### Dosing Considerations in the Use of Sodium Phosphate Bowel Preparations for Colonoscopy

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he 2 main classes of bowel preparation for colonoscopy in the US are sodium phosphate (NaP) products and polyethylene glycol electrolyte lavage solution (PEG-ELS). Bowel preparations are typically judged by their efficacy, safety, and tolerability, with all 3 criteria having obvious clinical importance. Recent reviews and a meta-analysis reported that NaP preparations are generally more effective<sup>1-3</sup> and better tolerated<sup>1-4</sup> compared with PEG-ELS formulations. The meta-analysis included 16 clinical trials involving 3484 patients and concluded that NaP solution is significantly more likely than PEG-ELS to provide good or excellent bowel preparation (p =0.0004).<sup>3</sup> Tolerability of bowel preparation, measured as the ability to complete the entire preparation, also favored NaP solution; data pooled from 15 trials involving 3293 patients demonstrated significantly higher completion rates for NaP versus PEG-ELS (94% vs 71%; p < 0.00001).<sup>3</sup> Similarly, a limited number of studies that compared NaP tablets with PEG-ELS favored NaP tablets in terms of completion of the preparation.5-7 In addition to measures of compliance, pa-

**OBJECTIVE:** To review dosing considerations and other treatment recommendations to maximize the efficacy, tolerability, and safety of sodium phosphate (NaP) preparations.

**DATA SOURCES:** Literature was accessed through PubMed (1990–May 2007) and abstracts from scientific meetings.

**STUDY SELECTION AND DATA EXTRACTION:** English-language publications including clinical trials and case reports were evaluated. Recent reports assessing newer bowel preparations containing reduced doses of NaP were reviewed to evaluate efficacy, tolerability, and safety.

**DATA SYNTHESIS:** Among commonly administered bowel preparations for colonoscopy, NaP preparations are generally more effective and better tolerated compared with polyethylene glycol electrolyte lavage solution regimens. However, NaP preparations are contraindicated in specific patient populations, and clinicians must use effective screening mechanisms to select proper patients to receive NaP preparation for colonoscopy. Recently, cases of renal failure in patients with previously normal renal function have been reported after NaP preparation for colonoscopy, heightening concerns about the safety of these agents. Newer products contain reduced doses of NaP and may improve the safety and tolerability of NaP purgatives without compromising efficacy of colon cleansing. In addition, accumulating clinical data and/or rationale support split dosing of NaP products, wide intervals between doses, and aggressive hydration before and during bowel preparation and after the colonoscopy procedure.

**CONCLUSIONS:** Safe administration of NaP products requires rigorous attention to dosing considerations and other treatment recommendations, including administration of minimally effective doses of NaP, split-dosing schedules, and aggressive hydration.

KEY WORDS: bowel purgatives, sodium phosphate.

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tient tolerability for NaP preparations was further demonstrated by willingness to repeat the preparation, expressed by significantly more patients who received NaP tablets<sup>5,6,8</sup> or NaP solution<sup>5,9-14</sup> compared with those who received

PEG-ELS preparations. Thus, NaP preparations are generally superior to PEG-ELS regimens with regard to efficacy and tolerability.

While complications can result from either NaP or PEG-ELS as bowel preparations, there is concern among clinical gastroenterologists that NaP products pose greater risks for patients. Whereas PEG-ELS preparations are os-

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motically balanced, nonabsorbable solutions that promote bowel cleansing without substantial shifts in fluid and electrolyte levels, NaP preparations employ an osmotic mechanism of action, drawing water from the colonic mucosal lining into the bowel lumen. Retention of water in the bowel lumen stimulates peristalsis and evacuation of the colon.<sup>15</sup> Thus, NaP preparations can result in substantial fluid shifts, alteration of electrolyte levels, and dehydration due to their osmotic nature. Thus, administration of NaP products should be restricted to patients who are at low risk for complications of fluid shifts and who are able to maintain hydration during the preparation process. In addition, recent reports of renal damage following NaP preparation in patients with previously normal renal function have raised major concerns about the use of NaP in general.<sup>16-19</sup>

This review discusses the effect of NaP purgatives on serum electrolyte levels, with particular attention to phosphate load, as well as available formulations and dosing schedules designed to minimize risks and maximize effectiveness associated with administration of NaP products in appropriate patient populations. Given that NaP preparations appear to be more effective and better tolerated than PEG-ELS preparations, improving the safety profile and maximizing efficacy and tolerability through optimal dosing schedules are critical to the current use of NaP in colonoscopy preparation.

