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Current Issues in Optimal Bowel Preparation

Excerpts From a Roundtable Discussion Among Colon-Cleansing Experts

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Foreword

Recent changes to the purgative armamentarium initiated by the Food and Drug Administration (FDA) are a shot across the bow of complacency for colonoscopists. Over-the-counter (OTC) sodium phosphate (NaP) solution, so long a cherished staple as a laxative because of its efficacy and tolerance, is no longer on the market or available as an option for colon cleansing before colonoscopy. The NaP tablet formulation has received a black box warning regarding its use as a bowel preparation before colonoscopy due to the risk of renal injury. Though acute phosphate nephropathy is a possible outcome that may occur with any NaP purgative, its true incidence remains unknown and is likely rare when this medication is used properly and in the appropriate patient population. Yet, the patient risk associated with an OTC NaP solution for bowel preparation is too great.

Both physicians and patients played a role in the withdrawal of OTC NaP solution and the new boxed warning for prescription NaP tablets. Too often, physicians have been lax in complying with an increasingly onerous process for properly selecting patients for NaP purgatives and in providing sound recommendations with respect to dosing (total dose and interval) and hydration. Confounding this laxity, even when provided with clear and correct instructions, the potential for patient-initiated administration and hydration errors is possible. This recent experience with NaP provides useful information for physicians who administered OTC laxatives that may not have been vetted for use as bowel preparations in large, adequate and well-designed clinical studies subject to peer review.

The attention to purgative safety has coincided with an increased interest in purgative efficacy, and it is about time! For a procedure performed 14 million times a year in this country alone, a ~75% rate of adequate colon cleansing for colonoscopy is unacceptable. Besides the costs associated with inadequate cleansing—early repeat colonoscopy, additional time off from work for the patient, nonproductive use of endoscopy time for the physician, and the risk and discomfort associated with repeating the preparation procedure, to name a few—it has become clear that colonoscopy quality is intimately related to cleansing adequacy. Polyp detection is one of many quality measures that improve when the preparation is adequate.

A large part of the discussion herein focuses on the relationship between the timing of purgative administration and colon cleansing. Data support administering at least part of the purgative close to the time of colonoscopy in order to achieve adequate cleansing. This is usually accomplished through a "split-dose" regimen, in which part of the purgative is ingested in the evening prior to colonoscopy and the remainder is ingested the morning of the procedure. Splitting the dose improves not only colon cleansing but also tolerability and overall safety, resulting in improved overall patient satisfaction.

Seemingly small changes in the selection and administration of purgatives may have a major effect in the performance of colonoscopy. We hope you find the following discussion helpful for your clinical practice.

Current Issues in Optimal Bowel Preparation

On October 5, 2008, a roundtable meeting was convened to discuss the current issues in optimal bowel preparation before optical colonoscopy for colorectal cancer (CRC) screening. Attendees were Lawrence B Cohen, MD, Associate Clinical Professor, The Mount Sinai School of Medicine, New York, New York; David M Kastenberg, MD, Associate Professor of Medicine, Thomas Jefferson University, Philadelphia, Pennsylvania; David B Mount, MD, Nephrologist, Renal Division, Brigham and Women's Hospital, Assistant Professor of Medicine, Harvard Medical School, Boston, Massachusetts; and Alan V Safdi, MD, President, Ohio Gastroenterology and Liver Institute, Chairman, Section of Gastroenterology, Deaconess Hospital System, Cincinnati, Ohio. The faculty addressed 3 key issues relating to the overall safety and efficacy of bowel preparations. Specific topics included (1) the benefits of a PM/AM split-dosing regimen; (2) the use of MiraLAX® (Schering-Plough, Kenilworth, NJ) combined with a sports drink for bowel cleansing before colonoscopy; and (3) the safety of sodium phosphate (NaP)–based purgatives with regard to renal damage. This article summarizes the comments and opinions of the discussants during the roundtable meeting and provides useful suggestions and recommendations on colonoscopy bowel preparation that are intended to maximize patient safety, convenience, and the quality of colon cleansing.

