Published in final edited form as:

Expert Opin Drug Metab Toxicol. 2011 January ; 7(1): 89–101. doi:10.1517/17425255.2011.542411.

Mechanism of Action and Toxicities of Purgatives Used for Colonoscopy Preparation

Margaret Adamcewicz, MD, Dilip Bearely, MD, Gail Porat, MD, and Frank K. Friedenberg, MD

Department of Medicine, Section of Gastroenterology, Temple University School of Medicine, Philadelphia, PA 19140

Abstract

Importance of the field—In developed countries colonoscopy volume has increased dramatically over the past 15 years and is the principle method used to screen for colon cancer. Preparations used for colon cleaning have evolved over the past 30 years. Some preparations have been shown to be unsafe and are now used on a limited basis. There has been progress on limiting the volume required and on taste improvement.

Areas covered in this review—This review provides an account of preparations used from 1980 when polyethylene glycol-based preparations became widely available, until the present day. The review highlights their mechanism of action and principle toxicities. The handling of solutes and solute-free fluid by the colon is also reviewed.

What the reader will gain—The reader will gain a perspective on the factors considered in developing colonic purgatives and the rationale for choosing selected preparations based on patient factors such as age, co-morbidities, and concomitant medications.

Take home message—Although generally safe and effective, colonic purgatives have both acute and permanent toxicities. The safest preparations utilize polyethylene glycol combined with a balanced electrolyte solution. Limitations of this preparation center on the volume required and poor taste. Alternative formulations are now available; however those using sodium phosphate have fallen out of favor due to a risk of renal toxicity.

Keywords

colonoscopy; nephrocalcinosis; polyethylene glycol; sodium phosphate

1. Introduction

Colorectal cancer screening with colonoscopy allows for the early detection and removal of precancerous adenomas. Colonoscopy is the preferred method for screening as it offers superior sensitivity in the detection of abnormalities and allows for therapeutic intervention, i.e. polypectomy, at the time of the procedure. As a direct result of colon cancer screening, incidence and mortality from colon cancer has decreased in the United States. [1] However, compliance with screening guidelines is reported to be as low as 34% in adults age >50 years. [2] This low compliance may be partially attributed to the patient's reluctance to undergo bowel preparation.

Bowel preparation is an essential part of high-quality colonoscopy for effective visualization and removal of adenomatous polyps. Suboptimal preparation occurs as often as 25% of cases [Figure 1].[3] It is associated with missed diagnoses and increased costs secondary to prolonged procedure times and repeat exams due to aborted procedures.[4] The ideal preparation would be well-tolerated, safe, and effective as a colon-cleansing agent. It should not affect the macroscopic or histological visualization of colonic mucosa. It also should not cause an imbalance of fluid or electrolytes in the vascular space.

2. History of Bowel Preparations

2.1 Physiology of Solute and Fluid Handling By the Colon

The colon is the most efficient site of absorption in the GI tract. Between 1–1.5 L of fluid reaches the cecum daily yet the total volume of water in stool is only 100–150 mL/day.[5] Net absorption of NaCl, short chain fatty acids [SCFA], and water, allow for the excretion of feces with very little water or salt content. The epithelium also has the capability to secrete mucous, bicarbonate, and KCL. Anatomically, the colon has been divided into proximal and distal zones and epithelial cells are characterized as either surface or crypt. [6] Recent data has shown that absorption and secretion can be handled by both cell types. [7] Goblet cells and enterochromaffin cells make up the remaining cells of the colonic epithelium. [8]

There are two mechanisms for Na⁺ absorption in the colon: electroneutral and electrogenic. Absorption of Na⁺ in the ascending colon is primarily via electroneutral absorption by parallel luminal Na⁺/H⁺ and Cl⁻/HCO₃⁻ exchange [Figure 2]. Conversely the epithelium of the descending colon transports Na⁺ by electrogenic absorption via amiloride-sensitive Na⁺ channels under the influence of aldosterone.[6] Active K⁺ absorption occurs in the distal colon where K⁺ is taken up on the luminal side by two different H⁺-K⁺- ATPases. [9] Short chain fatty acids [SCFA] are absorbed by colonic epithelium in parallel with NaCl. The SCFA's are produced during fermentation of dietary fibers by colonic bacteria. This absorption of SCFA's serves as an additional energy supply for colonic epithelial cells. Their absorption occurs via non-ionic diffusion and paracellular absorption in the proximal colon. [10]

Chloride secretion mainly occurs by the crypt cells, but also by surface epithelial cells of the proximal and distal colon. Secretion is activated by cyclic AMP-dependent stimulation of a luminal Cystic Fibrosis Transmembrane conductance Regulator [CFTR] channel. This is paralleled by secretion of KCl via luminal K⁺ channels and NaCl transport through a paracellular shunt. The chloride is taken up by the cells on the basolateral membrane via a Na⁺-K⁺-2Cl⁻ co-transporter. [11] Luminal K⁺ secretion occurs via specific channels and is upregulated by aldosterone and glucocorticoids in parallel with Na⁺ channels. The main function of the basolateral K⁺ channel is to maintain a hyperpolarized membrane voltage and is the electrical driving force required for Cl⁻ secretion and Na⁺ absorption. [6]

Bicarbonate is secreted by the luminal side of the epithelium in parallel with KCl, producing a slightly alkaline pH. It is taken up by the basolateral membrane via a Na⁺-dependent, electroneutral mechanism and is also generated inside colonocytes with the help of carbonic anhydrase. [12]

The secretion of electrolytes is paralleled by macromolecules and the largest of these is mucus. Mucus secretion creates a microenvironment near the epithelium and forms a barrier that protects the cells from abrasion and bacterial invasion. [13] It is released by goblet cells and crypt columnar epithelial cells.

The final function of the colon is water absorption. Although there is net absorption of water, it is both absorbed and secreted. It is not clear how much water is absorbed via paracellular pathways versus epithelial cells. [14] It is also unclear how water is absorbed against a high osmotic gradient generated by the high osmolality of feces. There are specific water channels called aquaporins that transport water, however, there is little evidence that these water channels are essential for colonic fluid absorption and fecal dehydration. [15] The CFTR channel may be important in epithelial ion and water transport.

2.2 Solutions Developed for Colon Cleansing

Bowel-cleansing methods were first developed for radiologic studies and surgical procedures [Figure 3]. The methods used consisted of dietary restrictions, oral cathartics and cathartic enemas. These preparations required several days of dietary changes, aimed at decreasing feces in the colon by following a clear liquid or low-residue diet for 2–3 days before the procedure.[16] Interestingly, in a prospective study comparing a clear liquid and low-residue diet, the clear liquid diet was found to be less effective. [17] Laxatives were given the day before the procedure, followed by enemas on the day of procedure. These methods interfered greatly with the patient's daily activities, and induced fluid and electrolyte disturbances. To accommodate for the malnutrition that ensued with these regimens, an elemental diet was developed to avoid electrolyte imbalances and inadequate caloric intake. [18] Although effective, it required inpatient admission for many days prior to the procedure. The enemas also required were inconvenient and caused significant patient discomfort. Some studies also reported inflammation of the rectal mucosa from enema use. [19]

Oral gut lavage became popular as an alternative to enemas and was given as either a saline solution or a balanced-electrolyte solution. This preparation resulted in rapid and effective bowel cleansing, but required an extremely large volume fluid intake [7–12 liters]. [20] Some patients required nasogastric tube placement for ingestion of the preparation. In one study, 11% of patients could not tolerate this method. [8,9] Besides the large volume required, this method fell out of favor because it also induced weight gain and caused significant fluid and electrolyte imbalances. [20]