#### Safety Issues with NaP Bowel Preparations

## SODIUM PHOSPHATE PURGATIVES AND ELECTROLYTE DISTURBANCES

Transient shifts in serum electrolyte levels are common with hyperosmotic purgatives. A recent meta-analysis reviewed 9 studies that evaluated electrolyte disturbances related to purgative administration and reported significantly increased biochemical changes associated with NaP preparations versus PEG-ELS products.<sup>3</sup> In particular, hyperphosphatemia and hypokalemia occurred more often in patients who took NaP liquid and tablet formulations versus PEG-ELS preparations.<sup>7,9,20-23</sup>

The disturbance in electrolyte levels associated with NaP purgatives is an important safety consideration for patients with certain risk factors, including preexisting renal insufficiency, dehydration, advanced age, and concurrent treatment with medications known to decrease gastrointestinal (GI) motility or to affect kidney function (eg, diuretics, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]).19,24 Preexisting kidney disease and medical conditions (eg, hypertension) associated with administration of medications that affect renal perfusion or function can have a substantial impact on electrolyte balance.<sup>19,25</sup> Sodium phosphate preparations should not be administered to patients with kidney disease, megacolon, bowel obstruction, ascites, or congestive heart failure and should be administered with caution in patients with impaired renal function, preexisting or increased risk for electrolyte disturbances, heart disease, acute myocardial infarction, unstable angina, and in elderly or debilitated patients.2

Most fatalities following NaP preparations have been related to arrhythmias or seizures associated with electrolyte and fluid shifts. The patients were typically inappropriate candidates for NaP or received overdoses of NaP.<sup>26</sup> Thus, clinicians need effective mechanisms to screen patients for their candidacy to receive NaP, and doses should never exceed the maximum recommended dose of 90 mL (59.4 g NaP) or 40 tablets (60 g NaP) (Table 1). Patients who are not effectively prepared after 90 mL or 40 tablets should have their preparation completed with PEG-ELS or another non-NaP purgative and/or enemas.<sup>27</sup>

Table 1. FDA-Approved Dosing Regimens for Sodium Phosphate Preparations					
Parameter	Solution	MCC-Containing Tablets	MCC-Free Tablets		
Preparation	75–90 mL	40 tablets	32 tablets		
NaP dose, g	49.5–59.4	60	48		
Minimum number of 8-oz glasses of clear liquids required	9	14	8		
Instructions					
evening before colonoscopy	45 mL, mixed in 1 glass of cold, clear liquid, followed by ≥6 glasses of clear liquid	20 tablets, taken as 3 tablets with 1 glass of clear liquid every 15 min (last dose is 2 tablets)	20 tablets, taken as 4 tablets with 1 glass of clear liquid every 15 min		
day of colonoscopy	30–45 mL, mixed in 1 glass of cold, clear liquid, followed immediately by ≥1 glass of clear liquid	20 tablets, taken as 3 tablets with 1 glass of clear liquid every 15 min (last dose is 2 tablets), starting 3–5 h before procedure	12 tablets, taken as 4 tablets with 1 glass of clear liquid every 15 min, starting 3–5 h before procedure		

FDA = Food and Drug Administration; MCC = microcrystalline cellulose; NaP = sodium phosphate.

#### ACUTE PHOSPHATE NEPHROPATHY

Recently, 24 cases of acute renal failure followed by chronic renal insufficiency have been documented after NaP bowel preparation for colonoscopy. This phenomenon has been termed acute phosphate nephropathy because renal biopsies in all cases were characterized by calcium phosphate crystal deposition in renal tubules. Cases have been linked to administration of NaP solution (23 cases) or tablet formulations (1 case).16-19 These cases occurred predominately in patients with normal renal function; mild baseline renal insufficiency was reported in only 4 (17%) cases. Predisposing factors appear to be female sex (83%) and hypertension (71%). As might be expected in hypertensive patients, the majority of patients were taking antihypertensive drugs including diuretics, ACE inhibitors, and ARBs. Recently, the Food and Drug Administration issued a warning that risk factors for acute phosphate nephropathy include advanced age, kidney disease or decreased intravascular volume, and use of drugs known to affect renal perfusion or function (eg, antihypertensives).<sup>25</sup> Although the incidence of acute phosphate nephropathy after NaP preparation is unknown, it is clear that the risk of serious toxicity associated with this preparation has been expanded to patients with normal renal function.