Importance of Adequate Bowel Preparation Before Colonoscopy

Colorectal cancer is the third most frequently diagnosed cancer in the United States, resulting in the second highest rate of cancer-related mortality.[1] Several bodies of evidence have demonstrated that routine screening of asymptomatic adults starting at 50 years of age can significantly reduce the number of CRCs and, consequently, reduce the number of CRC-related deaths. Detection of CRC at an early stage is associated with a 5-year survival rate of 90%.[2] Colonoscopy remains the "gold standard" for detection of polyps and precancerous lesions that may lead to CRC, yet less than half of individuals ≥50 years of age undergo screening colonoscopy. Mounting evidence suggests that fear of bowel preparation is a key reason many patients avoid colonoscopy.[3] Furthermore, patients who had undergone screening indicated that the bowel preparation was the worst part of the colonoscopy procedure, and they are sometimes reluctant to undergo the procedure again.[1] In addition, patients often experience adverse events such as abdominal pain, cramping, bloating, nausea, and vomiting in response to bowel preparation consumption. Unfortunately, individuals who are either unable or unwilling to complete a colon-cleansing regimen may have suboptimal bowel cleansing, resulting in incomplete visualization of the colon, missed colon pathology, and, possibly, increased procedural risks.[2] Results from randomized clinical trials[4] and clinical practice[5] suggest that suboptimal bowel preparation occurs with surprising frequency, in as many as 25% of all cases. In conjunction with variable tumor growth rates, technical limitations of polyp detection, failed cecal intubation, and suboptimal examination technique, inadequate bowel cleansing may be an important factor contributing to the findings of missed colorectal polyps and cancer after a negative colonoscopy.[6] Therefore, addressing the safety, tolerability, and effective administration of colon-cleansing regimens may enhance patient compliance, lead to a higher quality bowel preparation, and improve polyp detection.

Detection of Colonic Lesions

Colonoscopy provides an opportunity to visualize and remove benign adenomatous polyps before they have become cancerous.[7] Suboptimal bowel preparation, however, may obscure visualization of the colonic mucosa and lead to missed colonic lesions during the colonoscopy procedure. Using a population cohort of 110,402 patients in Canada with a negative colonoscopy result (no biopsy or CRC diagnosis at 6 months), Lakoff and colleagues[8] reported a significant reduction in overall colon cancer incidence up to 14 years following examination compared with the remainder of the population. However, relative risk of proximal colon cancer was not reduced over the initial 7 of the 14 years following colonoscopy. Specifically, there was no significant difference in proximal colon cancer risk 4 years after a negative colonoscopy. It is likely that inadequate bowel cleansing and failure to reach the cecum in specific cases, combined with the technical limitations to recognize flat lesions within the proximal bowel, contributed to an increased rate of missed cancers in the right side of the colon.

Small Lesions

Detection of small colonic lesions (≤9 mm in diameter) is often difficult due to the limitations of current

colonoscopic technology. Inadequate colon cleansing is one of several factors that may exacerbate this concern. In a study by Harewood et al,[5] records of 113,272 colonoscopy procedures were analyzed for the relationship between bowel preparation and polyp detection. Nearly 25% of patients did not achieve an adequate bowel preparation before their colonoscopy procedure. Smaller colon polyps, those measuring 9 mm or less in diameter, were found more often during colonoscopies performed in patients with adequate bowel preparation compared with those having an inadequate preparation (22% vs 19%, respectively; *P*<.0001). On the other hand, polyps larger than 9 mm in diameter were detected at the same rate (7%), irrespective of the quality of bowel preparation. In contrast, a European study by Froehlich and colleagues[4] found that polyps of all sizes, both large and small, were more likely to be discovered in an adequately prepared colon than in an inadequately prepared colon (large polyps, 6% vs 4%, respectively; *P*=.016; small polyps, 29% vs 24%, respectively; *P*=.007). Additional outcomes were affected by adequate bowel preparation, including completion of procedure, time to cecum, and colonoscope withdrawal time (Table 1). Results from these 2 studies suggest that improvements in the quality of bowel cleansing may lead to enhanced detection of precancerous polyps.

