University of Zurich
Zurich Open Repository and Archive

Winterthurerstr. 190
CH-8057 Zurich
http://www.zora.uzh.ch

Year: 2008

Risk of further decline in renal function after the use of oral sodium phosphate or polyethylene glycol in patients with a preexisting glomerular filtration rate below 60 ml/min

Russmann, S; Lamerato, L; Motsko, S P; Pezzullo, J C; Faber, M D; Jones, J K

Russmann, S; Lamerato, L; Motsko, S P; Pezzullo, J C; Faber, M D; Jones, J K (2008). Risk of further decline in renal function after the use of oral sodium phosphate or polyethylene glycol in patients with a preexisting glomerular filtration rate below 60 ml/min. American Journal of Gastroenterology, 103(11):2707-2716.
Postprint available at:
http://www.zora.uzh.ch

Posted at the Zurich Open Repository and Archive, University of Zurich.
http://www.zora.uzh.ch

Originally published at:
American Journal of Gastroenterology 2008, 103(11):2707-2716.

Risk of further decline in renal function after the use of oral sodium phosphate or polyethylene glycol in patients with a preexisting glomerular filtration rate below 60 ml/min

Abstract

OBJECTIVES: The aim of this study was to estimate the risk of further creatinine increase in patients with preexisting renal disease after the use of oral sodium phosphate (OSP) versus polyethylene glycol (PEG), and to study usage patterns of OSP in relation to renal function. METHODS: A cohort study was done using clinical records and electronic patient information from the Henry Ford Health System (HFHS) in patients who had used either OSP or PEG for colonoscopy between February 1999 and April 2006. Among patients with an estimated GFR <60 ml/min before colonoscopy, we identified cases with an unexplained creatinine increase of >/=0.5 mg/dl within 14 days after colonoscopy. RESULTS: We identified 7,971 OSP and 1,511 PEG users. Relative use of OSP versus PEG decreased from 88.0% before 2004 to 48.4% in 2006. 70.2% of OSP users had no recorded creatinine determination within 60 days before colonoscopy, and this proportion did not decrease over time. The study population included 317 patients with a baseline GFR <60 ml/min, and we identified one case with an unexplained creatinine increase >/=0.5 mg/dl among 191 PEG users (0.5%) versus eight cases among 126 OSP users (6.3%). Unadjusted and adjusted relative risk estimates on comparing OSP with PEG were 12.1 (95% CI, 1.5-95.8) and 12.6 (95% CI, 1.5-106.5), respectively. CONCLUSIONS: In patients with preexisting renal disease, OSP use was associated with an increased risk of aggravated renal dysfunction versus PEG. Creatinine measurement with GFR estimation should be done before OSP administration in order to avoid its use in patients with renal disease.

Risk of Further Decline in Renal Function After Use of Oral Sodium Phosphate or Polyethylene Glycol in Patients With a Preexisting Glomerular Filtration Rate Below 60 ml/min

Stefan Russmann, M.D.[1,2], Lois Lamerato, M.S, Dr. P.H.[3], Stephen P. Motsko, Pharm.D., Ph.D.[1], John C. Pezzullo, Ph.D.[1], Mark D. Faber, M.D.[4], Judith K. Jones, M.D., Ph.D.[1]

[1]The Degge Group, Arlington, VA, USA

[2]Division of Clinical Pharmacology and Toxicology, University of Zurich, Zurich, Switzerland

[3]Department of Biostatistics and Research Epidemiology, Henry Ford Health System, Detroit, MI, USA

[4]Division of Nephrology and Hypertension, Henry Ford Hospital, Detroit, MI, USA

Correspondence:

Judith K. Jones, MD, PhD

The Degge Group, 1616 North Fort Myer Drive, Suite 1430, Arlington, VA 22209, USA

Phone: (703) 276-0067; Fax: (703) 276-0069

e-mail: jkjones@deggegroup.com

Word count main text: 3'213

ABSTRACT

Objectives: To estimate the risk of further creatinine increase in patients with preexisting renal disease after use of oral sodium phosphate (OSP) vs. polyethylenglycol (PEG), and to study usage patterns of OSP in relation to renal function.

Methods: Cohort study using clinical records and electronic patient information from the Henry Ford Health System (HFHS) in patients who had used either OSP or PEG for colonoscopy between February 1999 and April 2006. Among patients with an estimated (MDRD) GFR <60 ml/min before colonoscopy, we identified cases with an unexplained creatinine increase of ≥0.5 mg/dl within 14 days after colonoscopy.

Results: We identified 7,971 OSP and 1,511 PEG users. Relative use of OSP vs. PEG decreased from 88.0% before 2004 to 48.4% in 2006. 70.2% of OSP users had no recorded creatinine determination within 60 days before colonoscopy, and this proportion did not decrease over time. The study population included 317 patients with a baseline GFR <60 ml/min, and we identified one case with an unexplained creatinine increase ≥0.5 mg/dl among 191 PEG users (0.5%) vs. eight cases among 126 OSP users (6.3%). Unadjusted and adjusted relative risk estimates comparing OSP with PEG were 12.1 (95% CI, 1.5-95.8) and 12.6 (95% CI, 1.5-106.5), respectively.

Conclusions: In patients with preexisting renal disease OSP use was associated with an increased risk of aggravated renal dysfunction vs. PEG. Creatinine measurement with GFR estimation should be done before OSP administration in order to avoid its use in patients with renal disease.