A recent single-center report of 12 cases of renal impairment after bowel preparation with NaP solution in patients in whom renal biopsies were not performed confirmed the clinical associations described above and further elevated concern about NaP safety.<sup>28</sup>

Recent recommendations on the safe and effective use of NaP products have emphasized the importance of patient selection, not exceeding recommended doses (Table 1), proper spacing of doses, and aggressive oral hydration prior to and during the preparation and also after the procedure.<sup>27</sup> Hydration results in dilute urine, reducing the concentration of calcium and phosphate in the urine, and thereby reducing the risk of crystal formation and tubular damage.<sup>19,29</sup>

#### RENAL HANDLING OF SODIUM PHOSPHATE PREPARATIONS

In the numerous published clinical trials of NaP preparation for colonoscopy, which typically exclude patients with serum creatinine levels above 1.5–2.0 mg/dL and prescribe specific fluid volumes to be taken with NaP, there has never been a clinical adverse event (AE) reported with regard to renal damage.<sup>3,26</sup> Although serum phosphate levels typically increase transiently above baseline after administration of NaP bowel preparations, the well-hydrated adult with normal kidney function can tolerate the standard phosphate load (60 g) without any clinically meaningful AEs.<sup>30</sup>

A small study of 5 healthy subjects (age 27–55 y) assessed the metabolism of NaP solution, administered as two 45 mL doses taken 11 hours apart, by quantifying fecal and urinary excretion of phosphate.<sup>29</sup> During the 18 hour period beginning with ingestion of the first dose, 57% of ingested phosphate was excreted in the stool, and an additional 15% was eliminated in the urine. These data suggested that 28% of the phosphate ingested with the standard dose of NaP solution was retained in the body 18 hours after beginning the bowel preparation. Clearance of retained phosphate was not assessed beyond 6 hours after the second dose. Consistent with previous recommendations,<sup>1,19,27</sup> the authors emphasized that adequate hydration plays a key role in renal handling of NaP preparations.<sup>29</sup>

Estimates of volume loss during NaP preparation suggest that patients average 3-4 L of fluid loss during and following a 60 g phosphate load.<sup>29,31</sup> If the urine becomes concentrated as a result of dehydration, the urinary calcium phosphate product could rise sufficiently to result in crystal formation, deposition, and tubular injury.<sup>19,29</sup> Thus, prescription of adequate fluid volume intake before and during NaP preparation can ensure dilute urine and, in theory, prevent the development of acute phosphate nephropathy. In support of this contention, in the 5 cases of acute phosphate nephropathy for which fluid volume intake during the preparation was described, intake was inadequate compared with recommended volume intake.32 The probable mechanism of calcium phosphate crystal deposition also emphasizes the importance of identifying the lowest effective doses of NaP liquid and tablets.

#### **Sodium Phosphate Preparations**

#### COMPOSITION OF FORMULATIONS

Each 45 mL dose of NaP solution contains 29.7 g of NaP in stable, buffered aqueous solution. Each NaP tablet contains 1.5 g of NaP and 0.5 g of inactive ingredients. Inactive ingredients in 1 NaP tablet formulation include microcrystalline cellulose (MCC), magnesium stearate, and colloidal silicon dioxide. Given reports that MCC hindered visibility of the colonic mucosa during colonoscopic examination,33 a newer tablet formulation does not contain this insoluble, inert binder; inactive ingredients in the MCC-free tablets include PEG 8000 and magnesium stearate. The recommended dose of NaP with liquid and tablet formulations ranges from 48 to 60 g of NaP (Table 1). Whereas NaP solution and MCC-containing NaP tablets contain similar amounts of NaP, the newer, MCCfree tablet regimen contains a 20% lower dose of NaP because the dosage has been reduced from 40 tablets (60 g NaP) to 32 tablets (48 g NaP).