Table 1. Effect of Bowel Preparation Quality on Outcome Measures[4]

Outcome	High-quality preparation	Low-quality preparation	*P* value
Completed preparation, %	90.4	71.1	<.001
Time to cecum, min	11.9	16.1	<.001
Withdrawal time, min	9.8	11.3	<.001
Polyps detected, %	29.4	23.9	.007
Polyps >10 mm detected, %	6.4	4.3	.016

Flat Lesions

The majority of CRC is thought to arise from polypoid adenomas.[9] However, recent evidence has suggested that nonpolypoid colorectal neoplasms (ie, flat lesions) may play an important role in the development of CRC. Flat lesions may appear slightly raised, completely flat, or slightly depressed, and are often hard to differentiate endoscopically from the normal mucosa due to only subtle differences in appearance.[10] Flat lesions may be associated with a greater rate of high-grade dysplasia and cancer than polypoid adenomas of similar sizes at the time of detection.[11] A study from Soetikno et al[9] found that flat lesions were detected in 9% of 1,819 patients who underwent colonoscopy. After adjusting for size, flat lesions carried a 3-fold increased risk for neoplasia compared with polypoid lesions. Strikingly, over half of the superficial carcinomas detected arose from flat lesions, further emphasizing the importance of optimal bowel preparation in lesion detection.

Split Dosing (PM/AM)

Quality of Bowel Preparation

It is well documented that a good-quality bowel preparation before colonoscopy improves the rate of detection of colonic polyps.[3,4,10] The best method of colon cleansing is not clear, however. Currently, the 2 major classes of bowel preparations are polyethylene glycol electrolyte solution (PEG-ELS) and NaP formulations.[1] Sodium phosphate and PEG-ELS bowel preparations have shown optimal cleansing when the first dose is administered the evening before the colonoscopy and the second dose is administered the morning of the procedure (Figure 1).[12-14] In a study from Aoun et al,[12] patients who received a PM/AM split dose of 4-L PEG-ELS were significantly more likely to receive a preparation rated excellent than patients who received the entire 4-L dose the evening before colonoscopy (44% vs 6%, respectively). An additional study compared 4-L PEG-ELS with NaP split-dosing regimens and found not only that NaP yielded a better bowel preparation, but that longer times between doses (6 hours vs 12–24 hours) resulted in improved colon cleansing (presumably due to greater fluid intake).[15] Separate studies have shown that administering the entire bowel preparation the day of colonoscopy results in a high-quality colon cleansing, suggesting that timing of the purgative dose in relation to colonoscopy, not split dosing, is imperative for adequate visualization of the colon.[10,16,17]

A chief concern regarding preparations administered entirely the day before colonoscopy is the impaired visualization of the colon due to residual fecal matter. In patients who take the last purgative dose 8 to 12 hours before colonoscopy, small bowel effluent can reaccumulate in the cecum and ascending colon, making visualization of mucosal detail difficult or even impossible.[14] One study showed that oral sodium phosphate solution (OSPS) taken as a PM/AM split dose resulted in significantly lower fecal material in the right colon compared with OSPS taken the day before the procedure (4% vs 30%, *P*<.001, respectively).[13] The bowel fluid was typically translucent in the PM/AM split-dosing group compared

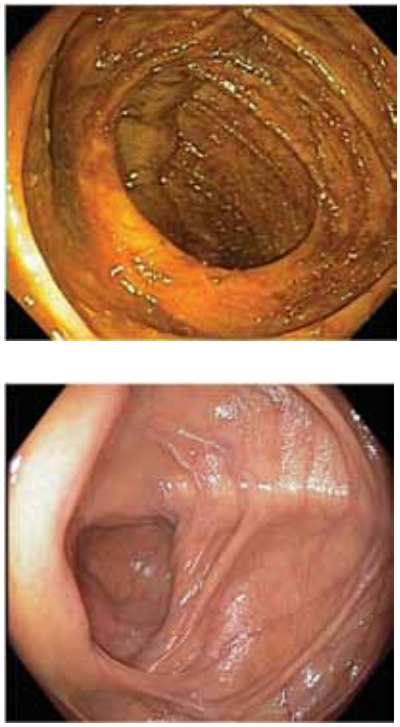

Figure 1. Single PM dose versus PM/AM split-dose bowel preparation. A) cecum after a PM-only purgative dose administered the evening before colonoscopy. B) cecum after the second dose of a PM/AM split-dose regimen.

