the correct OSP dose and drink sufficient quantities of clear fluids during bowel cleansing. Two published articles suggest that using an electrolyte rehydration solution may decrease the electrolyte abnormalities and hypovolemia associated with OSP bowel cleansing.<sup>1,6</sup>
- Obtain baseline and post-procedure labs (electrolytes, calcium, phosphate, BUN, and creatinine) in patients who may be at increased risk for a serious adverse event, including those with vomiting and/or signs of dehydration.
- Use hospitalization and intravenous hydration during bowel cleansing to support frail patients who may be unable to drink an appropriate volume of fluid or may be without assistance at home.

## **Discussion**

### ***What is acute phosphate nephropathy?***

Acute phosphate nephropathy (also called acute nephrocalcinosis) presents as acute renal failure with minimal proteinuria and a bland urine sediment in patients recently exposed to OSP. Renal biopsy reveals acute and/or chronic renal tubular injury (depending on time to diagnosis) with calcium-phosphate crystal deposition in the distal tubules and collecting ducts and no other pattern of histological injury.

Bowel cleansing with OSP causes dehydration, decreased intravascular volume, and hyperphosphatemia (due to a large oral phosphate load). The hyperphosphatemia increases phosphate levels in the renal tubules. Decreased intravascular volume stimulates reabsorption of water from the renal tubules further increasing the phosphate concentration in renal tubular fluid. An abnormally high  $[Ca^{2+}][PO_4^{2-}]$  product in renal tubular fluid causes precipitation of calcium-phosphate crystals in the kidney and the pattern of renal injury described above.

### ***Who may be at risk?***

Patients with the following conditions and/or taking the following medications may be at increased risk for acute phosphate nephropathy:

- Decreased intravascular volume (due to congestive heart failure, cirrhosis, or nephrotic syndrome)
- Acute or chronic kidney disease
- Advanced age (OSP-associated hyperphosphatemia may be more severe in individuals ages 57 years and above<sup>3</sup>)
- Medications that affect renal perfusion or renal function such as diuretics, ACE inhibitors, ARBs, and possibly NSAIDs.<sup>4,5</sup>

### ***What data suggest that OSP bowel cleansing can cause acute phosphate nephropathy?***

In September 2003, Desmeules et al. published a case report of acute phosphate nephropathy followed by persistent renal insufficiency in a 71-year old woman who took 90 mL of OSP solution as a cathartic.<sup>2</sup>

In November 2005, Markowitz et al. published a case series study describing 21 biopsy-proven cases of acute phosphate nephropathy in patients who took OSP and had no history of hypercalcemia or superimposed renal pathology.<sup>4</sup> Twenty of these 21 cases of acute phosphate nephropathy occurred in patients who used OSP solution, and one case occurred in a patient who used OSP tablets (Visicol). Of the 21 cases, 17 occurred in females; 13 patients were age 62 years or older; 14 patients were using an ACE inhibitor or ARB; 4 patients were using a diuretic; and 3 patients were using a NSAID. Four patients had mildly elevated baseline serum creatinine levels between 1.3 and 1.7 mg/dL, and 17 patients had normal baseline creatinine levels. Eighteen patients were diagnosed with acute renal failure within two months of colonoscopy, and all were diagnosed within five months. At follow-up (mean 16.7 months post-biopsy), four patients were on hemodialysis (two with normal pre-procedure creatinine), and 17 patients had chronic renal failure with a mean serum creatinine of 2.4 mg/dL.<sup>4</sup>

In addition to the published cases cited above, 10 unique cases of renal failure associated with use of OSP solution and 10 cases of renal failure associated with use of OSP tablets were identified through FDA's Adverse Event Reporting System (AERS). Most of these cases did not have a renal biopsy or biopsy results were not available; therefore, the causes of renal failure were not clearly established in these patients.

### ***Are there ways to reduce the risk of acute phosphate nephropathy?***

OSP bowel cleansing should be avoided in at-risk individuals for whom there is another bowel cleansing option. When OSP bowel cleansing is used, electrolyte abnormalities and intravascular volume depletion (dehydration) during its use may lower the risk of acute phosphate nephropathy. Clinical studies have not compared the safety of different volumes and/or different types of hydration during bowel cleansing. OSP tablet directions for use recommend drinking 2 to 3.4 liters of fluid during bowel cleansing, and various volumes of fluid are recommended during bowel cleansing with OSP solution (0.7 – 2.2 liters<sup>7</sup>). The volume of hydration necessary to minimize electrolyte abnormalities and to lower the risk of acute phosphate nephropathy is not known. Furthermore, it is not known whether hydration volume should be individualized based on weight, age, gender, concomitant medications, or medical conditions. Data from two published articles suggest that rehydration with an electrolyte solution may decrease the intravascular depletion and electrolyte abnormalities associated with OSP bowel cleansing.<sup>1, 6</sup>

## Conclusion

OSP products are commonly used for bowel cleansing prior to colonoscopy, radiographic procedures, and surgery. OSP bowel cleansing involves a large phosphate load, fluid shifts, decreased intravascular volume, and the potential for the rare, but serious, adverse event of acute phosphate nephropathy. In order to optimize safety for patients, healthcare providers should be familiar with the risk profile of OSP products used for bowel cleansing prior to directing their use.

Healthcare providers are encouraged to report cases of renal failure following OSP bowel cleansing and other unexpected adverse drug events to FDA through MedWatch:

<http://www.fda.gov/medwatch/how.htm>

## References

1. Barclay RL, Depew WT, Vanner SJ. Carbohydrate-electrolyte rehydration protects against intravascular volume contraction during colonic cleansing with orally administered sodium phosphate. *Gastrointest Endosc.* 2002; 56(5): 633 – 38.
2. Desmeules et al. Acute phosphate nephropathy and renal failure. *NEJM.* 2003 Sep 4; 349(10): 1006 – 7.
3. Gumurdulu et al. Age as a predictor of hyperphosphatemia after oral phosphosoda administration for colon preparation. *J Gastroent and Hepatol.* 2004; 19: 68 – 72.
4. Markowitz et al. Acute phosphate nephropathy following oral sodium phosphate bowel purgative: an under-recognized cause of chronic renal failure. *J Am Soc Nephrol.* 2005 Nov; 16 (11): 3389 – 96.
5. Perazella MA. Drug-induced nephropathy: an update. *Expert Opin. Drug Saf.* 2005; 4(4): 689 – 706.
6. Tjandra JJ, Tagkalidis P. Carbohydrate-electrolyte (E-lyte) solution enhances bowel preparation with oral FleetPhospho-soda. *Dis Colon Rectum* 2004 Jul; 47(7): 1181 – 86.
7. Fleet products: [www.phosphosoda.com](http://www.phosphosoda.com)
  - o [Fleet Phospho-Soda Label](#) 
  - o [Fleet Accu-Prep Label](#) 