Risk of Kidney Injury Following Oral Phosphosoda Bowel Preparations

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ABSTRACT
Case reports and case series suggest a potential link between oral sodium phosphosoda used in preparation for outpatient colonoscopy and kidney injury, but controlled studies are lacking. We performed a case-control study nested within a cohort of patients with baseline serum creatinine ≤1.5 mg/dL who underwent outpatient colonoscopy. We defined a case of kidney injury as a rise in serum creatinine ≥0.5 mg/dL and/or 25% between values obtained during the 6 months prior and during the 6 months following colonoscopy (n = 116). We found that exposure to phosphosoda was not more common among patients with incident kidney injury (adjusted odds ratio 0.70; 95% CI 0.44–1.11), and sensitivity analyses that considered other definitions of kidney injury did not suggest a different conclusion. Therefore, despite a plausible link, the current data do not support an association between oral phosphosoda and kidney injury at 6 months follow-up among patients with baseline serum creatinine ≤1.5 mg/dL. Further studies are warranted to validate and generalize our findings.


Nearly 14 million colonoscopies are performed each year in the United States.1 Bowel preparation is usually achieved using either polyethylene glycol or oral sodium phosphosoda (OPS). In many cases, OPS is the preferred bowel regimen on the basis of better tolerability, cost-effectiveness, and efficacy.2–4

Several uncontrolled case reports and case series5–9 suggested a potential link between receipt of OPS and nephrocalcinosis, acute kidney injury, and/or chronic kidney disease (CKD). Although data in animal models support a potentially causal relationship between OPS and kidney injury,10–13 to date, no controlled human studies have examined this potential association.

CKD’s mounting prevalence (20 million cases in the United States presently14), increasingly recognized morbid consequences,15 and unclear cause, in many cases, combine to make identification of novel risk factors a major public health concern. Considering the vast number of patients who are exposed to OPS each year, even a modest increase in risk conveyed by these agents could translate into a large number of cases of CKD in absolute terms. We undertook the following nested case-control study to determine whether an association exists between incident kidney injury and use of OPS to prepare patients undergoing routine outpatient colonoscopy at three University of Pennsylvania Health System–affiliated units.

RESULTS
A total of 8218 colonoscopies were identified between January 1, 2004, and February 1, 2006.

Received April 12, 2007. Accepted June 28, 2007.
Published online ahead of print. Publication date available at www.jasn.org.
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Among these, 2237 had adequate associated creatinine data to qualify for inclusion in the source cohort. The case definition was met in 141 instances, rendering 132 unique case patients; of these, bowel preparation data were available for 116 (Figure 1). Among the 2096 colonoscopies for which the case definition was not met, 398 unique patients were randomly selected as control subjects; of these, bowel preparation data were available for 349. Patients for whom exposure data were not available \( (n = 65) \) did not differ from those for whom they were \( (n = 465) \), except on the basis of clinical site (Table 1).

Median (interquartile range) baseline creatinine was 1.0 (0.8 to 1.1) and 0.8 mg/dl (0.75 to 1.1 mg/dl) among control subjects and case patients, respectively. The mean increase in creatinine concentration after colonoscopy was 0.41 and 0.00 mg/dl among case patients and control subjects, respectively. The mean (SD) and median (interquartile range) change in serum creatinine were 0.12 (0.34) and 0.1 mg/dl \((-0.1 \text{ to } 0.2 \text{ mg/dl})\) among OPS-unexposed patients and 0.08 (0.26) and 0.0 mg/dl \((-0.1 \text{ to } 0.2 \text{ mg/dl})\) among OPS-exposed patients \( (P = 0.28 \text{ for difference by OPS exposure status}).\)

Case patients were significantly more likely than control subjects to be female, to have congestive heart failure, and to have been exposed to diuretics (Table 2). No other significant baseline differences between case patients and control subjects existed.

Time to latest and maximum serum creatinine in the 6-mo postcolonoscopy period or latest available creatinine did not differ according to OPS exposure status (data not shown). OPS-exposed patients had significantly fewer measurements of serum creatinine in the 6 mo after colonoscopy \((2.5 \pm 3.5 \text{ versus } 3.9 \pm 8.1; P = 0.004)\) but a similar number of measurements overall \((7.0 \pm 11.6 \text{ versus } 8.7 \pm 13.2; P = 0.25)\).

### Association between Incident Kidney Injury and OPS Exposure

Among 116 case patients for whom exposure data were available, 66 (57%) were exposed to OPS; among 349 control subjects for whom exposure data were available, 230 (66%) were exposed to OPS. The crude odds ratio (OR) for OPS exposure case was 0.68 (95% confidence interval [CI] 0.44 to 1.08).