with the opaque fluid in the group taking OSPS the day before colonoscopy, resulting in enhanced visibility with a split dose. A separate study compared the effectiveness of the split-dosed NaP tablet preparation OsmoPrep® (Salix Pharmaceuticals, Inc, Morrisville, NC) with single-dosed PEG-ELS HalfLytely® (Braintree Laboratories, Inc, Braintree, MA) and found that OsmoPrep resulted in greater effectiveness of colon cleansing (90% rated good/excellent) compared with HalfLytely (82% rated good/excellent, *P*=.039).[14] Patients who took OsmoPrep experienced significantly fewer adverse events (66% vs 82%, *P*=.0003) than those receiving HalfLytely, suggesting that NaP split dosing provides not only superior colon cleansing but also results in increased patient tolerability. Similarly, a Taiwanese group studied patients who already had colon neoplasms detected during colonoscopy and were scheduled for a second colonoscopy.[18] Patients were divided into 2 groups, 1 group that received 2-L PEG-ELS 6 to 8 hours before examination (AM dosing) and a second group that received 2-L PEG-ELS 13 to 16 hours before examination (PM dosing). Of the patients who received the preparation the day of their procedure (AM dosing), only 7% had an inadequate preparation, compared with 28% of patients who received the preparation the night before (PM dosing).

Enhanced Detection of Flat Polyps

Flat polyps present an increased risk for neoplasm and malignancy. Due to the increased difficulty in detecting flat lesions, high-quality bowel preparation is essential. To determine which dosing strategy yields the best bowel preparation, Parra-Blanco and colleagues[10] investigated the timing of purgative dosing in relation to detection of flat polyps. Patients were divided into 4 groups. The first group received 3-L PEG-ELS the morning of colonoscopy (AM dosing). Group 2 received OSPS PM/AM split dosing, while groups 3 (3-L PEG-ELS) and 4 (OSPS) received the entire purgative dose the evening before colonoscopy (PM dosing). Quality of colon cleansing was determined as the rate at which patients received a good or excellent cleansing score (Table 2). More than 75% of patients who received all or part of the purgative dose the morning of the examination obtained a good or excellent colon cleansing score compared with <27% of patients who received the entire purgative dose the day before the procedure. The investigators also reported significantly better detection of flat lesions in the PM/AM split-dosing and AM dosing groups (22%) compared with the PM dosing groups (9%, *P*<.05). Furthermore, data suggested that the timing of the second dose in relation to the procedure was more important than the time between the first and second doses. As a consensus, the roundtable participants agreed the second dose should be administered ≤6 hours before the start of the colonoscopy procedure.

ASA Guidelines for Preoperative Fasting

Whereas PM/AM split dosing of NaP regimens has been demonstrated to be highly effective in bowel cleansing,[10] there is confusion regarding interference of the second purgative dose with the American Society of Anesthesiologists (ASA) guidelines. It is widely believed that patients undergoing anesthesia should not eat or consume liquids after midnight the day before their procedure. The ASA guidelines advise a minimum fasting period of 2 hours for clear liquids in healthy adults,[19] and following these guidelines allows patients to remain well hydrated. A PM/AM split-dosing NaP regimen would not interfere with these guidelines if the second dose is completed no less than 2 hours before colonoscopy. A prospective study from the United Kingdom[20] demonstrated that patients who were allowed to drink clear liquids up to 2 hours before surgery had no significant difference in residual gastric volume (RGV) or gastric pH compared with the control group that fasted for 6 hours (RGV, 21 mL vs 19 mL, respectively [*P*=.58]; gastric pH, 2.64 vs 2.26, respectively [*P*=.07]). The

Table 2. Rate of Patients With Good/Excellent Bowel Preparation[9]

Group	Treatment	n	GI segment (mean ± SD, %)		
			Global*	Cecum	Ascending
Group 1	PEG-ELS (AM)	43	78.6 ± 0.2	72.1 ± 0.2	79.1 ± 0.2
Group 2	OSPS (PM/AM)	45	80.0 ± 0.2	84.4 ± 0.1	77.8 ± 0.2
Group 3	PEG-ELS (PM)	45	26.7 ± 0.2	38.6 ± 0.2	22.2 ± 0.2
Group 4	OSPS (PM)	44	6.8 ± 0.1	14.6 ± 0.1	9.8 ± 0.1

GI=gastrointestinal; OSPS=oral sodium phosphate solution; PEG-ELS=polyethylene glycol electrolyte solution; SD=standard deviation.

*Global defined as cecum, rectum, and colonic segments: ascending, transverse, and descending/sigmoid.

authors concluded that although fasting after midnight was standard practice, preoperative dehydration may be a greater safety concern than drinking clear liquids before anesthesia. This concern about dehydration is especially pertinent in patients who have taken a purgative before colonoscopy.