Shortcomings of previous preparations led to the development of osmotically-balanced solutions. The first preparations contained mannitol, a non-absorbable oligosaccharide. A 10% solution resulted in rapid cleansing without fluid or electrolyte imbalances. [21] The major drawback of mannitol was its potential to become combustible. Mannitol is fermented by colonic bacteria to methane and hydrogen gas and there were several reports of explosions in the 1930s and 1940s. [22] This is of major concern for colonoscopy preparation as insufflation of the colon with oxygen and use of electrocautery is common during this procedure. [23]

In 1980, Davis et al, reported on the development of a polyethylene glycol-electrolyte lavage solution [PEG-ELS] which is non-fermentable and causes minimal water and electrolyte absorption and secretion. [24,25] Its salty taste and bad smell from the sodium sulfate component have led to the development of variations of this solution. For example, Fordtran et al. described a sulfate-free form of PEG solution [SF-PEG] with an improved taste. [26]

In 1990 Vanner et al developed a sodium phosphate solution which had the advantage of a much smaller volume leading to better tolerance. [27] This also led to the development of a sodium phosphate tablet form of this solution.[28] Although better tolerated, there has been much concern over these preparations recently secondary to data linking them to renal impairment. [29] The oral solution which was available over-the-counter in the United

States was taken off the market completely while the tablet form remains available by prescription and it now has an FDA black-box warning.

3. Preparations in Use

3.1 Polyethylene Glycol

Polyethylene glycol [PEG], also termed Macrogol, is a tasteless, inert polymer of ethylene oxide with a mean molecular weight of 3350 Da [PEG 3350]. It completely dissolves in any solution. PEG 3350-based formulations now represent the most frequently used forms of oral cleansing preparations for colonoscopy in Western countries. In 1980 Davis et al formulated an iso-osmotic colon cleansing preparation containing primarily PEG 3350 and an electrolyte lavage solution [ELS] containing sodium sulfate. Sodium sulfate itself contributes to the laxative effect of the mixture. This product carries the name PEG-ELS and is currently available under the branded names Golytely® [Braintree Laboratories, Inc, Braintree, MA] and Colyte® [Schwarz Pharma, Inc., Milwaukee, WI] and in generic form. Colyte® is marketed with fruit flavored saccharin-containing flavor packets. This “balanced” formulation was shown to traverse the luminal GI tract without any significant absorption or secretion of electrolytes or fluids.[24] Absorption of sodium from the gut requires chloride which is replaced by sulfates in the mixture. Colon cleansing thus occurs as a result of mechanical drag of fecal debris by the fluid load. Unfortunately, 4 liters of the solution is required to produce an adequate cathartic effect. Early studies demonstrated that poor taste and large volume contributes to about 5–15% of patients not being able to complete consuming the necessary amount of this solution.[30,31] A pooled analysis of 15 trials found that 29% of patients were unable to complete their PEG solution. [32] In one study most of the unsuccessful colonic preparations were caused by incomplete ingestion of PEG-ELS. [33] The most common side effects of standard 4L PEG-ELS are nausea, vomiting, abdominal fullness and bloating. [34]

Poor tolerability was also related to the sulfur component of the PEG-ELS, causing a rotten egg smell. This prompted the development of a sulfur-free electrolyte lavage solution [PEG SF-ELS] commercially available as Nulytely® and TriLyte®.[26] PEG SF-ELS has been shown to be safe and effective in clinical trials with better palatability compared to the PEG-ELS. [35–38] PEG SF-ELS is also available with sugar-free flavor packets to improve palatability and patient tolerance/compliance. [39]

PEG 3350 without electrolytes is available OTC and is FDA approved for the treatment of constipation in generic form and under branded names such as Miralax® [Schering-Plough, Memphis, TN]. In a small trial in children, PEG 3350 at a dose of 1.5 g/kg/day for 4 days was combined with any drink desired by the child before colonoscopy. The preparation was shown to be effective, safe, and well tolerating by the children.[40]. There is concern surrounding this preparation as fermentable carbohydrate could increase the risk for combustion. In adults, pilot trials combining PEG 3350 with 2 liters of Gatorade® have generally shown acceptable efficacy and tolerability although safety with respect to serum electrolyte balance has not been confirmed. [41] Three ongoing prospective randomized trials will hopefully clarify this issue.

Consuming all 4L of PEG on the day before colonoscopy is poorly tolerated as the volume can lead to nausea, cramping, and vomiting. This is especially relevant in the elderly who may have delayed gastric emptying. In one study, PEG-ELS administered in a divided dose of 3L the day before colonoscopy and 1L on the morning of colonoscopy was demonstrated to be equal or slightly more effective than 4L of PEG-ELS all given the day before colonoscopy. [42,43] The current practice is to split dose the PEG preparation into 2L doses the evening before and the morning of the exam, usually 5–6 hours before the procedure.

Church et al demonstrated that ingestion of the second dose of PEG 5h before the procedure resulted in better cleansing effect than when given more than 12 h before colonoscopy. [44]. Due to the widely recognized improvement in exam quality, the 2009 ACG Guidelines on Colorectal Cancer screening supports the use of a split dose bowel preparation. [45]

3.2 Low Volume PEG Preparations

As mentioned, other than taste, one of the major limitations with PEG-based preparations is the volume that needs to be consumed. A recently developed product combines PEG 3350 with 10.6 gm of Ascorbic acid/Sodium ascorbate and is commercially marketed as Moviprep [Salix Pharmaceuticals, Morrisville, NC]. Approximately 10% of the Ascorbic acid/Sodium ascorbate is absorbed in the proximal small bowel and the remainder produces an osmotic effect within the gut, potentiating the cathartic action of PEG. [46] The preparation contains sodium sulfate but is reported to have an acceptable taste due to the addition of ascorbate, two sweeteners, and lemon flavoring. [47] The final mixture volume is 2 liters but requires the patient to drink an additional liter of solute free liquid. Patients experience considerable cramping when completing the preparation in one sitting. Therefore split dosing, drinking half the PM before the exam and the remainder the day of exam, is recommended. Two studies comparing this formulation to standard 4 liter PEG-ELS have found it to be as efficacious with improved tolerability. [47,48] In the UK, PEG 3350 + Ascorbate was found to be comparable to a preparation containing sodium picosulphate [stimulant laxative] + magnesium citrate [osmotic laxative] which is a commonly used purgative combination used outside of the USA. [49]

Over the past 20 years PEG 3350 has been combined with prokinetics in order to improve colon cleansing and reduce the volume of PEG required. Studies comparing PEG-ELS + Cisapride vs. PEG-ELS alone did not reveal any added effect on bowel cleansing but significantly reduced nausea and bloating. [50] Another recent study combined Tegaserod [Zelnorm[®], Novartis International AG, Basel, Switzerland], a 5-hydroxytryptamine receptor agonist with PEG-ELS and revealed no improvement regarding tolerance, effectiveness or adverse effects. [51] Another study showed a marginal improvement in preparation quality. [52]

