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# Sodium Phosphate Tablets and Acute Phosphate Nephropathy

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We report 10 cases of acute phosphate nephropathy (APN), associated with acute renal failure (ARF), following administration of sodium phosphate tablets (SPTs) that were used as a bowel preparation before colonoscopy. SPTs were first approved by the US Food and Drug Administration (FDA) in September 2000 for bowel cleansing at a dose of 60 g (40 tablets) in two divided doses with adequate hydration (trade name Visicol). The proposed mechanism of action of SPTs is an osmotic effect. The Visicol product was subsequently reformulated, because it was found that one of the excipients, microcrystalline cellulose, was leaving a residue in the colons of some patients that impaired visibility during their colonoscopy (1). In addition, the manufacturer of this product provided data demonstrating that patients' bowels were effectively cleansed with the use of 48 g (32 tablets) of sodium phosphate (SP) in divided doses with adequate hydration. With these doses, a new product (trade name OsmoPrep) was approved by the FDA in March 2006. Both products are marketed by Salix Pharmaceuticals at a dose of 1.5 g SP per tablet. Note that APN also has been associated with the use of SP oral solution for bowel cleansing (2). This article addresses the SPT dosage form only. (SP oral solution is no longer available over the counter for the indication of bowel cleansing. CB Fleet is applying for prescription status (3).)

From July 2006 to September 2008, 10 cases of APN associated with SPT use for bowel cleansing were reported to the FDA's Adverse Event Reporting System (AERS) database (**Table 1**; patients 1–7 took Visicol and patients 8–10 took OsmoPrep). Note that two cases (patients 5 and 6 in **Table 1**) also have been reported in the literature; no additional cases have been published (2,4). Renal biopsy in these 10 patients revealed nephrocalcinosis (calcium phosphate crystal deposition in the distal tubules and collecting ducts). Decreased intravascular volume caused by bowel cleansing may also contribute to an increase in the phosphate concentration in renal tubular fluid.

The patients in this case series all had at least one underlying risk factor for ARF, and most had more than one (**Table 1**). In addition to decreased intravascular volume as described above, other risk factors for ARF include preexisting renal insufficiency, hypertension, diabetes mellitus, advanced age, underlying electrolyte imbalance, and concomitant medications that affect renal perfusion or function (e.g., angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blocker (ARB) drugs, nonsteroidal anti-inflammatory drugs (NSAIDs), or diuretics) (5,6). Patients with chronic inflammatory bowel disease may have enhanced absorption of SP (7). One retrospective case-controlled study using records from the University of Pennsylvania health-care system found a significant association between ACEI/ARB use and acute kidney injury in patients with baseline serum creatinines of  $\leq 1.5$  mg/dl who received SP for bowel cleansing before colonoscopy (8).

It has been documented in the literature that maintaining adequate hydration and dividing the two SP doses by 12 hours are important to prevent intravascular volume depletion and thereby minimize the risk of APN and ARF (9–11). The product labels for Visicol and OsmoPrep recommend that patients take a total of at least 112 ounces and 64 ounces of liquid, respectively, and that divided doses be taken in the evening and morning before colonoscopy (7,12). In this case series, there is little reported information on whether patients took SPTs correctly or incorrectly (information of this type is typically not provided in adverse-event reports and is difficult to obtain on follow-up inquiry); patient 9 separated the two SP doses by 3 hours only.

Four patients in this case series required dialysis. To date, there have been no reported deaths or kidney transplantations associated with SPT use.

From 1 January 2001 through 30 September 2008, 2,297,958 and 1,329,497 prescriptions were dispensed for Visicol and for OsmoPrep, respectively (**Figure 1**). These data were obtained from the SDI Vector One database, which measures retail dispensing of prescriptions.