From an endoscopist's perspective, there is no longer a rationale for the use of MCC-containing NaP tablets.<sup>27</sup> In

addition, NaP solution is available in a lower-dose regimen of 75 mL versus 90 mL.<sup>34</sup> A limited number of studies, discussed below, suggest that administration of lower doses of NaP may translate into an improved safety profile with comparable or better efficacy.<sup>34-36</sup>

#### SERUM ELECTROLYTE SHIFTS AND SAFETY CONCERNS

Differences between liquid and tablet formulations regarding shifts in serum electrolyte levels were not assessed in the 2 available studies comparing these formulations,<sup>5,33</sup> but recent investigations compared clinical laboratory parameters in patients taking different regimens of NaP solution<sup>34</sup> or tablets.<sup>35,36</sup> In a preliminary study of 321 patients, Rex et al.<sup>34</sup> found that administration of 45 mL plus 30 mL of NaP solution (75 mL regimen containing 49.5 g of NaP) resulted in significantly less pronounced mean shifts from baseline in several laboratory parameters, including serum sodium and phosphate levels, compared with administration of the standard 45 mL plus 45 mL regimen of NaP solution (90 mL regimen containing 59.4 g of NaP) (p ≤ 0.01).

Similar results have been reported for tablet formulations associated with a lower NaP dose. For example, a 32 tablet regimen (48 g NaP) of MCC-free tablets induced significantly smaller mean shifts in serum phosphate levels compared with a 40 tablet regimen (60 g of NaP) of the older, MCC-containing tablet formulation (Table 2).<sup>35</sup> A similar study reported smaller mean changes from baseline in serum phosphate levels in patients who took 28 MCCfree tablets (42 g of NaP; n = 31; mean shift, 2.8 mg/dL) or 32 MCC-free tablets (48 g of NaP; n = 33; mean shift, 3.4 mg/dL) compared with those who took 40 MCC-containing tablets (60 g of NaP; n = 30; mean shift, 4.2 mg/dL; p < 0.05 for comparison between 28 tablet and 40 tablet regimens).<sup>36</sup> Thus, although additional peer-reviewed studies

	Mean Change from Baseline to Colonoscopy	
Laboratory Parameter	40 MCC-Containing Tablets (n = 236)	32 MCC-Free Tablets (n = 239)
Inorganic phosphorus, mg/dL	4.0ª	3.5
Sodium, mEq/L	1.7	2.0
Calcium, mg/dL	-0.6	-0.6
Potassium, mEq/L	-0.7	-0.6
Magnesium, mg/dL	-0.07	-0.08
Chloride, mEq/L	-0.2	-0.1
Bicarbonate, mEq/L	-1.0ª	-0.06
Creatinine, mg/dL	-0.02	-0.01
Blood urea nitrogen, mg/dL	-5.1ª	-4.0

are warranted, recent evidence suggests that the lower dose of NaP associated with the 75 mL liquid regimen and the 32 tablet regimen reduces the disturbance in serum phosphate levels compared with the 90 mL liquid regimen and the 40 tablet regimen, respectively.

In addition to evaluation of laboratory parameters, assessment of AEs is an important measure of safety associated with bowel preparations. One study of patients who received a 90 mL NaP solution (n = 106) or 24 or 32 NaP tablets (n = 99) reported no clinically significant AEs in either treatment group and significantly less nausea in patients who took tablets compared with those who took NaP solution (24% vs 40%; p = 0.01).<sup>5</sup> In a study comparing 45 mL plus 30 mL of NaP solution versus the standard 45 mL plus 45 mL regimen, the lower dose regimen significantly reduced the incidence of vomiting (3% vs 8%; p = 0.04), abdominal cramps (36% vs 48%; p = 0.02), and overall discomfort (58% vs 69%; p = 0.03).<sup>34</sup> However, another study comparing these NaP liquid regimens failed to observe a difference in the frequency of reported AEs.<sup>37</sup> In a study comparing different NaP tablet formulations, Rex et al.35 reported significant reductions in the incidence of AEs (58% vs 68%; p = 0.03) and GI AEs (56% vs 66%; p < (0.05) in patients who received 32 MCC-free tablets (n = 239) compared with those who received 40 MCC-containing tablets (n = 238), respectively. In addition, abdominal distention was reported by significantly fewer patients who took the 32 tablet regimen versus the 40 tablet regimen (31% vs 42%, respectively; p < 0.05). Taken together, these results suggest that decreasing the phosphate load improves the safety and tolerability profile associated with NaP preparations by causing less-pronounced shifts in laboratory parameters and reducing the incidence of AEs.