A combination of low volume PEG-ELS with bisacodyl is now used commonly for colon cleansing. Bisacodyl is a diphenylmethane derivative that is poorly absorbed in the small intestine and is hydrolyzed by endogenous esterases. Its active metabolites stimulate colonic motility. The half-life of bisacodyl is between 6 and 10 hours. Bisacodyl is usually consumed 6 hours prior to PEG-ELS or earlier if a spontaneous bowel movement occurs. Sharma et al combined 20 mg of bisacodyl with 2L PEG-ELS and found that the combination was equally effective and more tolerable than 4L PEG-ELS. [53] Two studies demonstrated similar results with 20mg of bisacodyl as an adjunct to 2L PEG-ELS and 4L PEG SF-ELS respectively. [54,55] In another study, DiPalma et al demonstrated equal effectiveness of 2L of PEG SF-ELS combined with 10 mg of bisacodyl and the same solution with 20 mg Bisacodyl. There were fewer side effects such as cramping, nausea and overall discomfort in the 10 mg group compared to the 20 mg group. [56] Halflytely[®] [Braintree Laboratories, Inc] is a commercially available preparation of 2L PEG SF-ELS combined with bisacodyl. Initial combination therapy contained 20 of bisacodyl but was reduced to 5 mg due to adverse side-effects including reports of ischemic colitis with 10 and 20 mg doses of bisacodyl. [57]

Senna is an anthracene derivative stimulant preparation whose active ingredients, anthraquinones and their glucosides stimulate colonic peristalsis and inhibit water and electrolyte reabsorption. Intake usually results in a spontaneous bowel movement approximately six hours after ingestion. It has been tried as a cleansing agent with liquid diet

in children. [58] In one study, senna compounds reduced the dose of PEG-ELS required for effective colon cleansing, thus increasing tolerability. [59] A group in Italy has recently published two randomized trials evaluating high dose senna alone as a preparation for colonoscopy. In the first study, 24 tablets of 12mg senna given in divided doses the day before procedure were found to be superior to 4 L of PEG-ELS. Overall, 90.6% of senna patients had an excellent or good prep compared to 79.7% in the PEG-ELS group [P=0.003]. [60]. A recent follow-up study compared 24 tablets of senna vs. 12 tablets of senna plus 2L of PEG-ELS. Excellent or good colon preparation were found in both groups at a rate around 90% [P=0.62]. [61] For unclear reasons, in the US senna is not as widely used as an adjunct to PEG-ELS compared to bisacodyl and is not approved for this use. Of note, high doses of Senna can evoke severe abdominal pain.

3.3 Phosphate Preparations

Vanner et al in 1990 first introduced oral sodium phosphate [NaP] in an aqueous form and in 2000, Aronchick et al introduced the tablet form as an alternative agent for the purpose of colon cleansing. [27,28] There are 24 studies comparing PEG-ELS or PEG SF-ELS with NaP included in a recent metanalysis. The authors concluded that both preparations were equally efficacious but NaP had superior tolerability. [62]

Due to its hyperosmotic effect, NaP draws water and electrolytes from plasma into the gut promoting bowel cleansing. Aqueous NaP [Fleet® PhosphoSoda®, C.B. Fleet Company, Lynchburg, VA] solution contains 48 gm of monobasic and 18 gm of dibasic NaP per 100 ml. The mean onset of activity and duration of effect after consumption of the 1st and 2nd dose of oral sodium phosphate solution is 1.7, 4.6 hrs and 0.7, 2.9 hrs, respectively. [63] Each 45 ml of liquid preparation contains 29.7 g of NaP. A dose is given the night before and the morning of colonoscopy along with 1 L of water.

There are two available tablet forms of NaP tablets both of which contain a total of 1.5 grams of NaP monobasic monohydrate, and NaP dibasic anhydrous. The original tablets also contained an inactive ingredient called Micro Crystalline Cellulose [MCC] [Visicol®, Salix, Morrisville, NC]. MCC was thought to reduce colonic visibility necessitating the development of a second, MCC-free tablet [OSMOPREP®, Salix]. [64] OSMOPREP® contains 48grams of phosphate, a 20% reduction compared to the 90mL standard dose of NaP solution. The dose of OSMOPREP® is 32 tablets administered in divided doses separated by 10–12 hours, with at least two liters of water to avoid dehydration. After reports of acute phosphate nephropathy associated with all forms of NaP laxatives, the FDA issued an alert on 12/11/2008. This required a black box warning for Visicol® and Osmoprep®. NaP tablets, if used, should only be prescribed to individuals under the age of 55, without a history of heart or renal failure, and not taking ACE-inhibitors or diuretics. Liquid sodium phosphate products for colonoscopy preparation were removed from the market.

3.4 Magnesium Preparations

Magnesium Citrate is an osmotic laxative that, as a sole agent, has not been found effective for colonoscopy preparation. However, combination formulations are effective. Magnesium citrate combined with sodium picosulfate is approved as a colorectal cleansing agent for diagnostic colonoscopy in adults, adolescents and children in the UK. Each sachet contains 0.01g of Sodium picosulfate, 3.5gm of magnesium oxide and 12g of citric acid. [PICOLAX®, Norgine Ltd, Oxford, UK] Sodium picosulfate is a pro-drug that is hydrolyzed by bacteria in the colon to the active metabolite 4,4'-dihydroxy-diphenyl-[2-pyridyl]methane which acts as a stimulant laxative. [65] The formulation is locally active in the colon and is not absorbed in any detectable quantities. When dissolved in water,

magnesium oxide and citric acid components form magnesium citrate. [66,67] PICOLAX[®] has been compared to PEG-ELS and aqueous NaP and found to be equally effective and better tolerated. [68,69] Unfortunately, due to its osmotic activity, it can cause dehydration, electrolyte shift and magnesium retention. Recommended dosing is two sachets administered 6 hours apart.

A new preparation has recently been FDA-approved in the U.S. The split-dosed prep utilizes two, six ounce doses of sodium sulfate 17.5 g, potassium sulfate 3.13 g, and magnesium sulfate 1.6g, along with citric acid and other flavorings [SUPREP, Braintree]. Each dose is administered as a diluted solution with a total volume of 16 ounces. An additional 1 quart of water is consumed with each dose. In a randomized, single-blind, active-controlled study of 363 patients, SUPREP preparation quality was found to be comparable to a split-dose regimen of 4L of PEG-3350-ELS. [70]

Despite the potency of modern colonic purgatives, inadequate preparation often occurs. In randomized controlled clinical trials, inadequate colon cleansing can occur in up to 25% of cases.[3,71–73] One large prospective, multicenter trial European study concluded that cleansing quality was similar in men and women and not significantly related to age when adjusting for health status.[74] However, cleansing quality was lower in elderly patients and patients in the hospital. Single-center studies have found a variety of factors predictive of poor preparation such as male gender, inpatient status, diabetes, age greater than 60, obesity, Medicaid insurance, and unmarried status. [71–73,75] A history of serious medical problems, specifically cirrhosis, stroke, and dementia also appear to be associated with poor colon cleansing.[71–73,75]

4. Reported Toxicities from Bowel Preparations

Adverse events following bowel preparation are uncommon, but potentially serious [Table 1]. Given that many patients undergoing screening are healthy, the benefit: risk ratio must be carefully considered when deciding which preparation to prescribe. [62] The adverse effects of bowel preparations are magnified when there is inadequate hydration, inappropriate dosing and inappropriate patient selection. Preventing dehydration in patients undergoing bowel preparation can prevent severe adverse events, regardless of the purgative administered. [76]

Hyponatremia as a result of vomiting, diarrhea, renal disease or inappropriate secretion of ADH can develop with any colonoscopy preparation. [77] Vomiting leads to reduction in plasma volume, an increase in ADH concentration, and increased thirst. Patients with renal insufficiency, hypothyroidism, mineralocorticoid deficiency, liver cirrhosis, heart failure or those on diuretics, NSAIDs, or ACE inhibitors already have an impaired ability to excrete free water and are, therefore, at increased risk for hyponatremia.