An additional concern for patients taking bowel preparations is the risk of aspiration of gastric contents into the respiratory tract during colonoscopy. General anesthesia suppresses the normal throat reflexes that prevent aspiration, such as swallowing, coughing, or gagging. To help prevent aspiration, patients may be intubated, protecting the lungs from gastric contents. Generally, aspiration during anesthesia is rare. One study showed that the rate of aspiration in anesthetized patients was 1 in 8,671.[21] To reduce this risk, patients are typically instructed not to eat or drink anything for a specified number of hours before the administration of anesthesia in order to ensure that the stomach is empty. Patients with disorders that produce delayed emptying of the esophagus (achalasia) or stomach (gastroparesis) may be at greater risk for pulmonary aspiration and require a longer period of fasting. In these cases, moderate sedation may be safer and better tolerated than deep sedation (ie, monitored anesthesia care [MAC]). In a recent study, moderate sedation was associated with fewer low-quality preparations (14% vs 26%, $P<.05$) and a higher overall cleansing score compared with MAC.[22] Combined, these data suggest that the impact of bowel preparations on aspiration risk is minimal during colonoscopy, and no link has been established between PM/AM split dosing and increased risk of aspiration.

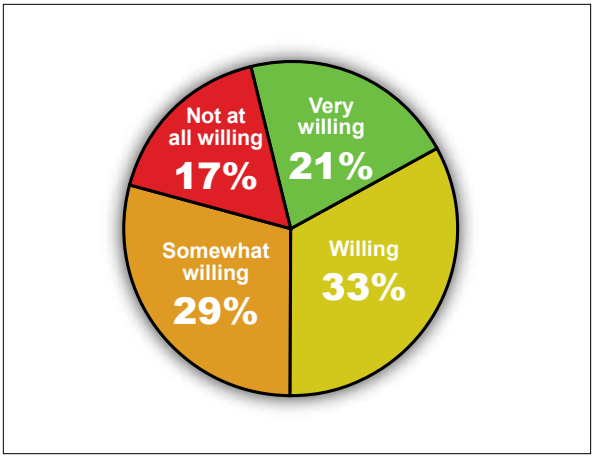

Figure 2. Results of patient survey.[23] The survey asked patients if they were willing to wake very early in the morning to take the second dose of a PM/AM split-dose regimen.

Considerations for Treatment Outcomes

Patient Acceptance of PM/AM Split Dosing

A growing body of literature indicates that a split-dosing regimen, irrespective of the bowel preparation used, is the most effective means to optimize bowel cleansing.[12-15] Clinicians are sometimes reluctant to prescribe a split-dose preparation, however, due to the belief that patients will not accept or comply with such a routine. One concern is the unwillingness of patients to awaken early in the morning on the day of the procedure to take the second purgative dose. There is evidence that 83% of patients would be willing to wake up as early as 3 AM to take the second dose* (Figure 2).[23] In a comparative study,[24]

*Question from Harris Interactive: Clinical studies have shown that taking a portion of a bowel preparation the morning of your colonoscopy provides the doctor with the best possible view of the colon. This is important because a clean colon is essential for detecting and removing polyps or flat lesions, which may cause cancer. If no polyps are detected, a colonoscopy will not need to be repeated for 5 to 10 years. Given this information, how willing would you be to wake up as early as 3 AM the morning of the colonoscopy to take the second dose of your bowel preparation?

patients who took a split-dose purgative were more often satisfied with the bowel cleansing than those who took a single-dose purgative (63% vs 46%, *P*<.0001; unpublished data). Patients were then asked which regimen was more convenient and less difficult to complete. Only 19% found the PM/AM split-dosing regimen difficult to finish, compared with 44% of patients who could not finish the evening-only purgative. These data suggest that most patients are relatively satisfied with a PM/AM split-dosing regimen and are willing to wake early if convinced the timing of the second dose will enhance the outcome of their colonoscopy. For the minority of patients who are unwilling to rise early, the clinician should be prepared to schedule the colonoscopy procedure later in the day, allowing for 2 to 6 hours between completion of the AM dose and the examination

Another concern regarding PM/AM split dosing is that patients will be nervous about traveling to the endoscopy center on the day of examination because of concerns about incontinence en route. In a study by Khan et al,[24] the percentage of patients who stopped en route to the procedure was not different between those who received either a single-day or PM/AM split-dose bowel preparation.