INTRODUCTION

Although oral sodium phosphate-containing bowel preparations (OSP) were found to be effective and safe in clinical trials (1, 2), a number of well-documented case reports suggested a causal relationship between OSP use and renal dysfunction at least in individual cases (3-5). Current mechanistic hypotheses focus on OSP-induced fluid and electrolyte dysbalances causing an increased phosphate-calcium product and possibly also decreased renal perfusion, particularly when hydration is insufficient (6-16). In line with these hypotheses there are two distinct safety concerns, i.e. irreversible acute renal failure (acute phosphate nephropathy / nephrocalcinosis), and usually reversible renal dysfunction of variable degree. Risk factors for renal dysfunction after OSP use have been proposed, and those are listed in the product information; e.g. the use of Fleet® Phosphosoda® EZ-Prep™ is not recommended in patients with clinically significant impairment of renal function, heart failure or ascites; and special caution is recommended in the elderly, in patients taking medications known to affect renal perfusion or function, with dehydration, or those taking drugs that affect fluid and electrolyte balance. In addition, the need for adequate hydration is emphasized and there is a warning not to exceed the recommended dose.

Whereas clinical studies tend to include a healthier population than that later exposed in clinical practice and do not consider how “real-life” drug usage may affect the risk of adverse effects, case reports allow no quantification of adverse drug effects. Several observational studies have therefore studied the risk of renal dysfunction associated with OSP use in clinical practice (17-21). Compared to polyethylenglycol (PEG) some studies found a similar risk (18, 21), whereas one study reported an approximately doubling of the risk (19). Data sources and methods differed between these observational studies, and a conflicting debate about the safety of OSP continues (22-24).

In our own previous study, we found no significant difference in the risk of renal dysfunction after colonoscopy comparing OSP with PEG (21). In this study patients with preexisting renal disease including all patients with an estimated glomerular filtration rate (GFR) below 60 ml/min were excluded, because we primarily aimed to study the risk of incident renal disease in those in whom OSP use was compatible with current recommendations. However, during identification of the study population we found that a substantial proportion of OSP users had preexisting renal dysfunction. Therefore, usage patterns of OSP in clinical practice, and the question whether preexisting renal function may modify the risk of (additional) renal dysfunction associated with OSP merit further investigation.

With the current study we now aimed to evaluate the risk of further creatinine increase in patients with preexisting renal dysfunction after use of OSP or PEG for colonoscopy. Furthermore we wanted to describe patient characteristics and usage patterns of OSP and PEG in relation to renal function.

METHODS

Data Source

Information for this study was derived from the procedure database of the Gastroenterology Department at Henry Ford Hospital (HFH), Detroit, MI, and the administrative databases within the Henry Ford Health System (HFHS). The Gastroenterology database contains detailed information on colonoscopies including date, bowel cleansing preparation, and adequacy of preparation, as well as the medical record number as a unique patient identifier that allows linkage to the HFHS administrative databases and electronic medical records. The HFHS database contains information on medical care encounters, diagnoses, procedures, outpatient drug prescriptions, laboratory results and patient demographics. Additionally, for patients

enrolled in Health Alliance Plan (HAP), an HFHS owned and operated health maintenance organization, external claims for care are also available. Drug prescriptions are coded using the National Drug Code (NDC) provided by the United States Food and Drug Administration (FDA). All diagnoses are coded using the International Classification of Diseases, Clinical Modification (ICD-9 CM) coding system; procedures are coded using the Current Procedural Terminology-(CPT-4) coding system. All events are noted with the date on which the initial service was delivered. We also had access to original medical records and laboratory results of all patients enrolled in HAP.

The HFHS Human Rights Committee approved the study with a waiver of authorization.

Study Population

The study was conducted among the base population of all patients who had a colonoscopy at the HFHS Detroit center gastroenterology clinic between 1 February 1999 and 30 April 2006, who received oral bowel cleansing preparations containing either OSP (Phospho-soda®, C.B. Fleet Company, Inc., Lynchburg, VA, USA) or PEG (COLYTE®, Schwarz Pharma, Inc., Milwaukee, WI, USA), and were enrolled in the HAP for at least 6 months prior to and at least 4 weeks post colonoscopy. From those patients we obtained all creatinine values determined within 60 days prior to and 14 days post colonoscopy, and calculated GFR estimates according to the MDRD study formula (25). From this base population we subsequently excluded patients according to the following criteria: diagnoses or claims relating to dialysis within 6 months prior colonoscopy (in dialysis patients creatinine values do not reflect renal function), no creatinine determination within 60 days prior to colonoscopy, last GFR before colonoscopy ≥60 ml/min, and/or no creatinine determination 14 days post colonoscopy. This selection process assured that our final study population included only patients with preexisting

renal dysfunction and sufficient information for identification and differential diagnostic evaluation of further renal impairment in relation to PEG or OSP exposure.

We also extracted additional electronic information on demographics, preexisting concomitant drug use and comorbidities for all patients in the study population. Drug prescriptions within 3 months prior to colonoscopy were identified as a proxy for current drug use. For the identification of comorbidities we searched for related diagnostic codes or procedures within 12 months prior to colonoscopy. In addition to specific conditions of interest, the diagnostic coding was used to calculate the Charlson comorbidity index. Originally developed to assess survival probability based on inpatient medical record review, this methodology is also useful with administrative databases as a means of measuring underlying burden of illness (26, 27).

Definition, identification and validation of cases

From the study population we identified all patients where plasma creatinine increased by at least 0.5 mg/dl within 14 days after colonoscopy vs. the last value before colonoscopy. Restriction to a short observation period after colonoscopy was based on the assumption that renal dysfunction in relation to bowel preparation products would manifest soon thereafter, and that particularly in patients with preexisting renal dysfunction who often also have other comorbidities a longer time period would increase the risk of misclassifying creatinine increase due to other reasons or “natural” fluctuations as related to bowel preparation exposure. Two physicians and one pharmacist with expertise in causality assessment of suspected adverse drug reactions then reviewed the original clinical records (SR) or abstracted case summaries (JKJ and SPM) of these patients, while being blinded with regard to the bowel preparation agent used (this information is not part of the clinical records but kept in the Gastroenterology database, which was later incorporated into the main dataset for the final analysis).