There was little confounding. In the fully adjusted model, including demographics, comorbid disease status, medication exposure, and colonoscopy indication, exposure to OPS was not associated with incident creatinine elevation (adjusted OR 0.70; 95% CI 0.44 to 1.11). Less saturated models yielded nearly identical results (Table 3). Inclusion of baseline estimated GFR (eGFR) as a covariate did not appreciably alter our findings (data not shown).

### Sensitivity Analyses

Several different definitions for case status were used in sensitivity analyses. Because OPS exposure may be associated with acute kidney injury without persistent elevation in serum creatinine (but with lasting clinical implications), we performed a sensitivity analysis in which case definition was defined on the basis of maximum serum creatinine in the 6-mo postcolonoscopy window (SA-1). Because a 25% rise in serum creatinine may in some cases not be the result of actual kidney injury, we performed sensitivity analyses in which case status was defined as an absolute rise of 0.5 mg/dl within 6 mo after colonoscopy (SA-2). Because kidney injury may require >6 mo to become apparent, sensitivity analyses in which case definition was based on a change in serum creatinine between baseline and last available creatinine (SA-3) were performed. A total of 119, 27, and 72 patients met the case definition (and had available exposure data) for SA-1, SA-2, and SA-3, respectively. Results of each of the sensitivity analyses were nearly identical to the primary analysis (Table 3).

In addition, we examined patients with documented rises in serum creatinine of >1 mg/dl. Three case patients had an increase in serum creatinine of this magnitude; only one was exposed to OPS. Considering that our source cohort consisted of >2200 people with a 64% exposure prevalence to OPS, the point estimate for incidence of kidney injury using this more restrictive definition would be seven and 14 cases per 10,000 among OPS-exposed and -unexposed patients, respectively.

### Effect Modification of the Association between OPS Exposure and Incident Kidney Injury

Interactions on the basis of gender, baseline CKD (eGFR <90), and exposure to angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB) were explored in separate models through inclusion of cross-product terms. No significant interaction with gender or baseline CKD was noted. There did seem to be interaction on the basis of ACEI/ARB exposure \((P = 0.03)\); the OR (95% CI) for the association between incident kidney injury and OPS exposure were 1.33 (0.63 to 2.83) and 0.48 (0.27 to 0.85) among ACEI/ARB-exposed and -unexposed patients, respectively (Table 4).
DISCUSSION

Using a nested case-control design, we were unable to demonstrate a relationship between exposure to OPS and kidney injury defined by a rise in serum creatinine of 0.5 mg/dl and/or 25% within 6 mo. As previously hypothesized, there seems to be effect modification on the basis of ACEI/ARB exposure.

Since its introduction in the early 1990s, a number of clinical trials have compared OPS to polyethylene glycol (PEG)-based bowel preparations on the basis of efficacy, safety,
tolerability, and cost-effectiveness. Three meta-analyses\textsuperscript{2–4} concluded that OPS is at least as effective and is more tolerable than PEG.

A number of case reports and case series\textsuperscript{5–9} described a potential association between receipt of OPS and development of nephrocalcinosis, acute kidney injury, and CKD. Existing data suggest a biologically plausible causal association between OPS and kidney injury. Intravenous infusion of phosphate to supraphysiologic levels causes acute kidney injury in rat models.\textsuperscript{16} Similarly, in humans, acute rises in serum phosphate on the basis of tumor lysis results in acute kidney injury\textsuperscript{17–20} from renal parenchymal calcification, alterations in renal hemodynamics, and direct tubular cell cytotoxicity.\textsuperscript{21,22} Multiple case reports and controlled human studies\textsuperscript{5–7,24–26} demonstrated that receipt of a standard regimen of OPS (which contains PEG).\textsuperscript{2} Comparison was made between model with main effects and cross-product term for CKD versus model that included only main effects term.