Use of MiraLAX in Bowel Preparations

MiraLAX (polyethylene glycol [PEG] 3350) is a laxative approved for the treatment of mild or occasional constipation. Several reports have indicated that clinicians often include MiraLAX as an alternative bowel preparation in the purgative armamentarium, however. Although MiraLAX has been used safely in a large body of patients, serious safety concerns have been raised regarding its off-label use as a bowel preparation. First, MiraLAX is not indicated by the US FDA for use as a bowel preparation before colonoscopy. Furthermore, no controlled clinical trials have been performed to assess the relative safety and efficacy of MiraLAX for colon cleansing. When used as a laxative, MiraLAX is not recommended for patients with kidney disease due to concerns of excessive depletion of the extracellular fluid volume (dehydration or, more accurately, volume depletion). These patients are at an even greater risk of volume depletion and potential electrolyte disturbances when MiraLAX is taken as a bowel preparation at a dose of 14 times (238 g) higher than the recommended laxative dose. Unlike PEG-based purgatives indicated for bowel preparation, MiraLAX does not contain a built-in electrolyte replacement solution (ELS), compounding the risk of fluid-electrolyte imbalance. Diarrhea induced by PEG-based laxatives correlates with volume depletion and electrolyte imbalance. In an attempt to limit this problem, MiraLAX is often administered in combination with a hydrating sports drink (eg, Gatorade®; PepsiCo, Inc, Purchase, NY) to boost electrolytes. While sports drinks can aid in the rehydration of athletes during physical exertion, the electrolyte load is insufficient for patients undergoing a purgative regimen. Notably, PEG-ELS bowel preparations contain roughly 9 times more sodium (grams per regimen) than a sports drink (Table 3). Sports drinks replace carbohydrates and electrolytes by rapidly moving sugar, electrolytes, and free water into the circulation, thereby increasing overall plasma volume.[25] Metabolism of the carbohydrate component leads to a net absorption of "free" water (water without associated electrolytes). This absorption of free water may pose an increased risk of water imbalance for patients with impaired water handling and may contribute to the development of hyponatremia.[26]

Table 3. Relative Electrolyte Concentrations

Ion	PEG-ELS (g/2 L)	Sports drink (g/2 L)	Ratio (PEG-ELS: Sports drink)
Na+	8.35	0.88	9:1
K+	1.06	0.24	4:1
Cl-	4.23	0.72	6:1

PEG-ELS=polyethylene glycol electrolyte solution.

Risk of Hyponatremia

The administration of purgatives can lead to hyponatremia by a variety of overlapping mechanisms. Hyponatremia, or the relative increase in the ratio of body water to sodium, usually occurs in the setting of increased levels of circulating antidiuretic hormone (ADH).[27] Antidiuretic hormone and water intake play primary roles in defending body water content; as circulating osmolality increases above a threshold of ~285 mOsm/kg, thirst is stimulated and the posterior pituitary is stimulated to release ADH. Volume depletion decreases this osmotic threshold for ADH release and augments ADH release as a function of systemic osmolality.[28] The volume depletion associated with purgative administration will thus lead to an increase in circulating ADH.[29] Nausea, frequently associated with purgative administration, is a very potent stimulus for ADH release.[27] Baseline ADH levels and/or the ADH response to volume depletion are also increased in patients taking certain medications, particularly thiazide diuretics and selective serotonin reuptake inhibitors, and in patients with hypervolemic disorders associated with increases in circulating ADH, such as congestive heart failure or cirrhosis. Other drugs, particularly nonsteroidal antiinflam-

matory drugs (NSAIDs), potentiate the renal response to ADH. In summary, the administration of purgatives, comorbid processes such as congestive heart failure, and patient medications all increase circulating ADH levels in patients receiving purgatives, which in turn leads to the retention of ingested free water and hyponatremia.

The sudden decrease in serum osmolality that occurs with purgative-associated hyponatremia and other causes of hyponatremia leads to an influx of water into cells down the new osmotic gradient. This influx of water can cause rapid brain swelling (cerebral edema) if the physiological response mechanisms are overwhelmed, leading to the various symptoms and signs of hyponatremic encephalopathy. Early stages of hyponatremic encephalopathy include nausea, vomiting, and mental confusion; more serious sequelae include neurogenic pulmonary edema, hypoxia, seizure, and death.[30] For reasons that are not entirely clear, severe hyponatremic encephalopathy is almost entirely limited to female patients, particularly those who are premenopausal.

