Sodium Phosphate Does Not Increase Risk for Acute Kidney Injury After Routine Colonoscopy, Compared With Polyethylene Glycol

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BACKGROUND & AIMS: **Oral sodium phosphate (OSP) is a common bowel purgative administered before colonoscopy; the Food and Drug Administration has warned against its use because of concerns about acute kidney injury (AKI) from the absorbed phosphate and dystrophic calcification. However, it is not clear if OSP is associated with AKI in the general population or in high-risk subgroups undergoing colonoscopy. We estimated the risk of AKI among patients undergoing a screening colonoscopy using OSP vs polyethylene glycol (PEG) for bowel cleansing in a large, US-based claims database.**

METHODS: **We used an insurance database to identify a cohort of patients ages 50 to 75 years who underwent screening colonoscopies as outpatients from January 2000 through November 2008 (before the Food and Drug Administration warning), receiving OSP (n = 121,266) or PEG (n = 429,430) within 30 days beforehand, without prior use of either drug. We collected data from patients for 6 months afterward to identify those who developed AKI or renal failure, or received dialysis. Adjusted and propensity score-matched hazard ratios (HR) and 95% confidence intervals (CI) were estimated using Cox proportional hazards models. We investigated the effects in subgroups with higher AKI risk (patients with chronic kidney disease, kidney stones, hypertension, or diabetes, or using antihypertensive or nonsteroidal anti-inflammatory drugs).**

RESULTS: **AKI occurred in 0.2% of OSP users and in 0.3% of PEG users (adjusted HR, 0.86; 95% CI, 0.75–0.99). OSP users matched well with PEG users, producing similar estimates (HR, 0.85; 95% CI, 0.72–1.01). We did not observe a consistent increase in the risk of AKI or other outcomes in any subgroups analyzed.**

CONCLUSIONS: **In a large database analysis, we did not associate administration of OSP before colonoscopy with increased risk of postprocedure AKI, even in high-risk clinical subgroups.**

Keywords: Comparative Safety; Pharmacoepidemiology; Endoscopy; Bowel Preparations.

Sodium phosphate preparations are effective agents for preprocedure bowel cleansing, although they may increase the risk of acute kidney injury (AKI). Healthy volunteers given oral sodium phosphate (OSP) solution showed enteric absorption of 50% of the phosphorus, an abrupt increase in serum phosphate concentration, and renal excretion of approximately 14% of the absorbed load.[1] Retained phosphate may have systemic consequences because it binds and precipitates with calcium,[2–4] leading to dystrophic soft-tissue deposition in various organ systems. Kidney biopsy series have detailed calcium phosphate deposition in the distal tubule and collecting duct of patients with AKI after sodium phosphate use.[5–9] Observed cases of phosphate renal injury led the Food and Drug Administration (FDA) to place warnings of kidney injury on all over-the-counter and prescription sodium phosphate products used for bowel cleansing, including multicomponent preparation kits and prescription OSP tablets. The over-the-counter kits now contain reduced phosphate content and are marketed for treatment of constipation rather than precolonoscopy bowel cleansing. Most published case series have focused on multicomponent sodium phosphate preparation kits, although the FDA warning additionally was extended to

Abbreviations used in this paper: AKI, acute kidney injury; CI, confidence interval; CKD, chronic kidney disease; FDA, Food and Drug Administration; HR, hazard ratio; OSP, oral sodium phosphate; PEG, polyethylene glycol; PS, propensity score.

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OSP tablets. Although biopsy-confirmed renal injury from OSP has been observed in individuals, it is unclear how these individual-level effects translate to population-level risks. Without the context of appropriate population denominators, the relative burden of OSP-induced AKI compared with other agents is unknown.