Patients with an identifiable likely cause of further renal impairment other than bowel preparation were subsequently excluded. The remaining patients were considered as "idiopathic" cases of further renal impairment and therefore to have at least a possible causal relationship to colonoscopy with bowel preparation.

Data Analysis

We calculated the incidence of further renal impairment during the 14-day period after colonoscopy, and estimated the unadjusted relative risk (RR) in patients receiving OSP vs. PEG as the period incidence ratio for these two groups. We used multivariate logistic regression in order to calculate odds ratios as an estimate of relative risks, and to control for the possible effects of patient demographics, drug use and comorbidities at the time of colonoscopy. In addition, we used propensity score methodology as an alternative way to control for confounding, i.e. we generated a logistic regression model that calculated a patient's propensity to receive OSP or PEG based on patient demographics, current drug use and medical history. Subsequently we used this propensity score as a continuous covariate in a logistic regression model that measured the association between bowel preparation and further renal impairment (28). Data was analyzed using STATA 8.2 for MacOS X (STATA Corp LP, College Station, TX).

RESULTS

Identification of the base population, study population and cases are summarized in Figure 1. We identified a base population of 9,482 patients with continuous health plan enrollment that underwent colonoscopy and used either OSP (n=7,971) or PEG (n=1,511) for bowel preparation. One hundred and fifty-seven patients had a recent history of dialysis. Among the remaining patients, 553 out of 1,390 PEG users (39.8%), and 5,572 out of 7,935 OSP users (70.2%) had no recorded creatinine measurement

within 60 days prior to colonoscopy; and also among 2,916 OSP users with an age ≥65 years, 1,874 (64.3%) had no creatinine measurement within 60 days prior to colonoscopy. Of the remaining 837 PEG and 2,363 OSP users, 319 (38.1%) and 362 (15.3%), respectively, had a GFR<60 ml/min. Finally, we excluded another 364 patients who had no creatinine determination within 14 days post colonoscopy, leading to a study population of 317 patients.

Trends in bowel preparation use over time are presented in Figure 2. As shown, in the base population OSP was the preferred bowel preparation until about 2004; then, starting in 2004 and coincident with the publication of several reports of renal failure after OSP use (3, 5), relative use of OSP decreased from 88.0% before 2004 to 48.4% in 2006. In the study population, which includes only patients with a GFR <60 ml/min, relative use of OSP was lower, i.e. 49.1% until 2004, and there was a further decrease in its relative use going down to 7.1% in 2006.

The proportion of patients with an available creatinine value within 60 days before OSP use over time is presented in Figure 3. As shown, there was no trend towards increased determinations of creatinine before OSP exposure over time; a similar pattern was found when looking only at patients with an age ≥65 years (data not shown).

Demographics and baseline characteristics of the study population are presented in Table 1. Compared to patients receiving OSP, a higher proportion of patients receiving PEG had a very low GFR below 30 ml/min, heart failure and other comorbidities according to the Charlson index. They were also more likely to have colonoscopy as an inpatient procedure.

Within the study population, we identified 20 patients with an increase in creatinine of at least 0.5 mg/dl within 14 days after colonoscopy, based on the last creatinine value before and the first value after colonoscopy. Eleven patients had other identifiable causes for renal dysfunction and were therefore not included as cases;

detailed reasons for not classifying those patients as cases are listed in Table 2. Among the remaining 9 cases, creatinine eventually returned to baseline in 6 patients, but did not do so during follow-up of more than one year in 3 patients (one PEG and two OSP users). One patient with a baseline creatinine of 3.9 mg/dl had creatinine values above 5 mg/dl during follow-up and finally progressed to end stage renal disease, and in the other two patients creatinine remained high at around 2.5 mg/dl (baseline 1.3 mg/dl) and 3.5 mg/dl (baseline 2.7 mg/dl), respectively. In order to account for the possibility of a delayed increase in creatinine we also reviewed the records of another 25 patients with a creatinine increase ≥0.5 mg/dl within 14 days after colonoscopy but where the *first* creatinine value after colonoscopy was less than 0.5 mg/dl above the baseline value; however, an alternative plausible cause for these creatinine increases was identified in all those patients.

Absolute and univariate relative risks of impaired renal function after colonoscopy in relation to baseline characteristics are presented in Table 3. As shown, use of OSP was significantly associated with further renal impairment when compared with PEG, but none of the other factors showed a significant association, neither in the univariate nor in the multivariate analyses. Adjusted relative risk estimates are presented in Table 4. Regardless of whether conventional logistic regression or propensity score methodology was used to control for confounding, adjusted relative risk estimates were similar to the unadjusted univariate relative risk and indicated an elevated risk of renal impairment after use of OSP vs. PEG.