4.1 Toxicity of PEG Preparations

Electrolyte disturbances are uncommon with the use of PEG. Due to its iso-osmolality, PEG appears to be relatively safe for patients at risk for electrolyte imbalances and those who cannot tolerate a significant fluid load [renal failure, congestive heart failure or advanced liver disease with ascites]. [78] In addition, no cases of renal toxicity were found in the literature from the use of PEG as a bowel preparation.[78]

Five cases of clinically significant disturbances in sodium homeostasis following the use of PEG have been reported. [79–81] In one case the patient consumed PEG-3350 mixed with 64 ounces of an electrolyte containing sports drink.[80] In four cases, hyponatremia and water intoxication causing confusion were diagnosed and, in three cases, convulsions

occurred that resulted in one death. It was thought that the stress from vomiting, concomitant diuretic use and co-existing diseases contributed to inappropriate ADH release and, therefore, hyponatremia. In a case by Ayus, a patient with end stage renal disease developed profound *hyponatremia* secondary to dehydration and died following ingestion of PEG.[79]

PEG has not been shown to alter the histological features of the colonic mucosa and may be used in patients suspected of having inflammatory bowel disease. [82] The only GI injuries associated with the use of PEG are seven reports of Mallory-Weiss tears and three cases of esophageal perforation caused by vomiting following ingestion of PEG-based bowel preparation. [83–89] Predisposing factors were not identified. All patients recovered after conservative management in the case of tears and surgical repair for the patients with perforation. One report of a perforated sigmoid diverticulum was published although whether PEG ingestion precipitated this event remains speculative. [90] In this report, the patient, who was admitted for sigmoid colectomy for diverticular disease, consumed 4L of PEG solution in preparation for the procedure. The patient fully recovered. As mentioned previously, PEG taken in conjunction with 20 mg [but not 10 mg] of bisacodyl has been associated with colonic ischemia. [57]

Rare episodes of mild volume overload have been reported with the use of PEG-ELS in patients with severe congestive heart failure and those with chronic renal insufficiency. [91] There have been no reports of a patient requiring hospitalization as a result of sodium and water retention after bowel preparation with PEG-ELS. CHF is not considered a contraindication to the use of this solution; however, most clinical trials that included patients with heart failure did not describe the degree of left ventricular dysfunction. In patients with severe left ventricular dysfunction with or without renal insufficiency who are being considered for procedures that necessitate bowel cleansing use of PEG-ELS is recommended.

4.2 Toxicity of Sodium Phosphate Preparations

Electrolyte disturbances—All NaP preparations have been associated with adverse events, including lethal outcomes. Their use should be limited to patients without cardiac or renal dysfunction, and caution should be exercised when they are administered to patients with pre-existing electrolyte disturbances, patients using medications that result in electrolyte disturbances, and elderly or debilitated patients. [92]

NaP preparations are associated with changes in electrolyte levels that usually resolve within 24 hours. The most common electrolyte imbalance includes increases in phosphate and decreases in calcium. [93] All patients who take the standard dose of NaP will develop hyperphosphatemia; the average increase in serum phosphate level is 1.0–1.3mmol/L. [32] Excessive or repeated NaP doses, and increased intestinal phosphate absorption due to bowel obstruction or impaired transit overwhelms the kidney's ability to process NaP and increases the risk of hyperphosphatemia. [94] Fatal cases of hyperphosphatemia have been reported in patients receiving more than the standard dose of NaP and in those with renal failure. [95,96] The risk of hyperphosphatemia is higher in elderly patients. This may be due to an age-related decline in renal function, decreased bowel motility, systemic and gastrointestinal diseases, or concomitant use of medications that affect kidney or gastrointestinal function. Beloosesky et al. showed that the increase in serum phosphorus level negatively correlates with baseline GFR. [97]

Studies on NaP show a small decrease [0.08–0.2mmol/L] in mean serum calcium levels but usually not in the range that would cause symptoms.[63] Hypocalcemia develops in order to maintain calcium-phosphate product in the normal range following NaP-induced

hyperphosphatemia. Hospitalized and elderly patients are particularly prone to develop hypocalcemia. [97]

The incidence of hypokalemia [serum potassium level $<3.5\text{mmol/L}$] is 20–30%, but increases to 56% in hospitalized patients aged 65 years or older. [27,97] NaP induces gastrointestinal loss of potassium and considerable amounts of potassium are excreted by the kidneys after a NaP dose because of the luminal electronegativity induced by hyperphosphaturia.

The standard dose of NaP contains 434 mmol of sodium. Mild hyponatremia is quite common after NaP use, particularly in elderly patients, and is mostly asymptomatic. One case of severe hyponatremia [serum sodium level 166mmol/L] with acute kidney injury has been reported in a patient with Alzheimer's and Parkinson's diseases after receiving NaP, and was probably due to inadequate fluid intake. [98]

Significant hyponatremia and seizures have also been reported with the use of NaP. [99] In spite of the high sodium content of NaP, seizure associated with acute hyponatremia has been reported in two female patients [serum sodium levels 116mmol/L and 132mmol/L respectively] after taking NaP, probably because of excessive free water intake. Both patients also had risk factors for hyponatremia, including use of a thiazide diuretic and an ACEI in one, and use of an antidepressant in the other. It may be reasonable to determine if patients have existing electrolyte abnormalities or renal dysfunction prior to administration of a Na P preparation although no specific guidelines exist.

Renal toxicity—Nephrocalcinosis is defined as a tubular injury with abundant tubular calcium phosphate deposits on renal biopsy. NaP purgatives have been associated with this rare form of kidney injury and in this setting it is termed Acute Phosphate Nephropathy. The phosphate load on the kidney promotes precipitation of calcium phosphate crystals in the kidneys [Figure 4]. Potential contributing factors include inadequate hydration during bowel preparation administration, increased patient age, a history of hypertension [with histological evidence of arterionephrosclerosis], and concurrent use of ACE inhibitors, ARBs, diuretics or NSAIDs. [29] Markowitz et al, looked at 21 individuals who received NaP for bowel preparation and developed Acute Phosphate Nephropathy. In all patients chronic renal insufficiency was from nephrocalcinosis as shown on biopsy. Overall 17 developed chronic renal insufficiency with a mean creatinine of 2.4mg/dl and four developed end stage renal disease. All patients included in the study were elderly [mean age 64 with 85% older than 51], mostly women [81%], and on antihypertensive medications such as ACEI, ARBs or diuretics. [29] In one study the incidence of acute kidney injury after bowel preparation with NaP was estimated to be 1–4% in the general population, although the true incidence may be far lower. [100]

Arrhythmias—Hypokalemia and hypocalcemia that occurs after NaP use may affect cardiac rhythm by prolonging the QT interval. In a prospective study in healthy volunteers, the increase in QTc interval after intake of NaP was greater in females [mean increase of 20–30ms], but this prolongation was not clinically meaningful. [101] Ventricular tachycardia associated with hypokalemia during bowel preparation with NaP has been reported in patients with underlying cardiac disease and arrhythmia. [102]

Ischemic Bowel Injury—Macroscopic and histological changes to the mucosa have been described in patients who received NaP as a preparation for colonoscopy. Two reports described aphthoid erosions after colonic cleansing with NaP mimicking those seen in inflammatory bowel disease. [103,104] For this reason, some clinicians avoid the use of NaP preparations in patients with suspected inflammatory bowel disease.

4.3 Toxicity of Magnesium Preparations

Magnesium citrate should be used with caution in patients on a low sodium diet. The major route of magnesium citrate excretion is renal, and fatal episodes of hypermagnesemia have been reported in patients with suspected or known renal failure or elderly patients. [105,106] Magnesium citrate combined with sodium picosulfate should be used with caution in patients on concomitant medications that affect electrolyte balance. In one study, magnesium citrate/sodium picosulfate was associated with significant decreases in chloride levels and significant increases in magnesium levels.[68] The Australian Adverse Drug Reactions Advisory Committee reported on eight adverse events due to hyponatremia associated with magnesium citrate/sodium picosulfate including convulsions, syncope, and loss of consciousness. There were four reports of syncope and dehydration without documented electrolyte abnormalities. It is recommended that magnesium containing bowel cleansers be used with caution in patients with renal impairment, heart disease, patients on concomitant medications that affect electrolyte balance [diuretics], and in elderly or debilitated patients.