Although the choice of a 6-mo postcolonoscopy outcome assessment window was not based on firm evidence, we believe that it was a reasonable choice for the following reasons. In selecting 6 mo, we sought to balance our desire to maximize sensitivity (\textit{i.e.}, using longer periods of follow-up) with our desire to maximize specificity (\textit{i.e.}, using shorter periods of follow-up). (In the largest case series to date, all cases were

Table 3. OPS exposure and kidney injury based on logistic regression models\textsuperscript{a}

<table>
<thead>
<tr>
<th>Covariate Terms</th>
<th>Primary Case Definition (aOR [95% CI])</th>
<th>SA-1 (aOR [95% CI])\textsuperscript{b}</th>
<th>SA-2 (aOR [95% CI])\textsuperscript{c}</th>
<th>SA-3 (aOR [95% CI])\textsuperscript{d}</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPS exposure</td>
<td>0.68 (0.44 to 1.05)</td>
<td>0.72 (0.47 to 1.11)</td>
<td>0.43 (0.20 to 0.95)</td>
<td>0.82 (0.49 to 1.37)</td>
</tr>
<tr>
<td>OPS exposure, age, race, gender, site</td>
<td>0.63 (0.40 to 0.99)</td>
<td>0.72 (0.41 to 1.13)</td>
<td>0.44 (0.20 to 1.00)</td>
<td>0.77 (0.45 to 1.32)</td>
</tr>
<tr>
<td>OPS exposure, age, race, gender, site, diabetes, CHF</td>
<td>0.67 (0.42 to 1.06)</td>
<td>0.77 (0.49 to 1.21)</td>
<td>0.55 (0.24 to 1.27)</td>
<td>0.83 (0.48 to 1.44)</td>
</tr>
<tr>
<td>OPS exposure, age, race, gender, site, diabetes, CHF, ACEI/ARB, diuretics</td>
<td>0.67 (0.42 to 1.06)</td>
<td>0.76 (0.48 to 1.20)</td>
<td>0.57 (0.24 to 1.34)</td>
<td>0.82 (0.47 to 1.42)</td>
</tr>
<tr>
<td>OPS exposure, age, race, gender, site, diabetes, CHF, ACEI/ARB, diuretics, indication</td>
<td>0.70 (0.44 to 1.11)</td>
<td>0.79 (0.50 to 1.25)</td>
<td>0.61 (0.26 to 1.46)</td>
<td>0.84 (0.48 to 1.45)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}aOR, adjusted odds ratio; CHF, congestive heart failure; CI, confidence interval; SA, sensitivity analysis.

\textsuperscript{b}Case status was defined as a rise of 25% or 0.5 mg/dl between baseline and maximum value observed within 6 mo after colonoscopy.

\textsuperscript{c}Case status was defined as an absolute rise of 0.5 mg/dl between baseline and last observed value within 6 mo after colonoscopy.

\textsuperscript{d}Case status was defined as a rise of 25% or 0.5 mg/dl between baseline and last observed value overall.

Table 4. OR of association between incident kidney injury and OPS exposure according to ACEI/ARB exposure status, gender, and baseline CKD\textsuperscript{a}

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OPS Exposure (OR [95% CI])</th>
<th>P (Interaction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI/ARB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>unexposed</td>
<td>0.48 (0.27 to 0.85)</td>
<td>0.03</td>
</tr>
<tr>
<td>exposed</td>
<td>1.33 (0.63 to 2.83)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td>0.37</td>
</tr>
<tr>
<td>female</td>
<td>0.60 (0.34 to 1.06)</td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>0.93 (0.34 to 2.02)</td>
<td></td>
</tr>
<tr>
<td>Baseline CKD\textsuperscript{b}</td>
<td></td>
<td>0.94</td>
</tr>
<tr>
<td>eGFR &gt;90 ml/min</td>
<td>0.72 (0.34 to 1.55)</td>
<td></td>
</tr>
<tr>
<td>eGFR &lt;90 ml/min</td>
<td>0.70 (0.38 to 1.27)</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}CKD, chronic kidney disease.

\textsuperscript{b}Comparison was made between model with main effects and cross-product term for CKD versus model that included only main effects term.

Despite this plausible link, our data do not support an association between receipt of OPS and kidney injury.

Our data do support potential effect modification by receipt of ACEI/ARB; specifically, that patients receiving ACEI/ARB fare less well after exposure to OPS. Given the potential for bias or residual confounding associated with retrospective study, this interaction should be viewed cautiously; future study of this interaction is warranted. Out data do not support interaction on the basis of gender, as previously hypothesized\textsuperscript{b}; however, it should be noted that this study was not designed to detect such interaction, and future work in this regard is necessary.

Several potential limitations of this study should be noted. With respect to exposure misclassification, a small proportion of our patients lacked data on bowel preparation; however, patients for whom bowel preparation data were and were not available did not differ on the basis of demographics, comorbid disease status, medication exposure, or case status, and missing data on bowel preparation is unlikely to explain our results.