DISCUSSION

Several observational studies have evaluated the risk of renal dysfunction associated with OSP use. Two studies, one of which did and one did not find an association of OSP with impaired renal function, included patients with creatinine

increases without a patient level medical record review for likely alternative causes (17, 20); furthermore, one of those studies modeled GFR changes as a continuous outcome and used a control group without colonoscopy, which provides only limited control over indication bias (20). Among three other studies one reported an elevated risk with an odds ratio of 2.35 (95%CI 1.51 to 3.66), whereas the other two found no increased risk of renal dysfunction comparing OSP with PEG (18, 21). Data sources and methods including the exact outcome definition of renal dysfunction differed between these observational studies, which may provide an explanation for different results; but it is also worth mentioning that confidence intervals for risk estimates overlap between all three studies, and differences may therefore also be due to chance. Although all three studies had included only a limited number of patients and were therefore not sufficiently powered to detect differences for small absolute risks in the range of 1:1000 or less, they are reassuring in the sense that in spite of convincing case reports of renal failure after OSP use, these indeed appear to be rare events in patients without preexisting renal dysfunction. Nevertheless, it has been clearly shown that OSP can cause fluid and electrolyte dysbalances, and it is also physiologically plausible that these may subsequently lead to renal dysfunction, particularly in patients with preexisting risk factors (6-16). In that context it is of particular interest that the current study is the first that focused on a subpopulation with a preexisting low GFR, and that limited the follow-up time to a short at risk period of only 14 days. On the one hand this led to a limited number of patients that could be included in the final study population and consequently also limited the statistical precision of relative risk estimates. On the other hand the likelihood of case misclassification due to other factors is decreased with a shorter follow-up time, particularly in patients with preexisting renal dysfunction with high intraindividual variability of creatinine values and most likely also a higher burden of comorbidities, which may themselves be associated with renal dysfunction. Also,

previous case reports as well as current mechanistic hypotheses suggest that renal dysfunction, should it be caused by OSP, occurs within days after colonoscopy. Therefore, this restrictive study design is an important and robust method to control for confounding. Furthermore, although we realize intrinsic limitations of observational non-randomized studies, ethical reasons would preclude the exposure of patients with preexisting significant renal impairment to OSP in a randomized clinical trial, leaving an observational study as the only option to study OSP's renal safety in this population.

Our current study found a statistically significant association between OSP use and further substantial increase in creatinine values for patients with a preexisting GFR <60 ml/min in the unadjusted as well as in two separate adjusted analyses. Whereas the conventional logistic regression model may be unstable for our dataset where the number of covariates is high in relation to cases, the propensity score-based regression analysis can be expected to offer an advantage for the analysis of our data and should provide reasonable additional control of potentially confounding factors. Furthermore, none of the other covariates had a significant association with creatinine increase after OSP use, neither in the univariate analysis nor in the multivariate model. Therefore, in spite of limited patient numbers and consequently wide confidence intervals, our results do indicate an association between OSP use and further renal dysfunction in patients with a preexisting GFR <60 ml/min. This is an important finding that certainly supports current warnings not to use OSP in patients with preexisting renal disease. Interestingly, on the basis of renal phosphate handling kinetics Mishra et al. postulated that a GFR below 50 ml/min may be a threshold for the development of significant hyperphosphatemia after commonly used OSP doses (13). As far as other possible risk factors are concerned, we incorporated information on these factors in the propensity score analysis in order to achieve reliable control for possible related confounding regarding the risk estimate for OSP vs. PEG use. However, one must consider that the

reported univariate unadjusted risks for these factors are subject to confounding, and furthermore based on low numbers of cases with these factors. As mentioned above, the conventional multivariate regression model is not sufficiently reliable, and our study therefore does not allow a reliable estimation of independent risks associated with these factors.

If preexisting renal disease modifies the effect of OSP use on renal function after colonoscopy, the drug usage patterns found in our study have important implications for the safe use of OSP in clinical practice. As seen in Figure 2, overall use of OSP decreased after 2004, and in patients with preexisting low GFR non-recommended use decreased from about 50% to less than 10%, which occurred in close temporal relationship with safety warnings and labeling changes for OSP. It is therefore likely that these had an impact on OSP use in clinical practice, causing both, an unspecific decrease of OSP use in patients without evidence for an increased risk of OSP-induced renal damage, as well as the desired avoidance of OSP in patients with preexisting renal dysfunction. However this trend was only documented for patients where recent creatinine values were available. Given that chronic renal impairment may remain clinically silent and undetected for a long time, it is worrisome that we did not observe a trend towards increased determinations of creatinine before OSP exposure, not even in OSP users with an age ≥65 years. Although this patient group has a high prevalence of renal impairment (29-31), screening for preexisting renal disease was apparently not done in the majority of patients. In the light of these findings, one may ask whether over-the-counter availability of OSP may play a role, which might make it difficult to identify contraindications for OSP use including preexisting renal disease, and therefore contribute to the high proportion of patients without recent creatinine determinations.

In summary, our results indicate that OSP use is associated with further and possibly irreversible creatinine increase in patients with preexisting renal impairment,

whereas current evidence does not indicate an increased risk of renal dysfunction in OSP users without preexisting renal dysfunction when compared to PEG users. Drug usage pattern in clinical practice is a major issue in relation to the renal safety of OSP. In clinical practice, OSP use has recently decreased, but this change in drug use did not focus on at-risk populations. We must assume that a substantial number of patients with preexisting renal disease continues to be exposed to OSP because creatinine is not measured and renal dysfunction may therefore remain unrecognized. Therefore, it must be reemphasized that OSP should not be used in patients with moderate or severe renal impairment and that renal function should be monitored before and after colonoscopy in those at risk for renal dysfunction.

ACKNOWLEDGMENTS

The authors would like to thank the staff of the Gastroenterology Department at Henry Ford Hospital for their collaboration and access to their procedure database.

STUDY HIGHLIGHTS

1) What Is Current Knowledge

- Although case reports have suggested a causal relationship between acute renal failure and use of oral sodium phosphates (OSP) in several cases, neither clinical nor observational studies have consistently identified an association between use of OSP and renal dysfunction in patients without preexisting renal disease.
- Non-recommended use of OSP by patients with impaired renal function is not uncommon in clinical practice.

2) What Is New Here

- In patients with a GFR <60 ml/min, OSP use was associated with further renal impairment after colonoscopy when compared to PEG.
- We observed a recent increase in the use of PEG vs. OSP, particularly in patients with a low GFR. However, the proportion of OSP users with a creatinine determination in order to screen for renal dysfunction before colonoscopy remains stable and at a low level.