5. Conclusions

There has been considerable advancement in the field of colonic purgatives over the past 30 years. This industry has been driven by the widespread adoption of colonoscopy as a means to screen for colon cancer. The real breakthrough came with the use of polyethylene glycol as a cleansing agent. Formulation to allow for electrolyte homeostasis required the addition of a balanced electrolyte solution to polyethylene glycol. This large volume preparation has a poor taste due to the addition of sodium sulfate. Modification of PEG including sulfate-free preparations, combining with bisacodyl to reduce volume, “split dosing”, and adding large amounts of ascorbic acid have been improvements. Longstanding use of sodium phosphate either in liquid or tablet form was widespread until 2008 when reports of nephrocalcinosis resulted in action by the Food and Drug Administration. Liquid formulations are now unavailable in the US and tablet preparations carry a black box warning. Magnesium-based preparations are widely used in the UK and a new low volume magnesium containing preparation recently became FDA-approved in the US. Table 2 highlights areas of uncertainty and future research.

6. Expert Opinion

The safest and most effective preparations available are those which use polyethylene glycol as the purgative agent. In order to avoid dehydration, volume overload, and electrolyte disturbances it is necessary to combine PEG with a balanced electrolyte solution. Four liters of tap water are added to this powdered mixture. To improve taste and reduce volume several acceptable strategies are available. PEG can be combined with a sulfate-free electrolyte solution and a sugar-free sweetener added. PEG can be given as a “split dose”, giving two liters the evening before the exam and the second half 4–6 hours prior to the exam. The addition of ascorbic acid in high concentration is safe and better tolerated due to improved taste and smaller volume [3L]. Combining PEG with 10 mg of bisacodyl is safe and reduces the volume to two liters. However, it should be avoided in the elderly [age > 65] and those with a history of ischemic or inflammatory bowel disease due to the potential for ischemic colonic injury. There is no recommendation to check serum electrolytes after consuming PEG-based purgatives; however interval or amplitude abnormalities on electrocardiography [such as peaked-T waves, prolonged QTc interval, etc.] prior to or during colonoscopy should prompt an assessment.

Use of PEG in combination with an electrolyte sport drink such as Gatorade® and given as a final two liter preparation is in widespread use. There are no safety data on this approach and its use cannot be recommended until results from randomized trials are available.

Sodium phosphate tablet preparations should be used with caution. They should not be used in the elderly [age > 55], those with underlying cardiac, liver, or renal disorders, and in those taking ACE inhibitors, angiotensin-receptor blockers, and diuretics. As with PEG preparations, monitoring of electrolytes and renal function after colonoscopy is not routinely recommended.

References

1. Jemal A, Center MM, Desantis C, et al. Global patterns of cancer incidence and mortality rates and trends. *Cancer Epidemiol Biomarkers Prev* 2010;19(8):1893–907. [PubMed: 20647400]
2. Seeff LC, Nadel MR, Klabunde CN, et al. Patterns and predictors of colorectal cancer test use in the adult U.S. population. *Cancer* 2004;100(10):2093–103. [PubMed: 15139050]
3. Froehlich F, Wietlisbach V, Gonvers JJ, et al. Impact of colonic cleansing on quality and diagnostic yield of colonoscopy: the European Panel of Appropriateness of Gastrointestinal Endoscopy European multicenter study. *Gastrointest Endosc* 2005;61(3):378–84. [PubMed: 15758907]
4. Harewood GC, Sharma VK, de Garmo P. Impact of colonoscopy preparation quality on detection of suspected colonic neoplasia. *Gastrointest Endosc* 2003;58(1):76–9. [PubMed: 12838225]
5. Binder HJ. Mechanisms underlying the absorption of water and ions. *Int Rev Physiol* 1977;12:285–304. [PubMed: 14083]
6. Kunzelmann K, Mall M. Electrolyte transport in the mammalian colon: mechanisms and implications for disease. *Physiol Rev* 2002;82(1):245–89. [PubMed: 11773614]
7. Kockerling A, Fromm M. Origin of cAMP-dependent Cl[−] secretion from both crypts and surface epithelia of rat intestine. *Am J Physiol* 1993;264(5 Pt 1):C1294–301. [PubMed: 8388634]
8. Chang WW, Leblond CP. Renewal of the epithelium in the descending colon of the mouse. I. Presence of three cell populations: vacuolated-columnar, mucous and argentaffin. *Am J Anat* 1971;131(1):73–99. [PubMed: 4103773]
9. Dorge A, Beck FX, Rechkemmer G. Cellular site of active K absorption in the guinea-pig distal colonic epithelium. *Pflügers Arch* 1998;436(2):280–8. [PubMed: 9594029]
10. Luciano L, Reale E, Rechkemmer G, et al. Structure of zonulae occludentes and the permeability of the epithelium to short-chain fatty acids in the proximal and the distal colon of guinea pig. *J Membr Biol* 1984;82(2):145–56. [PubMed: 6512849]
11. Dawson DC. Ion channels and colonic salt transport. *Annu Rev Physiol* 1991;53:321–39. [PubMed: 1710437]
12. Feldman GM. HCO₃[−] secretion by rat distal colon: effects of inhibitors and extracellular Na⁺. *Gastroenterology* 1994;107(2):329–38. [PubMed: 8039609]
13. Halm DR, Halm ST. Secretagogue response of goblet cells and columnar cells in human colonic crypts. *Am J Physiol Cell Physiol* 2000;278(1):C212–33. [PubMed: 10644530]
14. Spring KR. Routes and mechanism of fluid transport by epithelia. *Annu Rev Physiol* 1998;60:105–19. [PubMed: 9558456]
15. Koyama Y, Yamamoto T, Tani T, et al. Expression and localization of aquaporins in rat gastrointestinal tract. *Am J Physiol* 1999;276(3 Pt 1):C621–7. [PubMed: 10069989]
16. Beck DE, Harford FJ, DiPalma JA. Comparison of cleansing methods in preparation for colonic surgery. *Dis Colon Rectum* 1985;28(7):491–5. [PubMed: 4017808]
17. Brown AR, DiPalma JA. Bowel preparation for gastrointestinal procedures. *Curr Gastroenterol Rep* 2004;6(5):395–401. [PubMed: 15341716]
18. Johnson WC. Oral elemental diet: a new bowel preparation. *Arch Surg* 1974;108(1):32–4. [PubMed: 4859599]
19. Lever EL, Walter MH, Condon SC, et al. Addition of enemas to oral lavage preparation for colonoscopy is not necessary. *Gastrointest Endosc* 1992;38(3):369–72. [PubMed: 1607091]