Appropriately, these and other studies excluded patients with heart failure, renal failure, GI obstruction, and base-

> line electrolyte abnormalities.<sup>5,26,33,34,36</sup> Rigid exclusion criteria must be employed in clinical practice to promote safe administration of NaP preparations in appropriate patient populations.<sup>26,27</sup> In addition, patient selection should involve more than a checklist for contraindications, because other risk factors such as an inability to maintain adequate hydration may be identified.<sup>26</sup>

#### EFFICACY AND TOLERABILITY

As discussed, NaP preparations are generally more favorable than PEG-ELS formulations in measures of efficacy and tolerability.<sup>1-3,5-14</sup> Few studies have directly compared aqueous and tablet NaP formulations. One study reported comparable colon cleansing with different NaP preparations, with good or excellent clean-

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sing observed in 87% of patients who received a 90 mL solution (59.4 g of NaP; n = 106) and in 83% of patients who received a regimen of 24 or 32 tablets (36 g or 48 g of NaP, respectively; n = 99).<sup>5</sup> However, patient tolerability favored tablets; more patients in the NaP tablet groups compared with those in the NaP solution group rated the taste as "no taste/pleasant" (59% vs 5%, respectively; p < (0.001) and would choose the same preparation again (82%vs 53%, respectively; p < 0.001). In contrast, a smaller study of 100 patients reported better cleansing (good or excellent cleansing in 92% vs 74% of patients; p = 0.03) and greater willingness to repeat the preparation (90% vs 74%; p < 0.04) with a 90 mL NaP solution versus 40 NaP tablets.<sup>33</sup> Thus, additional studies are needed to determine whether NaP solution and tablets differ with regard to efficacy or tolerability.

The MCC-free tablet formulation demonstrated comparable or better efficacy than the MCC-containing tablet formulation in clinical trials published in 2006 and 2007 (Table 3).<sup>35,36</sup> This result is almost certainly related to the elimination of MCC, which is reported to impair bowel preparation. In addition to measures of efficacy, patient tolerability and acceptance also favored the newer, MCC-free tablet formulation. Rex et al.<sup>35</sup> reported that more patients who took 32 MCC-free tablets versus 40 MCC-containing tablets found the preparation "easy" to take (77% vs 48%; p < 0.0001), tolerated the liquid requirements easily (71% vs 52%; p = 0.0002), and expressed willingness to repeat the preparation (95% vs 88%; p = 0.003). These results are not surprising, given that the newer tablet formulation includes smaller tablets with a smoother, waxier coating, fewer tablets to ingest, and reduced fluid requirements compared with the older tablet formulation.

Preliminary studies comparing 45 mL plus 45 mL of NaP solution (90 mL, 59.4 g of NaP) with the lower 45 mL plus 30 mL dose (75 mL, 49.5 g NaP) reported similar efficacy with both preparations. In one study, 98% of patients who received the 90 mL preparation (n = 40)achieved good or excellent colon cleansing compared with 88% of patients who received the 75 mL preparation (n =40); the difference was not significant.<sup>37</sup> More patients who took the 75 mL regimen (95%) versus the 90 mL regimen (88%) expressed willingness to repeat the preparation but reported no difference in ease of drinking or taste of the preparation. A larger study of 321 subjects reported comparable cleansing with 90 mL and 75 mL regimens; good or excellent cleansing was reported in 90% of patients who took the 90 mL regimen and in 87% of patients who took the 75 mL regimen.<sup>34</sup> While these preliminary trials were not powered to establish equivalence between the study arms, they suggest very similar efficacy for the 90 mL and 75 mL preparations.

The results of these studies suggest that reducing the dose of NaP associated with liquid and tablet purgative

Table 3. Efficacy of Different NaP Tablet Formulations				
	MCC-Containing Tablets <sup>a</sup>	MCC-Free Tablets <sup>a</sup>		
Study	40 Tablets (60 g)	40 Tablets (60 g)	32 Tablets (48 g)	28 Tablets (42 g)
Rex (2006) <sup>35</sup> overall colon cleansing	n = 235	n = 233	n = 236	NA
pts. with good or excellent cleansing, n (%)	222 (95)	226 (97)	225 (95)	
mean score ± SD ascending colon cleansing	$1.5 \pm 0.6$	$1.3 \pm 0.6^{b}$	$1.3 \pm 0.6^{b}$	
pts. with good or excellent cleansing, n (%)	208 (89)	220 (96)	220 (94)	
mean score ± SD	$1.6 \pm 0.7$	$1.3 \pm 0.5^{b}$	$1.3 \pm 0.6^{b}$	
irrigation requirements, mean score ± SD <sup>c</sup>	0.9 ± 1.1	$0.4 \pm 0.9^{b}$	$0.5 \pm 0.9^{b}$	
Wruble (2007) <sup>36</sup>	n = 29	n = 29	n = 33	n = 29
pts. with good or excellent cleansing, n (%)	25 (86)	29 (100)	32 (97)	26 (90)
mean score ± SD ascending colon cleansing	$1.7 \pm 0.7$	$1.2 \pm 0.4^{b}$	$1.2 \pm 0.5^{b}$	1.4 ± 0.8
pts. with good or excellent cleansing, n (%)	23 (82)	28 (100)	33 (100)	26 (90)
mean score ± SD	1.8 ± 0.7	$1.3\pm0.4^{\text{b}}$	$1.2 \pm 0.4^{b}$	1.5 ± 0.8