CONFLICT OF INTEREST

Guarantor of the article

Stefan Russmann, M.D., and Judith K. Jones, M.D., Ph.D.

Specific Author contributions

Stefan Russmann and Judith K. Jones had full access to all study data and take responsibility for the integrity and accuracy of the data analysis; study concept and design: Stefan Russmann, Judith K. Jones, Lois Lamerato, Mark D. Faber, and Stephen P. Motsko; data extraction: Lois Lamerato; case review: Stefan Russmann, Judith K. Jones, and Stephen P. Motsko; analysis and interpretation of data: Stefan Russmann, Judith K. Jones, Lois Lamerato, John C. Pezzullo, Stephen P. Motsko, and Mark D. Faber; drafting of the manuscript: Stefan Russmann; critical revision of the manuscript: Stefan Russmann, Judith K. Jones, Lois Lamerato, Stephen P. Motsko; John C. Pezzullo, and Mark D. Faber; statistical expertise: John C. Pezzullo, Stefan Russmann, and Stephen P. Motsko; and supervision: Judith K. Jones.

Funding/Support

This study was supported by a grant from C.B. Fleet Pharmaceuticals Company, Inc, Lynchburg, VA. The sponsor had no role in conducting the study, collecting or analyzing data, interpreting the results, or in preparing the manuscript.

Potential competing interests

None of the authors are employees of C.B. Fleet Co. Judith K. Jones is president of the Degge Group and member of a panel of experts commissioned by C.B. Fleet Co. to evaluate the safety of oral sodium phosphate solution.

REFERENCES

1. Hsu CW, Imperiale TF. Meta-analysis and cost comparison of polyethylene glycol lavage versus sodium phosphate for colonoscopy preparation. Gastrointestinal Endoscopy 1998;48:276-82.
2. Tan JJ, Tjandra JJ. Which is the optimal bowel preparation for colonoscopy - a meta-analysis. Colorectal Dis 2006;8:247-58.
3. Desmeules S, Bergeron MJ, Isenring P. Acute phosphate nephropathy and renal failure. N Engl J Med 2003;349:1006-7.
4. Gonlusen G, Akgun H, Ertan A, et al. Renal failure and nephrocalcinosis associated with oral sodium phosphate bowel cleansing: clinical patterns and renal biopsy findings. Arch Pathol Lab Med 2006;130:101-6.
5. Markowitz GS, Nasr SH, Klein P, et al. Renal failure due to acute nephrocalcinosis following oral sodium phosphate bowel cleansing. Hum Pathol 2004;35:675-84.
6. 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.
7. Aasebo W, Scott H, Ganss R. Kidney biopsies taken before and after oral sodium phosphate bowel cleansing. Nephrol Dial Transplant 2006.
8. Ainley EJ, Winwood PJ, Begley JP. Measurement of serum electrolytes and phosphate after sodium phosphate colonoscopy bowel preparation: an evaluation. Dig Dis Sci 2005;50:1319-23.
9. Azzam I, Kovalev Y, Storch S, et al. Life threatening hyperphosphataemia after administration of sodium phosphate in preparation for colonoscopy. Postgraduate Medical Journal 2004;80:487-8.

10. Beloosesky Y, Grinblat J, Weiss A, et al. Electrolyte disorders following oral sodium phosphate administration for bowel cleansing in elderly patients. Archives of Internal Medicine 2003;163:803-8.
11. DiPalma JA, Buckley SE, Warner BA, et al. Biochemical effects of oral sodium phosphate. Dig Dis Sci 1996;41:749-53.
12. Lieberman DA, Ghormley J, Flora K. Effect of oral sodium phosphate colon preparation on serum electrolytes in patients with normal serum creatinine. Gastrointestinal Endoscopy 1996;43:467-9.
13. Mishra R, Kaufman D, Mattern J, 3rd, et al. Severe hyperphosphatemia and hypocalcemia caused by bowel preparation for colonoscopy using oral sodium phosphate in end-stage renal disease. Endoscopy 2005;37:1259-60.
14. Ullah N, Yeh R, Ehrinpreis M. Fatal hyperphosphatemia from a phosphosoda bowel preparation. J Clin Gastroenterol 2002;34:457-8.
15. Mathus-Vliegen EM, Kemble UM. A prospective randomized blinded comparison of sodium phosphate and polyethylene glycol-electrolyte solution for safe bowel cleansing. Alimentary Pharmacology & Therapeutics 2006;23:543-52.
16. Seinela L, Pehkonen E, Laasanen T, et al. Bowel preparation for colonoscopy in very old patients: a randomized prospective trial comparing oral sodium phosphate and polyethylene glycol electrolyte lavage solution. Scandinavian Journal of Gastroenterology 2003;38:216-20.
17. Abaskharoun R, Depew W, Vanner S. Changes in renal function following administration of oral sodium phosphate or polyethylene glycol for colon cleansing before colonoscopy. Can J Gastroenterol 2007;21:227-31.
18. 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.

19. Hurst FP, Bohen EM, Osgard EM, et al. Association of oral sodium phosphate purgative use with acute kidney injury. J Am Soc Nephrol 2007;18:3192-8.

20. Khurana A, McLean L, Atkinson S, et al. The effect of oral sodium phosphate drug products on renal function in adults undergoing bowel endoscopy. Archives of Internal Medicine 2008;168:593-7.

21. Russmann S, Lamerato L, Marfatia A, et al. Risk of impaired renal function after colonoscopy: a cohort study in patients receiving either oral sodium phosphate or polyethylene glycol. American Journal of Gastroenterology 2007;102:2655-63.