Misclassification of study outcomes could have arisen from (1) our choice to base outcomes on serum creatinine rather that eGFR, (2) our choice of outcome assessment window, (3) our definition of kidney injury (based on a 25% rise in serum creatinine), and (4) differential opportunity for outcome identification on the basis of exposure status. We based our case definition on change in serum creatinine level rather than on eGFR for two reasons: (1) Estimating equations (\textit{e.g.}, Modification of Diet in Renal Disease [MDRD] equation) systematically underestimate kidney function in patients with normal serum creatinine levels, and (2) use of serum creatinine levels may increase clinical applicability.

Although the choice of a 6-mo postcolonoscopy outcome assessment window was not based on firm evidence, we believe that it was a reasonable choice for the following reasons. In selecting 6 mo, we sought to balance our desire to maximize sensitivity (\textit{i.e.}, using longer periods of follow-up) with our desire to maximize specificity (\textit{i.e.}, using shorter periods of follow-up). (In the largest case series to date, all cases were
discovers within 6 mo of OPS exposure [range 3 d to 5 mo].

Realizing that OPS exposure might result in transient rises in serum creatinine, or, conversely, resultant kidney injury may take longer than 6 mo to become clinically manifest, we performed sensitivity analyses using alternative case definitions. In addition, outcome may have been misclassified by our choice of a 25% rise in serum creatinine. (Patients with lower baseline levels will experience greater proportional rise for a given absolute rise in serum creatinine.) Thus, we performed sensitivity analyses in which the case definition was defined solely in terms of an absolute creatinine rise. In each of these, the results were similar. That results did not qualitatively differ between the primary analyses and any of the sensitivity analyses suggests that our findings were robust despite potential misclassification of outcome.

Moreover, one might expect patients receiving OPS to be more likely to undergo repeat creatinine testing than unexposed patients. In fact, the data indicate the OPS-exposed patients had fewer measurements of serum creatinine in the first 6 mo after colonoscopy and a similar number overall. Timing of serum creatinine measurements was not appreciably affected by OPS exposure; therefore, misclassification of the outcome is unlikely to have explained the lack of association between exposure to OPS and development of kidney injury.

As with all observational studies, there is the potential for residual confounding. Although we adjusted analyses on the basis of many potential confounders, it is possible that other potential confounders for which we were not able to adjust exist; however, for residual confounding to have masked a true association between OPS use and incident kidney injury, the unadjusted confounder would need to have been extremely strongly associated with both OPS use and kidney injury. Given that we adjusted for the common reasons that a physician would choose to use PEG in preference to OPS (e.g., diabetes, heart failure) and excluded patients with elevated baseline creatinine levels, such residual confounding seems extremely unlikely.

Any negative study such as this raises concerns about potentially insufficient study power. In planning this study, we realized that we would have a fixed sample size and performed power calculations on the basis of assumptions regarding this sample size, OPS prevalence, and detectable OR. Our initial power calculations indicated an 80% power to detect a true OR of 1.77; however, missing exposure data slightly attenuated the power. Despite this, all of our OR point estimates were less than unity, with upper confidence bounds near 1, thereby providing reassurance that our not finding a strong association between OPS exposure and kidney failure was not due to type 2 error. Nonetheless, it is possible that a very weak association could have gone undetected. Rather than performing post hoc power calculations, which are generally not considered appropriate, we suggest that future studies be planned using our upper confidence bounds as targeted OR.

Finally, the generalizability of our findings may have been limited by virtue of the performance of this study in a single large medical center and the inclusion only of individuals with a baseline serum creatinine \( \leq 1.5 \text{ mg/dl} \). Although it possible that patients with impaired baseline kidney function (serum creatinine > 1.5 mg/dl) are at increased risk for kidney injury, we did not include these patients for two reasons. First, previous work suggested that OPS is associated with nephrotoxicity among patients with normal kidney function: Markowitz et al. reported that all but one of the 21 cases of kidney injury that they observed had baseline creatinine \( \leq 1.5 \text{ mg/dl} \); therefore, 95% of the patients in that series would have met the inclusion criteria for our study. Second, OPS is contraindicated in patients with kidney disease and, in our institution, carefully avoided in this setting. Focusing on this group with CKD would have yielded a small group of patients with a very low exposure prevalence to OPS. Such a study not only would have been grossly underpowered as a result, but also would have missed any opportunity to detect the association of OPS and kidney injury among individuals with normal kidney function at baseline, the group of patients for whom understanding this relationship is most clinically relevant. Given that we did not investigate whether OPS contributes to worsening kidney function among patients with baseline CKD, our findings should not be extrapolated to that population.