20. DiPalma JA, Brady CE 3rd. Colon cleansing for diagnostic and surgical procedures: polyethylene glycol-electrolyte lavage solution. *Am J Gastroenterol* 1989;84(9):1008–16. [PubMed: 2672787]
21. Donovan IA, Arabi Y, Keighley MR, et al. Modification of the physiological disturbances produced by whole gut irrigation by preliminary mannitol administration. *Br J Surg* 1980;67(2):138–9. [PubMed: 6767517]
22. Shawki S, Wexner SD. Oral colorectal cleansing preparations in adults. *Drugs* 2008;68(4):417–37. [PubMed: 18318561]
23. Taylor EW, Bentley S, Youngs D, et al. Bowel preparation and the safety of colonoscopic polypectomy. *Gastroenterology* 1981;81(1):1–4. [PubMed: 6786947]
24. Davis GR, Santa Ana CA, Morawski SG, et al. Development of a lavage solution associated with minimal water and electrolyte absorption or secretion. *Gastroenterology* 1980;78(5 Pt 1):991–5. [PubMed: 7380204]
25. Tooson JD, Gates LK. Bowel preparation before colonoscopy. Choosing the best lavage regimen. *Postgrad Med* 1996;100(2):203,4, 207–12, 214. [PubMed: 8700818]
26. Fordtran JS, Santa Ana CA, Cleveland M. A low-sodium solution for gastrointestinal lavage. *Gastroenterology* 1990;98(1):11–6. [PubMed: 2293568]
27. Vanner SJ, MacDonald PH, Paterson WG, et al. A randomized prospective trial comparing oral sodium phosphate with standard polyethylene glycol-based lavage solution [Golytely] in the preparation of patients for colonoscopy. *Am J Gastroenterol* 1990;85(4):422–7. [PubMed: 2183591]
28. Aronchick CA, Lipshutz WH, Wright SH, et al. A novel tableted purgative for colonoscopic preparation: efficacy and safety comparisons with Colyte and Fleet Phospho-Soda. *Gastrointest Endosc* 2000;52(3):346–52. [PubMed: 10968848]
29. 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(11):3389–96. [PubMed: 16192415]
30. Golub RW, Kerner BA, Wise WE, et al. Colonoscopic bowel preparations--which one? A blinded, prospective, randomized trial. *Dis Colon Rectum* 1995;38(6):594–9. [PubMed: 7774469]
31. Marshall JB, Pineda JJ, Barthel JS, et al. Prospective, randomized trial comparing sodium phosphate solution with polyethylene glycol-electrolyte lavage for colonoscopy preparation. *Gastrointest Endosc* 1993;39(5):631–4. [PubMed: 8224683]
32. Tan JJ, Tjandra JJ. Which is the optimal bowel preparation for colonoscopy - a meta- analysis. *Colorectal Dis* 2006;8(4):247–58. [PubMed: 16630226]
33. Parente F, Marino B, DeVecchi N, et al. Colorectal Cancer Screening Group. Faecal occult blood test-based screening programme with high compliance for colonoscopy has a strong clinical impact on colorectal cancer. *Br J Surg* 2009;96(5):533–40. [PubMed: 19358181]
34. Clark LE, DiPalma JA. Safety issues regarding colonic cleansing for diagnostic and surgical procedures. *Drug Saf* 2004;27(15):1235–42. [PubMed: 15588118]
35. DiPalma JA, Marshall JB. Comparison of a new sulfate-free polyethylene glycol electrolyte lavage solution versus a standard solution for colonoscopy cleansing. *Gastrointest Endosc* 1990;36(3):285–9. [PubMed: 2365214]
36. Tomlinson TL, DiPalma JA, Mangano FA. Comparison of a new colon lavage solution [Golytely-RSS] with a standard preparation for air-contrast barium enema. *AJR Am J Roentgenol* 1988;151(5):947–50. [PubMed: 3051962]
37. Froehlich F, Fried M, Schnegg JF, et al. Palatability of a new solution compared with standard polyethylene glycol solution for gastrointestinal lavage. *Gastrointest Endosc* 1991;37(3):325–8. [PubMed: 2070983]
38. Raymond JM, Beyssac R, Capdenat E, et al. Tolerance, effectiveness, and acceptability of sulfate-free electrolyte lavage solution for colon cleaning before colonoscopy. *Endoscopy* 1996;28(7):555–8. [PubMed: 8911803]
39. Matter SE, Rice PS, Campbell DR. Colonic lavage solutions: plain versus flavored. *Am J Gastroenterol* 1993;88(1):49–52. [PubMed: 8420273]

40. Pashankar DS, Uc A, Bishop WP. Polyethylene glycol 3350 without electrolytes: a new safe, effective, and palatable bowel preparation for colonoscopy in children. *J Pediatr* 2004;144(3):358–62. [PubMed: 15001943]
41. Mamula P, Adler DG, Conway JD, et al. ASGE Technology Committee. Colonoscopy preparation. *Gastrointest Endosc* 2009;69(7):1201–9. [PubMed: 19481646]
42. Aoun E, Abdul-Baki H, Azar C, et al. A randomized single-blind trial of split-dose PEG-electrolyte solution without dietary restriction compared with whole dose PEG-electrolyte solution with dietary restriction for colonoscopy preparation. *Gastrointest Endosc* 2005;62(2):213–8. [PubMed: 16046981]
43. Rosch T, Classen M. Fractional cleansing of the large bowel with “Golytely” for colonoscopic preparation: a controlled trial. *Endoscopy* 1987;19(5):198–200. [PubMed: 3678160]
44. Church JM. Effectiveness of polyethylene glycol antegrade gut lavage bowel preparation for colonoscopy--timing is the key! *Dis Colon Rectum* 1998;41(10):1223–5. [PubMed: 9788383]
45. Rex DK, Johnson DA, Anderson JC, et al. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected. *Am J Gastroenterol* 2009;104(3):739–50. [PubMed: 19240699]
46. Padayatty SJ, Levine M. New insights into the physiology and pharmacology of vitamin C. *CMAJ* 2001;164(3):353–5. [PubMed: 11232136]
47. Cohen LB, Sanyal SM, von Althann C, et al. Clinical trial: 2-L polyethylene glycol-based lavage solutions for colonoscopy preparation - a randomized, single-blind study of two formulations. *Aliment Pharmacol Ther*. 2010
48. Corporaal S, Kleibeuker JH, Koornstra JJ. Low-volume PEG plus ascorbic acid versus high-volume PEG as bowel preparation for colonoscopy. *Scand J Gastroenterol*. 2010
49. Worthington J, Thyssen M, Chapman G, et al. A randomised controlled trial of a new 2 litre polyethylene glycol solution versus sodium picosulphate + magnesium citrate solution for bowel cleansing prior to colonoscopy. *Curr Med Res Opin* 2008;24(2):481–8. [PubMed: 18179734]
50. Martinek J, Hess J, Delarive J, et al. Cisapride does not improve precolonoscopy bowel preparation with either sodium phosphate or polyethylene glycol electrolyte lavage. *Gastrointest Endosc* 2001;54(2):180–5. [PubMed: 11474387]
51. Abdul-Baki H, Hashash JG, Elhajj II, et al. A randomized, controlled, double-blind trial of the adjunct use of tegaserod in whole-dose or split-dose polyethylene glycol electrolyte solution for colonoscopy preparation. *Gastrointest Endosc* 2008;68(2):294–300. quiz 334, 336. [PubMed: 18511049]
52. Sanaka MR, Super DM, Mullen KD, et al. Use of tegaserod along with polyethylene glycol electrolyte solution for colonoscopy bowel preparation: a prospective, randomized, double-blind, placebo-controlled study. *Aliment Pharmacol Ther* 2006;23(5):669–74. [PubMed: 16480406]
53. Sharma VK, Chockalingham SK, Ugheoke EA, et al. Prospective, randomized, controlled comparison of the use of polyethylene glycol electrolyte lavage solution in four-liter versus two-liter volumes and pretreatment with either magnesium citrate or bisacodyl for colonoscopy preparation. *Gastrointest Endosc* 1998;47(2):167–71. [PubMed: 9512283]
54. Adams WJ, Meagher AP, Lubowski DZ, et al. Bisacodyl reduces the volume of polyethylene glycol solution required for bowel preparation. *Dis Colon Rectum* 1994;37(3):229, 33. discussion 233–4. [PubMed: 8137669]
55. DiPalma JA, Wolff BG, Meagher A, et al. Comparison of reduced volume versus four liters sulfate-free electrolyte lavage solutions for colonoscopy colon cleansing. *Am J Gastroenterol* 2003;98(10):2187–91. [PubMed: 14572566]
56. DiPalma JA, McGowan J, Cleveland MV. Clinical trial: an efficacy evaluation of reduced bisacodyl given as part of a polyethylene glycol electrolyte solution preparation prior to colonoscopy. *Aliment Pharmacol Ther* 2007;26(8):1113–9. [PubMed: 17894653]
57. Baudet JS, Castro V, Redondo I. Recurrent ischemic colitis induced by colonoscopy bowel lavage. *Am J Gastroenterol* 2010;105(3):700–1. [PubMed: 20203651]
58. Trautwein AL, Vinitzki LA, Peck SN. Bowel preparation before colonoscopy in the pediatric patient: a randomized study. *Gastroenterol Nurs* 1996;19(4):137–9. [PubMed: 8852159]