22. Markowitz GS, Radhakrishnan J, D'Agati VD. Towards the incidence of acute phosphate nephropathy. J Am Soc Nephrol 2007;18:3020-2.

23. Roy HK, Bianchi LK. Purging the colon while preserving the kidneys. Archives of Internal Medicine 2008;168:565-7.

24. Zuccaro G, Jr., Connor JT, Schreiber M, Jr. Colonoscopy preparation: are our patients at risk? American Journal of Gastroenterology 2007;102:2664-6.

25. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461-70.

26. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.

27. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613-9.

28. Glynn RJ, Schneeweiss S, Sturmer T. Indications for propensity scores and review of their use in pharmacoepidemiology. Basic Clin Pharmacol Toxicol 2006;98:253-9.

29. Ouseph R, Hendricks P, Hollon JA, et al. Under-recognition of chronic kidney disease in elderly outpatients. Clinical Nephrology 2007;68:373-8.

30. Sesso R, Prado F, Vicioso B, et al. Prospective study of progression of kidney dysfunction in community-dwelling older adults. Nephrology 2008;13:99-103.

31. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. JAMA 2007;298:2038-47.

FIGURES AND TABLES

Figure 1. Identification of study population and cases

Figure 2. Comparative relative use of PEG and OSP in the base population and study population over time

Figure 3. Proportion of OSP users in the base population with creatinine determinations within 60 days before colonoscopy over time

(see separately uploaded graphic files for all figures)

Table 1. Baseline Characteristics of the Study Population

	PEG users (N=191)		**OSP users** (N=126)		
	n	**(%)**	**n**	**(%)**	**p-value**[1]
Female	99	(51.8)	73	(57.9)	0.29
Age ≥65	133	(69.6)	98	(77.8)	0.11
African American Race	100	(52.4)	62	(49.2)	0.58
Year of Colonoscopy					
1999 / 2000	44	(23.0)	32	(25.4)	0.63
2001 / 2002	27	(14.1)	35	(27.8)	<0.01
2003 / 2004	47	(24.6)	47	(37.3)	0.02
2005 / 2006	73	(38.2)	12	(9.5)	<0.01
Inpatient colonoscopy	151	(79.0)	77	(61.1)	<0.01
GI bleeding 30 days prior colonoscopy	103	(53.9)	58	(46.0)	0.17
Hospitalization 12 months prior colonoscopy	98	(51.3)	51	(40.5)	0.06
Baseline GFR <30 ml/min	45	(23.6)	16	(12.7)	0.02
Baseline comorbidities[2]					
Diabetes mellitus	73	(38.2)	41	(32.5)	0.30
Congestive heart failure	79	(41.4)	37	(29.4)	0.03
Charlson comorbidity index ≥3	103	(53.9)	53	(42.1)	0.04
Current drug therapy[3]					
ACE inhibitors or ARB	88	(46.1)	52	(41.3)	0.40
Diuretics	111	(58.1)	69	(54.8)	0.56
Beta blockers	66	(34.6)	44	(34.9)	0.95
Calcium channel blockers	21	(11.0)	20	(15.9)	0.21
Nonsteroidal anti-inflammatory drugs	16	(8.4)	12	(9.5)	0.72

[1]Chi-square two-sample test of proportion

[2]Diagnoses within 12 months prior colonoscopy

[3]Prescriptions within three months prior colonoscopy

Table 2. Reasons for exclusion of 11 patients with creatinine increase after colonoscopy from study cases because other likely causes of renal dysfunction were identified during review blinded to bowel preparation.

No.	Likely cause for renal dysfunction
1.	Creatinine increase started before colonoscopy; associated with urinary tract infection, heart failure and pneumonia.
2.	Obstructive uropathy; recovery of renal function after passage of urinary catheter.
3.	Hospital admission in unstable condition with diabetic ketoacidosis and foot gangrene; discharge letter also mentions acute renal failure secondary to nephrotoxic immunosuppressive drugs.
4.	Discharge letter describes dehydration with acute tubular necrosis before colonoscopy.
5.	Admitted in unstable condition with diabetes and severe anemia requiring transfusion. Pronounced fluctuations of creatinine values before colonoscopy.
6.	Neurogenic bladder with urinary retention.
7.	Creatinine increase started before colonoscopy; associated with dehydration and acute heart failure.
8.	Pronounced fluctuations of creatinine values before colonoscopy; associated with decompensated heart failure with anemia followed by forced diuresis.
9.	Pronounced fluctuations of creatinine values before colonoscopy; associated with rectal bleeding with severe anemia requiring transfusion, decompensated heart failure treated with forced diuresis.
10.	Very high creatinine values above 6 mg/dl with pronounced fluctuations before colonoscopy. Medical records indicate recent dialysis treatment.
11.	After colonoscopy infection requiring antibiotic treatment with clindamycin and ciprofloxacin plus intravenous fluids for dehydration.

Table 3. Absolute and univariate relative risks of impaired renal function after colonoscopy in relation to selected factors.