At 6 mo of follow-up, in patients with baseline serum creatinine \( \leq 1.5 \text{ mg/dl} \), there was no apparent increase in the risk for incident kidney injury defined as a 0.5-mg/dl and/or 25% rise in serum creatinine. Additional studies are necessary to validate and generalize findings.

**CONCISE METHODS**

The protocol was approved by the University of Pennsylvania institutional review board.

**Patients and Sites**

We conducted a case-control study nested within a source cohort of patients who underwent outpatient colonoscopy at one of three University of Pennsylvania Health System–affiliated units (two hospital-based and one free-standing unit) between January 1, 2004, and February 1, 2006. January 1, 2004, was chosen because it was the date when it became standard clinical practice to record bowel preparation type in the medical chart. The presence of colonoscopies and relevant demographics, diagnoses, medications, and laboratories were identified through the Pennsylvania Integrated Clinical and Administrative Research Database (PICARD) system, a database of resource use and clinical findings collected through the daily operation of the University of Pennsylvania Health System.

To be included in the source cohort, patients were also required to have evidence of at least one visit to the health system predating the colonoscopy (to provide opportunity for capture of covariate data) and at least one measurement of serum creatinine in the 6 mo before and 6 mo after colonoscopy (to enable longitudinal assessment of kidney function). Patients with a baseline serum creatinine > 1.5 mg/dl were excluded (see the Discussion section).
Identification of Case Patients and Control Subjects

Baseline serum creatinine was defined as the most proximate measurement before colonoscopy; follow-up creatinine was defined as the latest measurement recorded in the 6-mo post-colonoscopy window. For patients meeting the case definition at more than one colonoscopy, only the first episode was considered. Control subjects were chosen by simple random selection from among those not meeting the case definition at a ratio of 3:1 (control subjects:case patients).

Data Collection

Exposure data and colonoscopy indication were abstracted from colonoscopy reports by two investigators who were blinded to case/control status. Patients were considered exposed when their bowel preparation was recorded as either Fleet’s Oral Phosphosoda (C.B. Fleet Co., Lynchburg, VA) or Visicol (Salix Pharmaceuticals, Morrisville, CA) and unexposed when when bowel preparation was recorded as another agent or none. Colonoscopy indication was categorized as either screening/surveillance or symptomatic.

Additional covariates of interest included age; race; gender; clinical site; congestive heart failure; diabetes; and receipt of ACEI, ARB, or diuretic. Baseline eGFR was estimated by the four-variable MDRD equation. Diabetes was defined by diagnosis of diabetes (International Classification of Diseases, Ninth Revision code 250.xx); elevated glycosylated hemoglobin (>6%) predating colonoscopy; or a prescription for oral hypoglycemic medication, insulin, or diabetic testing materials spanning the date of colonoscopy. Congestive heart failure was defined by an International Classification of Diseases, Ninth Revision diagnosis (425.xx, 428.xx, 401.x1, 404.x1, or 404.x3) predating colonoscopy. Patients were considered exposed to ACEI, ARB, or diuretics when they had an active prescription spanning the date of colonoscopy.

Statistical Analyses

Bivariable measures of association were determined by \( \chi^2 \) testing for categorical variables and t test or Wilcoxon rank sum test for continuous variables, as appropriate. The primary outcome of interest was the adjusted exposure OR for OPS in case patients versus control subjects. The exposure OR based on survival sampling of control subjects provides an unbiased estimate of the risk ratio when the disease in question is rare, as in this case (132/2337 = 0.059).28,29

Adjusted OR were determined via multiple logistic regression models. Prespecified interactions on the basis of gender,8 ACEI/ARB exposure,9 and baseline CKD were examined by inclusion of cross-product terms (with exposure) and compared with parent models via likelihood ratio test. A similar series of models was created for each of the sensitivity analyses—SA-1, SA-2, and SA-3—except that outcome status was reclassified according to alternative case definitions (see the Results section for description).

Power Analysis

Power analyses were conducted assuming a fixed sample size of 132 case patients. Assuming a 3:1 control subject:case patient ratio, an exposure prevalence of 50% among control subjects provided 80%; the study had 80% power to detect a true OR of 1.77 (or greater), at a significance level of 0.05. All analyses were performed using Stata 9.0 (Stata Corp., College Station, TX).

Acknowledgments

This study was supported in part by National Institutes of Health institutional training grant for clinical nephrology T32-DK-07785 (S.M.B.). S.M.B. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosures

None.

References