In addition to the 10 cases of APN, the AERS has received 31 cases reported as ARF associated with SPT use. These patients did not have a renal biopsy to document nephrocalcinosis; therefore, the mechanism of renal failure with SPT exposure could not be verified. Of these 31 cases, 12 patients used Visicol, 4 patients used a foreign SP product (1 g per tablet, total dose of 50 g in divided doses with adequate hydration), and 15 patients used OsmoPrep. A total

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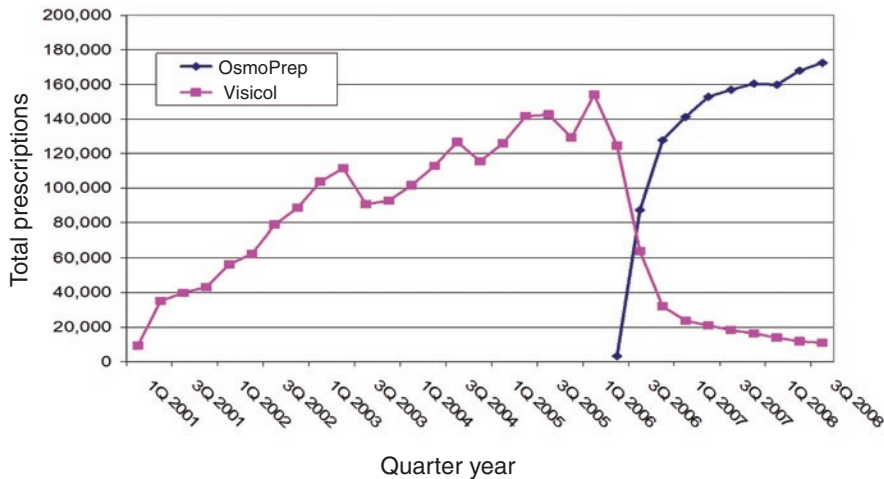
**Table 1.** Summary of case reports of acute phosphate nephropathy associated with use of sodium phosphate tablets for bowel cleansing as reported to the Food and Drug Administration's Adverse Event Reporting System from July 2006 to September 2008

Patient no.	1	2	3	4	5	6	7 <sup>a</sup>	8 <sup>a</sup>	9	10
Age/sex	67/F	70/F	66/F	55/F	60/F	44/M	65/M	58/F	58/F	63/F
Date of colonoscopy	Feb. 2006	Apr. 2006	Mar. 2006	Oct. 2007	Apr. 2005	Feb. 2003	Dec. 2005	Oct. 2007	Apr. 2007	Jan. 2008
Reason for colonoscopy	Not stated	Not stated	Screening	Abd. pain	Screening	Bloody stool	Not stated	Not stated	Abd. pain, possible CD	Screening
SPTs (grams)	Not stated	30 (As one dose)	Not stated	Not stated	42 (As one dose)	48 (Divided doses of 30 in the evening and 18 the next morning)	48 (Over a 2-day period)	Not stated	48 (Divided doses of 30 and 18 separated by 3 hours)	Not stated
Time to detection <sup>b</sup> (after use of preparation)	Not stated	11 Days	1 Day	Not stated	4 Months	2 Months	<12 Days	15 Days	21 Days	14 Days
Risk factors for renal dysfunction	HTN, DM type 2, ACEI, diuretic	HTN, ACEI	HTN, ACEI	HTN, ARB, NSAID	HTN, ACEI	RI, HTN, colitis, ACEI (high dose), NSAID	HTN, DM, gastrectomy, ACEI, diuretic	HTN, NSAID, diuretic	HTN; possible CD, ACEI, NSAID (p.r.n.)	NSAID
Outcome	HO	Not stated	HO	HO, dialysis	Not stated	Not stated	HO, dialysis	HO, dialysis	HO	HO, dialysis
<b>Serum creatinine values (mg/dl)<sup>c</sup></b>										
Baseline <sup>d</sup>	1.2	1	Not stated	WNL	0.9	1.7	1.2	1.1	0.5	Not stated
Value measured after procedure	2.8	2.6 – 2.8	4.5	4 Range	1.8	2.3	7.3	3.1	2	10.6

Attempts were made to contact reporters for follow-up information on these cases. One case reported as moderate acute tubular necrosis and extensive luminal calcification in a 53-year-old woman who took OsmoPrep, and one case reported as acute tubular necrosis with intratubular calcifications consistent with acute phosphate nephropathy in a 69-year-old woman have been excluded because nephrocalcinosis was not reported (these cases are included in our discussion of patients who developed acute renal failure). (Special thanks to Lynne Yao for her expertise in the review of these cases.)