	Patients with factor and with ≥0.5 mg/dl creatinine increase[1]		Patients without factor and with ≥0.5 mg/dl creatinine increase[1]			
Factors	**n**	**Risk[2a]**	**n**	**Risk[2b]**	**RR[3]**	**(95% CI)**
OSP use (vs. PEG)	8	6.3%	1	0.5%	12.1	(1.5-95.8)
Female	6	3.5%	3	2.1%	1.7	(0.4-6.6)
Age ≥65 years	6	2.6%	3	3.5%	0.7	(0.2-2.9)
African American race	6	3.7%	6	1.9%	1.9	(0.5-7.5)
Inpatient colonoscopy	5	2.2%	4	4.5%	0.5	(0.1-1.8)
Hospitalization 12 months prior to colonoscopy	1	0.7%	8	4.8%	0.1	(<0.1-1.1)
GI bleeding 30 days prior	4	2.5%	5	3.2%	0.8	(0.2-2.8)
GFR <30 ml/min	2	3.3%	7	2.7%	1.2	(0.3-5.6)
Comorbidities[4]						
Diabetes mellitus	2	1.7%	7	3.4%	0.5	(0.1-2.4)
Congestive heart failure	1	0.9%	8	4.0%	0.2	(<0.1-1.7)
Charlson index ≥2	3	1.9%	6	3.7%	0.5	(0.1-2.0)
Current drug therapy[5]						
ACE inhibitors or ARB[6]	4	2.9%	5	2.8%	1.0	(0.3-3.7)
Diuretics	5	2.8%	4	2.9%	1.0	(0.3-3.5)
Beta blockers	3	2.7%	6	2.9%	0.9	(0.2-3.7)
Calcium channel blockers	2	4.9%	7	2.5%	1.9	(0.4-8.9)
Nonsteroidal anti-inflammatories	1	3.6%	8	2.8%	1.3	(0.2-9.9)

[1]At least 0.5 mg/dl creatinine increase within 14 days after colonoscopy

[2]Risk of ≥0.5 mg/dl creatinine increase in patients with (2a) or without factor (2b).

[3]Unadjusted relative risk (=risk ratio) of ≥0.5 mg/dl creatinine increase after colonoscopy for presence vs. absence of factor

[4]Diagnoses within 12 months prior colonoscopy

[5]Prescriptions within three months prior colonoscopy

[6]Angiotensin converting enzyme inhibitors or angiotensin renin blockers

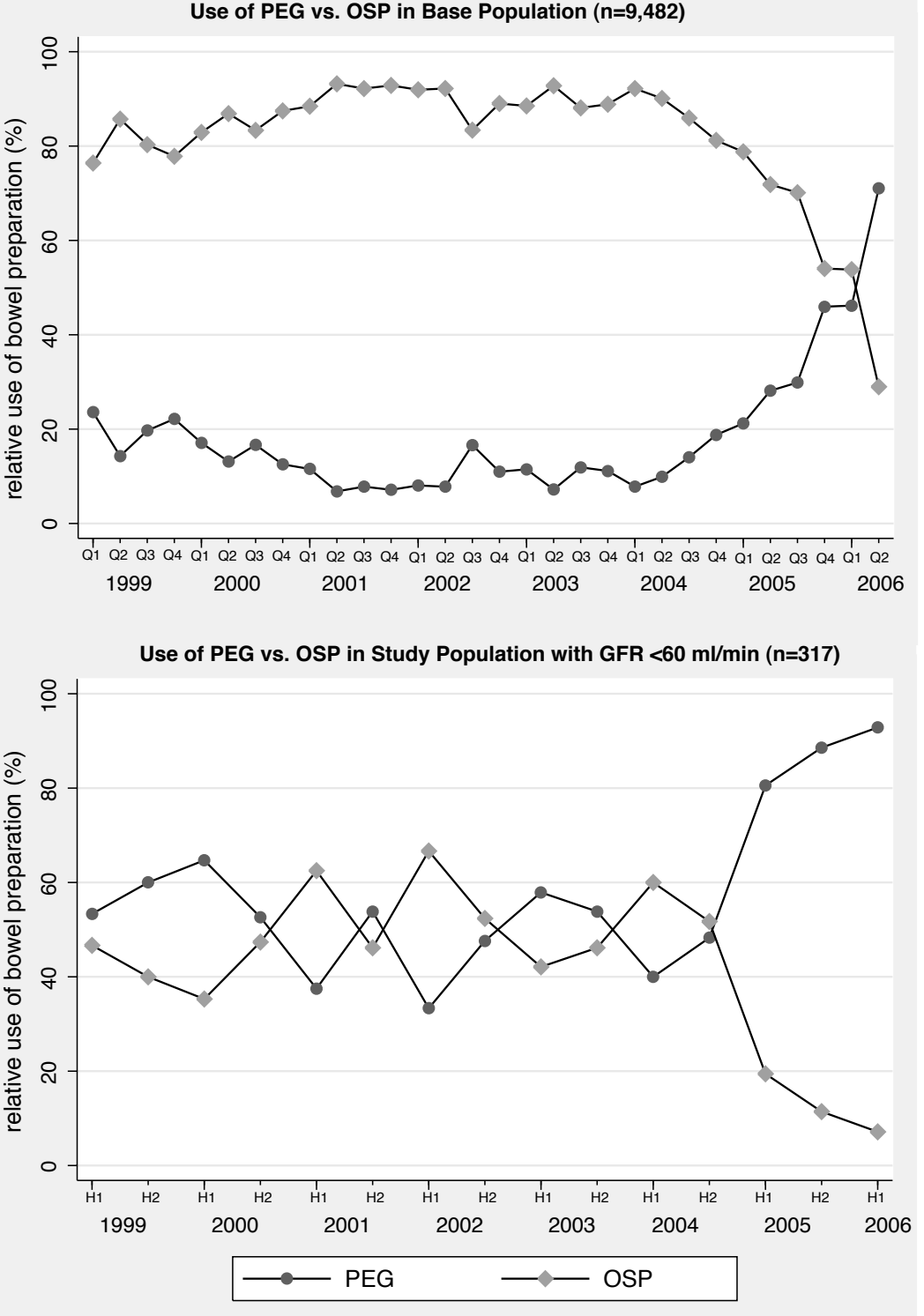
Table 4. Absolute numbers and risk of impaired renal function after colonoscopy, and adjusted odds ratios estimating the risk for renal impairment associated with OSP vs. PEG exposure.