MCC = microcrystalline cellulose; NA = not assessed; NaP = sodium phosphate.

<sup>a</sup>In both studies, tablets were taken as recommended in Table 1. Quality of cleansing was rated by endoscopist as 1 (excellent), 2 (good), 3 (fair), or 4 (inadequate).

<sup>b</sup>Significant difference between MCC-free tablets and MCC-containing tablets.

clrrigation requirements were scored as 0 (none), 1 (<50 mL), 2 (50-100 mL), or 3 (>100 mL).

formulations may improve patient tolerability without substantially impacting cleansing efficacy. Additional studies, including large, prospective, double-blind clinical trials, are needed to confirm these findings. Moreover, trials comparing NaP solution and tablet formulations are warranted to determine which regimen is preferred by patients. These studies should include considerations such as cost of the preparations (currently an advantage of NaP solution<sup>27</sup>) as well as taste, ease of completion, and willingness to repeat the preparation.

# Dosing Considerations for Sodium Phosphate Preparations

#### MINIMALLY EFFECTIVE SODIUM PHOSPHATE DOSE

Recommended dosing regimens (Table 1) are based on clinical trials evaluating the minimally effective dose of NaP. Recent studies reported similar cleansing efficacy with a reduced-volume 75 mL (45 mL plus 30 mL) regimen of NaP solution compared with the standard 90 mL (45 mL plus 45 mL) regimen.<sup>34,37</sup> However, ingestion of less than 75 mL of NaP solution may compromise cleansing quality. For example, studies suggest that bowel preparation with 45 mL of NaP solution does not provide acceptable cleansing for colonoscopic examination.<sup>11,38</sup> Available dosing regimens for tablet formulations are also based on clinical studies that evaluated the minimally effective dose of NaP. For the MCC-containing tablet formulation, a 40 tablet regimen (60 g NaP) is the approved dose; studies have demonstrated effective colon cleansing with 28 tablets (42 g NaP) and 32 tablets (48 g NaP),<sup>39,40</sup> but these regimens were not directly compared with the 40 tablet regimen. A 32 tablet regimen has been approved for the newer, MCC-free tablet formulation and is supported by the finding that a regimen of 32 or 40 MCC-free tablets, but not 28 tablets, achieved better cleansing compared with a regimen of 40 MCC-containing tablets (Table 3).36 Thus, at this time, 75 mL of NaP solution and 32 NaP tablets appear to be the minimally effective doses. As noted above, there is increased risk when more than 90 mL or 40 tablets are taken.

## SPLIT-DOSING SCHEDULES ARE MOST EFFECTIVE AND POTENTIALLY SAFER

The recommended dosing schedules for NaP preparations (Table 1) are supported by several clinical studies.<sup>34-46</sup> An important component of these schedules is split dosing, in which a portion of the dose is administered on the day before colonoscopy and the remaining dose is administered on the day of the procedure.

In clinical practice, there are often 2 objections to split dosing. One is that patients are inconvenienced if they have to get up early in the morning to take the second dose. However, if the importance of split dosing is explained to the patient, anecdotal experience suggests that nearly all patients will comply. Second, many anesthesiologists insist that patients take nothing by mouth after midnight the night before colonoscopy. This is an unfortunate interference with the efficacy and safety of colonoscopy, particularly since the official policy of the American Society of Anesthesiologists is that patients may ingest clear liquids until 2 hours before sedation.<sup>47</sup> In my practice, we instruct patients to take the second dose of NaP 4–5 hours before the time their colonoscopy is scheduled, with completion of the accompanying hydration by 3 hours before the scheduled time of colonoscopy.