Acute hyponatremic encephalopathy has been associated with several methods of bowel preparation, including PEG-ELS, oral NaP, and off-label use of MiraLAX plus Gatorade.[26,27,31] To investigate the frequency of hyponatremia in patients undergoing colonoscopy, Cohen et al[29] followed 40 patients from initial bowel preparation with PEG-ELS to 1 hour after colonoscopy, measuring serum sodium and ADH levels. Initially, serum sodium and ADH levels were normal; however, after bowel cleansing and immediately before colonoscopy, 25% of patients had elevated serum ADH levels. Eight percent of patients experienced a decrease in serum sodium concentration to <130 mmol/L after colonoscopy.[29] The relative frequency of purgative-associated hyponatremia associated with PEG-ELS versus OSPS versus MiraLAX plus Gatorade is not known, nor is the relative risk known for severe hyponatremic encephalopathy. However, the relative risk of purgative-associated volume depletion is expected to be greater for MiraLAX plus Gatorade, given that this preparation does not provide enough electrolytes to replenish PEG-associated intestinal losses. The carbohydrate content of Gatorade is expected to lead to a greater gain of free water, with an augmentation of intestinal water absorption followed by metabolism of the absorbed carbohydrate.[25] MiraLAX plus Gatorade is thus hypothesized to increase the risk of purgative-associated hypovolemia, and thus the risk of hypovolemic increases in ADH, and promote the absorption of excess free water; these 2 factors are hypothesized to predispose colonoscopy patients to acute hyponatremia. However, at the current time, these statements have not been validated through clinical studies, and further investigation is warranted.

Assessing Safety of NaP Preparations

Proper Dosing and Indications

Although complications can result from either NaP or PEG-ELS bowel preparations, some clinicians have demonstrated more concern about the adverse events associated with NaP purgatives. PEG-ELS is an osmotically balanced, nonabsorbable solution that promotes bowel cleansing without causing substantial shifts in fluid and electrolyte levels, whereas a NaP preparation works through an osmotic mechanism of action, drawing water from the colonic mucosal lining into the bowel lumen.[32] While effective and generally well tolerated, several reports have suggested that NaP preparations are associated with renal damage.[33-36] To further examine this claim, large-scale studies have compared the frequency of renal dysfunction in NaP versus PEG-ELS preparations. A recent meta-analysis reviewed several studies that evaluated the efficacy, safety, and compliance associated with NaP versus PEG-ELS formulations.[37] The analysis concluded that NaP preparations were more effective at bowel cleansing, more frequently completed, and associated with a similar frequency of adverse events compared with PEG-ELS preparations. It should be noted, however, that NaP preparations were more frequently associated with biochemical (eg, serum phosphate) changes, indicating caution should be exercised when prescribing these formulations to patients with cardiac or renal impairment. In contrast, selected studies did not find changes in renal function with NaP or PEG-ELS preparations. One study found that of 2,352 patients who underwent colonoscopy (with no preexisting renal dysfunction 12 months before the procedure), only 4% of patients who received a NaP preparation experienced renal impairment compared with 3% of patients who took a PEG-ELS preparation.[38] A second study sought to determine the relative risk of acute kidney injury (AKI) in response to OSPS purgative administration. In a large, retrospective analysis of 9,799 patients, 114 (1%) developed AKI (≥50% increase from baseline in serum creatinine levels).[39] Of those patients, 73% had received a NaP preparation and 27% had received a PEG-ELS. Using a multiple logistic regression model, the use of OSPS was associated with an increased risk for AKI (odds ratio of 2.35, $P<.001$).

The complications arising from NaP preparations are frequently associated with patients who have preexisting renal insufficiency, suffer from preexisting and/or purgative-associated volume depletion, or are taking medications that decrease gastrointestinal motility or that affect kidney function (eg, diuretics, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]).[32] Inappropriate dosing may also contribute to adverse events associated with NaP preparations. Hookey

et al[40] examined adverse events from 29 patients in 20 studies and found that 19 cases (66%) were a result of inappropriate dosing. In addition, 6 cases (21%) of adverse events were reported in patients with preexisting renal impairment, and 25 of 29 patients (86%) had predisposing risk factors before NaP administration.[40] In summary, these studies emphasize the importance of clinician education and careful patient preparation in order to ensure appropriate patient selection, dosing, and hydration when using a NaP preparation.