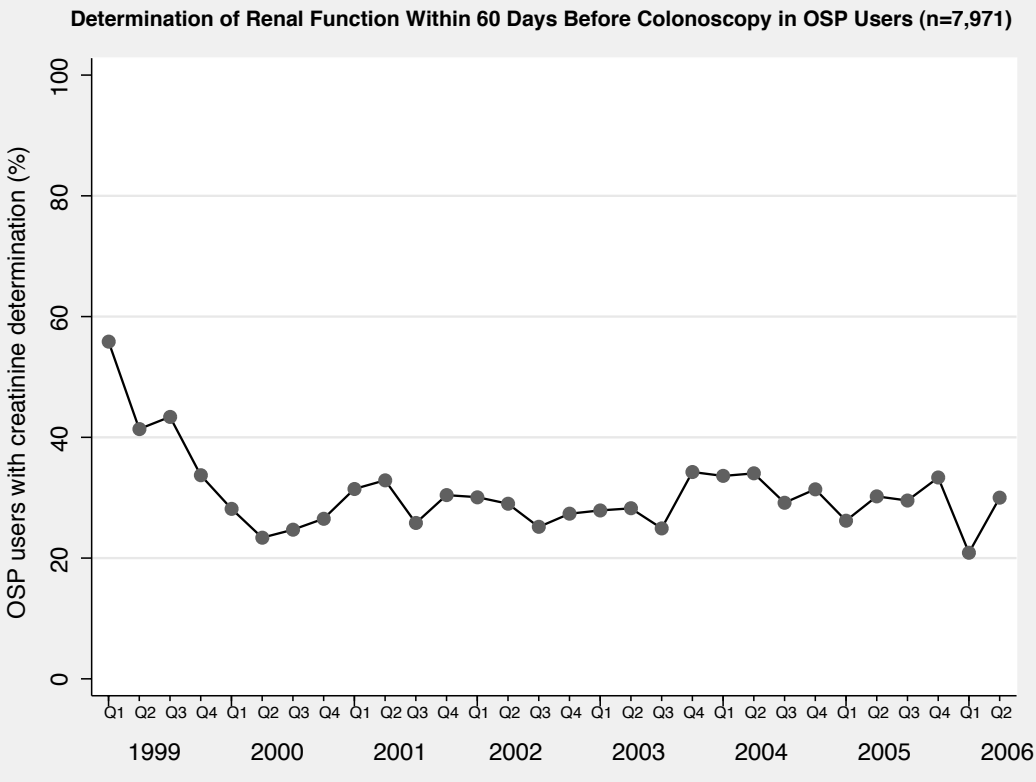
	All patients	**Cases with creatinine increase ≥0.5 mg/dl**	**Adjusted odds ratio using conventional logistic regression[1] (95% CI)**	**Adjusted odds ratio using propensity score based logistic regression[2] (95% CI)**
	n	n (risk)		
PEG	191	1 (0.5%)	1.0 (ref)	1.0 (ref)
OSP	126	8 (6.3%)	14.4 (1.6-131.2)	12.6 (1.5-106.5)

[1]Adjusted odds ratios and 95% confidence intervals estimated from a logistic regression model with case of creatinine increase as the outcome variable and the following cofactors: OSP use, age ≥65 yrs, female gender, African American race, baseline GFR <30 ml/min, congestive heart failure, diabetes mellitus, Charlson comorbidity score ≥4, inpatient colonoscopy, current use of angiotensin converting enzyme inhibitors or angiotensin renin blockers, calcium channel blockers, diuretics.

[2]Propensity score predicting the likelihood of PEG or OSP use conditional on all other cofactors listed above for the conventional logistic regression model; this score was then used as a covariate in a logistic regression model where case of creatinine increase was the outcome variable and OSP exposure a cofactor.

	PEG	OSP	Total
BASE POPULATION Patients undergoing colonoscopy with PEG or OSP between Feb 1999 and Apr 2006, and enrollment in Health Aliance Plan 6 months prior to 4 weeks post colonoscopy.	**1,511**	**7,971**	**9,482**
Exclusions			
Patients with dialysis within 6 months prior colonoscopy.	121	36	157
Patients without creatinine determination within 60 days prior colonoscopy.	553	5,572	6,125
Patients with GFR >60 ml/min (last value before colonoscopy).	518	2,001	2,519
Patients without creatinine determination within 14 days post colonoscopy.	128	236	364
STUDY POPULATION Patients with GFR<60 ml/min, available medical records, and creatinine determination within 60 days prior *and* 14 days post colonoscopy.	**191**	**126**	**317**
Case identification and validation			
Creatinine increase of at least 0.5 mg/dl within 14 days post colonoscopy (first value after minus last value before colonoscopy).			
No cause for renal impairment identifiable in medical records.			
CASES Patients with aggravated renal impairment after colonoscopy.	**1**	**8**	**9**


Use of PEG vs. OSP in Base Population (n=9,482)
relative use of bowel preparation (%)
0
20
40
60
80
100
Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2
1999 2000 2001 2002 2003 2004 2005 2006
Use of PEG vs. OSP in Study Population with GFR <60 ml/min (n=317)
relative use of bowel preparation (%)
0
20
40
60
80
100
H1 H2 H1 H2 H1 H2 H1 H2 H1 H2 H1 H2 H1 H2 H1
1999 2000 2001 2002 2003 2004 2005 2006
PEG
OSP


Determination of Renal Function Within 60 Days Before Colonoscopy in OSP Users (n=7,971)
OSP users with creatinine determination (%)
0
20
40
60
80
100
Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2
1999
2000
2001
2002
2003
2004
2005
2006