Abd, abdominal; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CD, Crohn's disease; DM, diabetes mellitus; F, female; HO, hospitalization; HTN, hypertension; M, male; NSAID, nonsteroidal anti-inflammatory drug; RI, renal insufficiency; SPT, sodium phosphate tablet; WNL, within normal limits.

<sup>a</sup>In addition to nephrocalcinosis, the biopsy for patient 7 showed intermediate stages of diabetic glomerulopathy, and the biopsy for patient 8 showed moderate chronic tubulointerstitial nephritis. <sup>b</sup>Time to detection is reported based on when the patient had symptoms of renal impairment, sought medical advice, and was tested. <sup>c</sup>Normal serum creatinine value = 0.5–1.5 mg/dl. <sup>d</sup>Where reported, baseline creatinine laboratory values were measured in samples obtained up to 3 months before SPT administration with the following exceptions: time frame not specified for patient 1, and baseline for patient 4 was taken 4–5 months before SPT administration.



**Figure 1.** Drug-use data: total number of dispensed prescriptions for sodium phosphate tablets (i.e., Visicol, OsmoPrep) in outpatient retail pharmacies, 1 January 2001 through 30 September 2008. (From SDI Vector One: National; data extracted January 2009 by Patty Greene, Drug Utilization Data Analysis, Division of Epidemiology, Office of Surveillance and Epidemiology, US Food and Drug Administration.)

of 27 cases were reported from domestic sources, and 4 cases were reported from foreign sources. The patients ranged in age from 45 to 77 years (mean 65 years; age not reported for 1 patient); 22 patients were female, and 9 patients were male. The doses used ranged from 30 to 60 g (mean 49 g;  $n=23$ ; dose was not reported for 8 patients). It was reported that 21 patients used a split-dose regimen (3 of the 21 patients split their dose with an interval of only 3–4 hours); 12 patients were reported to have followed hydration directions (information on dose and hydration was not reported for the remaining patients). Of the 31 patients, 4 patients used additional laxatives with SPTs (i.e., bisacodyl, magnesium citrate). The time to ARF detection after SPT use ranged from 0.5 to 60 days (mean 6.3 days;  $n=25$ ; information was not provided for 6 patients). The following risk factors for renal dysfunction were reported (not mutually exclusive): hypertension (22 patients), diabetes mellitus (9 patients), preexisting renal insufficiency (2 patients), inflammatory bowel disease (2 patients), ACEI/ARB use (20 patients), diuretic use (8 patients), NSAID use (7 patients), and contrast dye use (2 patients). At least 25 patients were hospitalized for ARF, including 4 patients who required dialysis (outcome was not

reported for 6 patients). Baseline creatinine values were reported for 13 patients (these were within normal limits except for one patient with preexisting renal insufficiency); postprocedure creatinine values were reported for 20 patients and ranged from 1.2 to 10 mg/dl (mean 5.7 mg/dl). Two patients' creatinine values were reported as "elevated"; postprocedure creatinine values were not included in reports for 9 patients.

The AERS is a spontaneous, voluntary surveillance system that collects reports of adverse events for US marketed medicinal products. Manufacturers holding New Drug Applications or Biologic Licensing Applications must submit adverse-event reports to the AERS according to the Code of Federal Regulations. Data from the AERS cannot be used to estimate true incidence rates of events, because the numerator is underestimated and the denominator can only be estimated. The AERS is subject to underreporting; fewer than 10% of adverse events are reported to the FDA, so there may be additional cases of APN associated with SPT use for bowel cleansing (13).