59. Iida Y, Miura S, Asada Y, et al. Bowel preparation for the total colonoscopy by 2,000 ml of balanced lavage solution [Golytely] and sennoside. *Gastroenterol Jpn* 1992;27(6):728–33. [PubMed: 1468604]
60. Radaelli F, Meucci G, Imperiali G, et al. High-dose senna compared with conventional PEG-ES lavage as bowel preparation for elective colonoscopy: a prospective, randomized, investigator-blinded trial. *Am J Gastroenterol* 2005;100(12):2674–80. [PubMed: 16393219]
61. Amato A, Radaelli F, Paggi S, et al. Half doses of PEG-ES and senna vs. high-dose senna for bowel cleansing before colonoscopy: a randomized, investigator-blinded trial. *Am J Gastroenterol* 2010;105(3):675–81. [PubMed: 19844199]
62. Belsey J, Epstein O, Heresbach D. Systematic review: adverse event reports for oral sodium phosphate and polyethylene glycol. *Aliment Pharmacol Ther*. 2008
63. Hookey LC, Depew WT, Vanner S. The safety profile of oral sodium phosphate for colonic cleansing before colonoscopy in adults. *Gastrointest Endosc* 2002;56(6):895–902. [PubMed: 12447305]
64. Rex DK. Dosing considerations in the use of sodium phosphate bowel preparations for colonoscopy. *Ann Pharmacother* 2007;41(9):1466–75. [PubMed: 17652123]
65. Kim DH, Hyun SH, Shim SB, et al. The role of intestinal bacteria in the transformation of sodium picosulfate. *Jpn J Pharmacol* 1992;59(1):1–5. [PubMed: 1507649]
66. Wexner SD, Beck DE, Baron TH, et al. A consensus document on bowel preparation before colonoscopy: prepared by a task force from the American Society of Colon and Rectal Surgeons [ASCRS], the American Society for Gastrointestinal Endoscopy [ASGE], and the Society of American Gastrointestinal and Endoscopic Surgeons [SAGES]. *Gastrointest Endosc* 2006;63(7):894–909. [PubMed: 16733101]
67. Nelson DB, Barkun AN, Block KP, et al. Technology Status Evaluation report. Colonoscopy preparations. *Gastrointest Endosc* May;2001 54(6):829–32. [PubMed: 11726878]
68. Hamilton D, Mulcahy D, Walsh D, et al. Sodium picosulphate compared with polyethylene glycol solution for large bowel lavage: a prospective randomised trial. *Br J Clin Pract* 1996;50(2):73–5. [PubMed: 8731641]
69. Yoshioka K, Connolly AB, Ogunbiyi OA, et al. Randomized trial of oral sodium phosphate compared with oral sodium picosulphate [Picolax] for elective colorectal surgery and colonoscopy. *Dig Surg* 2000;17(1):66–70. [PubMed: 10720834]
70. Di Palma JA, Rodriguez R, McGowan J, et al. A randomized clinical study evaluating the safety and efficacy of a new, reduced-volume, oral sulfate colon-cleansing preparation for colonoscopy. *Am J Gastroenterol* 2009;104(9):2275–84. [PubMed: 19584830]
71. Ness RM, Manam R, Hoen H, et al. Predictors of inadequate bowel preparation for colonoscopy. *Am J Gastroenterol* 2001;96(6):1797–802. [PubMed: 11419832]
72. Chung YW, Han DS, Park KH, et al. Patient factors predictive of inadequate bowel preparation using polyethylene glycol: a prospective study in Korea. *J Clin Gastroenterol* 2009;43(5):448–52. [PubMed: 18978506]
73. Lebwohl B, Wang TC, Neugut AI. Socioeconomic and other predictors of colonoscopy preparation quality. *Dig Dis Sci* 2010;55(7):2014–20. [PubMed: 20082217]
74. Froehlich F, Wietlisbach V, Gonvers JJ, et al. Impact of colonic cleansing on quality and diagnostic yield of colonoscopy: the European Panel of Appropriateness of Gastrointestinal Endoscopy European multicenter study. *Gastrointest Endosc* 2005;61(3):378–84. [PubMed: 15758907]
75. Borg BB, Gupta NK, Zuckerman GR, et al. Impact of obesity on bowel preparation for colonoscopy. *Clin Gastroenterol Hepatol* 2009;7(6):670–5. [PubMed: 19245852]
76. Lichtenstein G. Bowel preparations for colonoscopy: a review. *Am J Health Syst Pharm* 2009;66(1):27–37. [PubMed: 19106342]
77. Cohen CD, Keuneke C, Schiemann U, et al. Hyponatraemia as a complication of colonoscopy. *Lancet* 2001;357(9252):282–3. [PubMed: 11214135]
78. Marschall HU, Bartels F. Life-threatening complications of nasogastric administration of polyethylene glycol-electrolyte solutions [Golytely] for bowel cleansing. *Gastrointest Endosc* 1998;47(5):408–10. [PubMed: 9609437]