Acute Phosphate Nephropathy and Renal Injury

Acute renal failure associated with NaP-based bowel preparations is a very serious condition known as acute phosphate nephropathy (APN).[36] Acute phosphate nephropathy is characterized by the presence of calcium phosphate crystals in the renal tubules and can lead to chronic irreversible kidney injury. In a report from Rex et al,[32] 24 cases (23 OSPS, 1 NaP tablets) of acute renal failure followed by chronic renal insufficiency in patients taking NaP bowel preparation for colonoscopy were reviewed. Although rare, APN was usually associated with predisposing risk factors. For example, 83% of patients experiencing APN were female and 71% had a history of hypertension, the majority of whom were taking diuretics, ACE inhibitors, or ARBs. Despite the low incidence of APN, the severity of potential renal damage and associated long-term dialysis prompted the US FDA to issue a warning on December 11, 2008, indicating that potential risk factors for APN include advanced age, renal disease, decreased intravascular volume, and the use of drugs that affect renal perfusion or function.[41] Although the pathogenesis of APN is not entirely clear, it is likely that adequate volume repletion may reduce the risk of this serious complication.

Conclusions

Discussions during this roundtable meeting of the current issues in bowel preparation for colonoscopy included benefits of purgative PM/AM split dosing, the potential risks associated with MiraLAX combined with a sports drink as a bowel preparation, and safety concerns of NaP preparations. In closing, all of the expert physicians agreed on specific important issues that were addressed (Table 4). First, it was concluded that PM/AM split dosing was more effective in polyp detection than PM-only dosing when properly administered. The timing of the AM (second) dose <6 hours before examination was determined to be more important than the time between the first (PM) and second (AM) dose. Second, physician and patient education regarding ASA guidelines permitting clear liquids up to 2 hours before anesthesia is safe (in patients with no preexisting conditions that would increase the risk for aspiration) and should be implemented. Third, the panel concluded the use of MiraLAX as a bowel preparation could lead to an increased risk of hyponatremia and should be used judiciously in a select group of patients. Without controlled clinical trial data to support the use of MiraLAX, clinicians should educate patients on the potential associated risks. Finally, prescription NaP preparations were concluded to be safe and effective in patients without predisposing risk factors if dosed appropriately and accompanied with adequate hydration.

Table 4. Key Messages Conveyed

1	PM/AM split dosing is more effective in polyp detection than PM-only dosing
2	Intake of clear liquids ≥2 hours before anesthesia is safe and complies with ASA guidelines
3	MiraLAX is not approved by the US FDA for use as a bowel preparation and may increase the risk of hyponatremia
4	NaP bowel preparations are safe and effective when used in properly selected patients and dosed appropriately with adequate hydration

ASA=American Society of Anesthesiologists; FDA=Food and Drug Administration; NaP=sodium phosphate.

Addendum

On December 11, 2008, the US FDA announced the requirement of a boxed warning to prescription oral NaP products, Visicol® (Salix Pharmaceuticals, Inc) and OsmoPrep, concerning the risk of AKI including APN. The letter issued from the US FDA references 20 cases of AKI with 3 confirmed biopsies of APN. Over 1.5 million prescriptions for OsmoPrep were written during this time. The US FDA has indicated that NaP bowel preparations should be available by prescription only; as such, over-the-counter Fleet® Phospho-soda® and Fleet Phospho-soda EZ-Prep® Bowel Cleansing System have been voluntarily recalled by C.B. Fleet Company (Lynchburg, VA). Therefore, prescription Visicol and OsmoPrep remain the only NaP products available as bowel preparations for colonoscopy. On March 25, 2009, the FDA approved the final labeling for OsmoPrep. In an effort to ensure that the most accurate and up-to-date information is provided, publication of this article was delayed.

Proceedings from this roundtable discussion highlight the importance of prescribing only products indicated for bowel preparation for colonoscopy. In addition, it should be noted that this roundtable discussion took

place prior to the statement from the US FDA, yet the topics covered herein relate directly to the concerns of the boxed warning.

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