The manufacturer of SPTs added APN to the warnings section of the labels for its products in March 2006. At that time, the FDA posted information about the

association of APN and SP product use for bowel cleansing on its Web site (14). Since May 2006, the FDA has received additional cases of APN and ARF associated with SPT use. As a result of this new safety information, the FDA has required the manufacturer of prescription SPT products (Visicol and OsmoPrep) to strengthen product labeling to include a boxed warning, provide a medication guide for patients, and implement a risk evaluation and mitigation strategy to ensure that the benefits of SP products outweigh the risks. The FDA is also requiring that a postmarketing clinical trial be conducted to further assess the risk of acute kidney injury with use of these products. For additional information, see the December 2008 FDA Alert at the FDA's website (15).

The patients in this case series had potentially confounding medical conditions or were taking concomitant medications that put them at increased risk for nephrotoxicity; however, a causal or contributory role of SPTs cannot be ruled out. It appears that some patients, especially those with risk factors, developed APN with doses as small as 30 g of SP.

Clinicians should be aware when prescribing SPTs that some patients who developed renal injury did not present with symptoms of APN for up to several months after using SPTs. Until further information is available (e.g., a recently proposed clinical trial by the FDA (15)), there is insufficient information to make global recommendations regarding standard pre- and postprocedure renal-function testing for patients who may be at risk. In addition, the importance of taking SPTs correctly (i.e., with adequate hydration and splitting the two SP doses by 12 hours) should be stressed in order to reduce the risk of developing APN and ARF.

#### CONFLICT OF INTEREST

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## REFERENCES

1. Wruble L, DeMicco M, Medoff J *et al*. Residue-free sodium phosphate tablets (OsmoPrep) versus Visicol for colon cleansing: a randomized, investigator-blinded trial. *Gastrointest Endosc* 2007;65:660–70.
2. Markowitz GS, Stokes MB, Radhakrishnan J *et al*. Acute phosphate nephropathy following oral sodium phosphate bowel purgative: an underrecognized cause of chronic renal failure. *J Am Soc Nephrol* 2005;16:3389–96.
3. US Food and Drug Administration. Oral Sodium Phosphate (OSP) Products for Bowel Cleansing (marketed as Visicol and OsmoPrep, and oral sodium phosphate products available without a prescription) - Healthcare Professional Sheet text version <<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126084.htm>> (2008).
4. Carl KE, Sica DA. Acute phosphate nephropathy following colonoscopy preparation. *Am J Med Sci* 2007;334:151–4.
5. Schetz M, Dasta J, Goldstein S *et al*. Drug-induced acute kidney injury. *Curr Opin Crit Care* 2005;11:55–65.
6. Leblanc M, Kellum JA, Gibney RTN *et al*. Risk factors for acute renal failure: inherent and modifiable risks. *Curr Opin Crit Care* 2005;11:553–6.
7. OsmoPrep [product label]. Salix Pharmaceuticals: Morrisville, NC, revised April 2006.
8. Brunelli SM, Lewis JD, Gupta M *et al*. Risk of kidney injury following oral phosphosoda bowel preparations. *J Am Soc Nephrol* 2007;18:3199–205.
9. Lichtenstein GR, Cohen LB, Uribarri J. Bowel preparation for colonoscopy: the importance of adequate hydration. *Aliment Pharmacol Ther* 2007;26:633–41.
10. Rex DK. Dosing considerations in the use of sodium phosphate bowel preparations for colonoscopy. *Ann Pharmacother* 2007;41:1466–75.
11. Caswell M, Thompson WO, Kanapka JA *et al*. The time course and effect on serum electrolytes of oral sodium phosphates solution in healthy male and female volunteers. *Can J Clin Pharmacol* 2007; 14:e260–74.
12. Visicol [product label]. Salix Pharmaceuticals: Morrisville, NC, revised March 2006.
13. Rogers AS, Israel E, Smith CR. Physician knowledge, attitudes, and behavior related to reporting of adverse drug event. *Arch Intern Med* 1998;148:1596–600.
14. US Food and Drug Administration. Science Background Paper: Acute phosphate nephropathy and renal failure associated with use of oral sodium phosphate bowel cleansing product. Posted May 2006 <<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm161581.htm>>.
15. US Food and Drug Administration. December 2008 FDA Alert <<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103362.pdf>>