The available epidemiologic data from large populations are inconclusive regarding the risk of AKI after OSP use in large populations,[10] with roughly half of the studies suggesting increased risk,[11–14] and the remainder suggesting no risk.[15–19] A major limitation of all of these studies was inadequate power given the relatively small numbers of participants, compounded by the low frequency of AKI events. In addition, these studies may be subject to confounding by indication, include both inpatient and outpatient colonoscopies, and rely on poorly defined or inappropriate comparison groups. The single randomized study[20] comparing OSP with polyethylene glycol (PEG), another commonly used bowel preparation agent, was funded by a maker of OSP and showed no difference in renal injury, but it also was limited by low power. The FDA warning on OSP notes that patients undergoing precolonoscopy bowel cleansing are at risk for dehydration, and it is possible that the observed AKI in OSP users may have resulted from inadequate rehydration rather than from the OSP directly.[21] Given that OSP may be a more effective and less expensive purgative,[22–26] quantifying the comparative risk of renal injury after its use may lead to more informed clinical decision making.

We conducted a large retrospective cohort study of middle-aged and older adults undergoing an outpatient colonoscopy from 2000 to 2008 to determine the risk of AKI associated with OSP tablet exposure compared with PEG. We examined the risk of AKI among all participants as well as among high-AKI-risk subgroups, including those with alterations in renal calcium metabolism, which potentially can increase the risk from high-phosphate products.

Methods

We conducted a cohort study using a large, US-based administrative claims database. All analyses were performed with SAS 9.2 (SAS Institute, Inc, Cary, NC). This secondary analysis of de-identified administrative claims data was exempt from further review by the University of North Carolina at Chapel Hill Institutional Review Board.

Data Source

We used Truven MarketScan database (Truven Health Analytics Inc, Ann Arbor, MI), which is composed of 2 portions: (1) Commercial Claims and Encounters, employer-based commercial insurance plans for employees, spouses and dependents aged younger than 65 years from large insurers throughout the United States; and (2) Medicare Supplementary and Coordination of Benefit, employer-based Medicare supplementary insurance for individuals aged 65 years or older. These databases contain enrollment information, inpatient and outpatient diagnosis and procedure claims, and pharmacy dispensing information. Participants have unique identifiers that permit longitudinal follow-up evaluation through linkage of claims.

Study Population

We identified individuals aged 50 to 75 years undergoing an outpatient screening colonoscopy between January 1, 2000, and November 11, 2008—1 month before the FDA warning to avoid channeling of high-risk AKI patients away from OSP—using Current Procedural Terminology codes (4523, 45355, 45378, 45379, 45380, 45381, 45382, 45384, 45385, 45386, 45387, 45391, 45392, G0105, and G0121). We required at least 1 year of continuous enrollment before colonoscopy. If a patient had multiple eligible colonoscopies, only the first was considered. Individuals with AKI, end-stage renal disease, unspecified renal failure, rhabdomyolysis, dialysis, or renal transplantation in the baseline year before colonoscopy were excluded. To ensure utilization of the observed insurance plan for pharmacy benefits, patients were required to fill at least one other medication during the baseline period, providing assurance that medication use and medical interactions all would be observable in the billing claims database.

Exposure Information

The 30 days before colonoscopy were considered the exposure period (Figure 1), during which pharmacy claims were queried for dispensing of prescription OSP tablets or PEG bowel preparation solutions. We could observe only pharmacy-dispensed OSP use; over-the-counter products would not appear in claims and thus were unavailable for analysis. Supplementary Table 1 lists the included OSP and PEG formulations of interest. It was assumed that regardless of when the prescription was dispensed in the 30-day exposure window, it would be ingested on the day before or the day of the colonoscopy. Thus, the date of the colonoscopy was the beginning of the follow-up period. To restrict the analysis

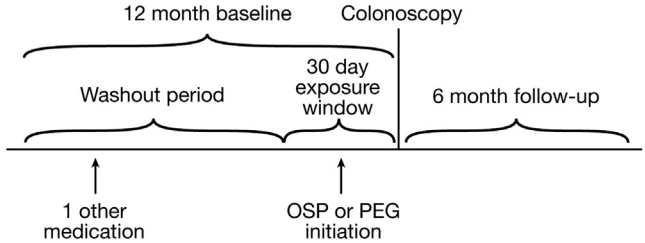

Figure 1. Cohort schematic of new users of OSP or PEG before colonoscopy.