79. Ayus JC, Levine R, Arieff AI. Fatal dysnatraemia caused by elective colonoscopy. *BMJ* 2003;326(7385):382–4. [PubMed: 12586675]
80. Nagler J, Poppers D, Turetz M. Severe hyponatremia and seizure following a polyethylene glycol-based bowel preparation for colonoscopy. *J Clin Gastroenterol* 2006;40(6):558–9. [PubMed: 16825941]
81. Schroppel B, Segerer S, Keuneke C, et al. Hyponatremic encephalopathy after preparation for colonoscopy. *Gastrointest Endosc* 2001;53(4):527–9. [PubMed: 11275905]
82. Pockros PJ, Foroozan P. Golytely lavage versus a standard colonoscopy preparation. Effect on normal colonic mucosal histology. *Gastroenterology* 1985;88(2):545–8. [PubMed: 3965343]
83. Brinberg DE, Stein J. Mallory-Weiss tear with colonic lavage. *Ann Intern Med* 1986;104(6):894–5. [PubMed: 3706948]
84. Eisen GM, Jowell PS. Esophageal perforation after ingestion of colon lavage solution. *Am J Gastroenterol* 1995;90(11):2074. [PubMed: 7485041]
85. Hroncich ME. Colonoscopy preparation complicated by Mallory-Weiss tear. *South Med J* 1992;85(3):328. [PubMed: 1546360]
86. McBride MA, Vanagunas A. Esophageal perforation associated with polyethylene glycol electrolyte lavage solution. *Gastrointest Endosc* 1993;39(6):856–7. [PubMed: 8293924]
87. Pham T, Porter T, Carroll G. A case report of Boerhaave's syndrome following colonoscopy preparation. *Med J Aust* 1993;159(10):708. [PubMed: 8232021]
88. Raymond PL. Mallory-Weiss tear associated with polyethylene glycol electrolyte lavage solution. *Gastrointest Endosc* 1991;37(3):410–1. [PubMed: 2071009]
89. Santoro MJ, Chen YK, Collen MJ. Polyethylene glycol electrolyte lavage solution-induced Mallory-Weiss tears. *Am J Gastroenterol* 1993;88(8):1292–3. [PubMed: 8338109]
90. Langdon DE. Colonic perforation with volume laxatives. *Am J Gastroenterol* 1996;91(3):622–3. [PubMed: 8633537]
91. Granberry MC, White LM, Gardner SF. Exacerbation of congestive heart failure after administration of polyethylene glycol-electrolyte lavage solution. *Ann Pharmacother* 1995;29(12):1232–5. [PubMed: 8672827]
92. Barkun A, Chiba N, Enns R, et al. Commonly used preparations for colonoscopy: efficacy, tolerability, and safety--a Canadian Association of Gastroenterology position paper. *Can J Gastroenterol* 2006;20(11):699–710. [PubMed: 17111052]
93. 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(7):1319–23. [PubMed: 16047480]
94. DiPalma JA, Buckley SE, Warner BA, et al. Biochemical effects of oral sodium phosphate. *Dig Dis Sci* 1996;41(4):749–53. [PubMed: 8674396]
95. Tan HL, Liew QY, Loo S, et al. Severe hyperphosphataemia and associated electrolyte and metabolic derangement following the administration of sodium phosphate for bowel preparation. *Anaesthesia* 2002;57(5):478–83. [PubMed: 11966559]
96. Fass R, Do S, Hixson LJ. Fatal hyperphosphatemia following Fleet Phospho-Soda in a patient with colonic ileus. *Am J Gastroenterol* 1993;88(6):929–32. [PubMed: 8503390]
97. Beloosesky Y, Grinblat J, Weiss A, et al. Electrolyte disorders following oral sodium phosphate administration for bowel cleansing in elderly patients. *Arch Intern Med* 2003;163(7):803–8. [PubMed: 12695271]
98. Ahmed M, Raval P, Buganza G. Oral sodium phosphate catharsis and acute renal failure. *Am J Gastroenterol* 1996;91(6):1261–2. [PubMed: 8651185]
99. Frizelle FA, Colls BM. Hyponatremia and seizures after bowel preparation: report of three cases. *Dis Colon Rectum* 2005;48(2):393–6. [PubMed: 15812590]
100. Lien YH. Is bowel preparation before colonoscopy a risky business for the kidney? *Nat Clin Pract Nephrol* 2008;4(11):606–14. [PubMed: 18797448]
101. Caswell M, Thompson WO, Kanapka JA, et al. The time course and effect on serum electrolytes of oral sodium phosphates solution in healthy male and female volunteers. *Can J Clin Pharmacol* 2007;14(3):e260–74. [PubMed: 18000319]

102. Clarkston WK, Tsen TN, Dies DF, et al. Oral sodium phosphate versus sulfate-free polyethylene glycol electrolyte lavage solution in outpatient preparation for colonoscopy: a prospective comparison. *Gastrointest Endosc* 1996;43(1):42–8. [PubMed: 8903817]
103. Hixson LJ. Colorectal ulcers associated with sodium phosphate catharsis. *Gastrointest Endosc* 1995;42(1):101–2. [PubMed: 7557166]
104. Zwas FR, Cirillo NW, el-Serag HB, et al. Colonic mucosal abnormalities associated with oral sodium phosphate solution. *Gastrointest Endosc* 1996;43(5):463–6. [PubMed: 8726758]
105. Kontani M, Hara A, Ohta S, Ikeda T. Hypermagnesemia induced by massive cathartic ingestion in an elderly woman without pre-existing renal dysfunction. *Intern Med* 2005;44(5):448–52. [PubMed: 15942092]
106. Schelling JR. Fatal hypermagnesemia. *Clin Nephrol* 2000;53(1):61–5. [PubMed: 10661484]

Figure 1.
Figure 1a. Photograph of the transverse colon demonstrating an excellent preparation.

Figure 1b. Photograph of the colon in another patient who only drank approximately 2 liters of the recommended 4 liters of polyethylene glycol preparation. Note the film of stool precluding optimal mucosal evaluation. Figures courtesy of Dr. Friedenber.

Figure 2.

Models for electrolyte transport in proximal and distal colonic epithelium and expression of different ion transporters along the crypt axis. Electroneutral NaCl absorption [parallel Na⁺/H⁺ and Cl⁻/HCO₃⁻ exchange] dominates in the surface epithelium and is also present in the crypts. Electrogenic Na⁺ absorption via the epithelial Na⁺ channel [ENaC] takes place in the surface epithelium and upper crypts of the distal colon. The cystic fibrosis transmembrane conductance regulator [CFTR] is expressed throughout the colonic epithelium and dominates in the crypts. Kunzelmann and Mall, *Physiol Rev*, 2002, Am Physiol Soc, used with permission.

Figure 3.
Timeline of colonoscopy preparations.

Figure 4.

Renal biopsy specimen demonstrating precipitates of calcium phosphate [arrow] in a patient who received sodium phosphate for colon preparation and developed progressive deterioration of renal function. H+E stain at magnification 40X. Image courtesy of Dr. Nathan Hellman.

Table 1

Comparison of the two most commonly used bowel preparations.

	PEG-ELS	Sodium Phosphate
Mechanism of action	Osmotically balanced (iso-osmolar) prep that promotes bowel cleansing thru ingestion of non-absorbable fluid (large volume)	Hyperosmotic purgative that promotes bowel cleansing by osmotically drawing fluid into bowel lumen for evacuation (small volume)
Volume needed	Large	Small
Effectiveness	Effective	Effective
Tolerability	Lesser	Better
Side effects	Lesser volume loss and electrolyte shifts (hyponatremia>hyperphosphatemia), Single rare reports of pulmonary aspiration, Mallory-Weiss tear, pancreatitis, allergic reactions, colitis and cardiac dysrhythmia, a mild asymptomatic increase in plasma volume, one case of exacerbation of CHF, no cases of nephrocalcinosis reported	Fluid and electrolyte shifts (transient hyperphosphatemia, hypocalcemia, hypokalemia, hypo/hypernatremia), Acute phosphate nephropathy/nephrocalcinosis seizures, tetany, colonic aphthoid ulceration
Avoid in patients with	Ileus, gastric retention, bowel perforation, gastrointestinal obstruction, or severe colitis	Kidney disease, advanced liver failure, chronic heart failure, patients using medications that result in electrolyte disturbance, elderly patients, patients with poor gut motility, intestinal obstruction, ascities
Pediatric population	Less side effects but worse tolerability	Better tolerated, higher degree of asymptomatic hyperphosphatemia than in adults {{645 Gremse,D.A. 1996; }}

PEG-ELS : polyethylene glycol electrolyte solution

Table 2

Areas for future research in colonic purgatives

-
- Safety of new PEG 3350-based preparations in special populations (cirrhosis, end-stage renal disease, advanced congestive heart failure)
 - Safety and efficacy of PEG-3350 combined with a 2 liter electrolyte sports drink
 - Tailored colonic preparation based on patient factors such as age, obesity and ambulatory status
 - Optimal preparation of hospitalized patients
 - Ongoing surveillance to assess risk of phosphate tablet preparations on renal function
-