#### Split Dosing for NaP Solution

A prospective study randomized patients scheduled for colonoscopy to receive 90 mL of NaP solution, administered as 45 mL taken at 0700 and 45 mL taken at 1900 on the day before examination (group 1, n = 161) or as 45 mL taken at 1800 on the day before colonoscopy and 45 mL taken at 0600 on the morning of the procedure (group 2, n = 166).<sup>41</sup> Bowel cleansing, rated on a scale of 0 (worst) to 5 (best), was significantly superior in group 2 versus group 1 (4.1 vs 3.2; p < 0.0005), and the incidence of AEs was similar between groups. Similarly, Berkelhammer et al.42 reported that significantly more patients (84% vs 73%; p < 0.001) achieved good or excellent colon cleansing when NaP solution was taken as 45 mL on the evening before and 45 mL on the morning of the day of colonoscopy (n =297) compared with patients who received two 45 mL doses 9 hours apart on the day before colonoscopy (n = 160).

A more recent study of 44 patients who took two 45 mL doses of NaP 5 hours apart on the day before colonoscopy (group 1) and 45 patients who took 1 dose on the evening before colonoscopy and the second dose on the morning of the procedure (group 2) reported a significant benefit with the latter dosing schedule, not only in the percentage of patients who achieved good or excellent colon cleansing (80% vs 7%; p < 0.01) but also in the detection of flat lesions.<sup>43</sup>

One advantage of split dosing, with the second 45 mL dose of NaP administered on the morning of colonoscopy, is that the time between the bowel preparation and the examination is minimized. One group of investigators reported that cleansing efficacy was inversely related to the time from administration of the second dose of NaP to colonoscopy (p = 0.0001).<sup>44</sup> Patients who underwent colonoscopy within 6 hours of ingesting the second dose of NaP achieved significantly better cleansing compared with those who underwent colonoscopy 6-12 hours (p = 0.023) or 12 hours or more (p = 0.0001) after administration of the second dose.

Another advantage of split dosing is that the interval between doses is maximized. A thorough investigation was

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conducted of 3 different dosing regimens: 200 patients were randomized to receive two 45 mL NaP doses 6, 12, or 24 hours apart.<sup>45</sup> Colon cleansing, assessed on a 5 point scale (0 = best and 4 = worst), was significantly poorer with the 6 hour regimen versus the 12 hour schedule (mean scores 3.3 vs 2.3, respectively; p = 0.047). Moreover, patients who took the 2 doses 24 hours apart versus 12 hours apart achieved comparable cleansing (mean score of 2.2 vs 2.3, respectively). The incidence of AEs was generally comparable among groups, although dizziness was more common in patients who took the 6 hour regimen, and the 24 hour group required more time off from work. Although that study reported no difference in clinical laboratory parameters among patients who took the NaP doses 6, 12, or 24 hours apart,45 another investigation reported that hyperphosphatemia was more pronounced when the two 45 mL doses of NaP solution were separated by a shorter interval (5 vs 12 h).46

#### Split Dosing for NaP Tablets

Tablet NaP preparations are also more effective when administered in a split-dosing schedule. Wruble et al.<sup>36</sup> reported better bowel cleansing with a regimen of 32 MCCfree tablets in patients who followed a split-dosing regimen (n = 33) versus those who took all 32 tablets on the evening before colonoscopy (n = 30). All patients received 20 tablets, taken as 4 tablets every 15 minutes, beginning at 1800 on the evening before examination. However, the remaining 12 tablets were administered 3 hours later in the evening-only group and the next morning (3-5 hours before colonoscopy) in the split-dosing group. Although statistical comparisons between these groups were not performed, mean overall and ascending colon-cleansing scores favored split dosing. Moreover, the split-dosing regimen, but not the evening-only regimen, of 32 tablets was statistically superior in mean overall and ascending colon-cleansing quality versus a split-dosing regimen of 40 MCC-containing tablets.

Collectively, these studies<sup>36,41-46</sup> support the administration of NaP preparations in a split-dosing schedule, for optimal safety and efficacy of the bowel purgative.

#### DOSE SEPARATION

Longer intervals between doses of NaP allow more time for ingestion of additional clear fluids, and greater fluid intake may be associated with better bowel preparation.<sup>45</sup> Longer intervals between doses are associated with a reduced risk of dehydration. In theory, dose separation could reduce the risk of acute phosphate nephropathy. Peak serum phosphate levels occur 4–6 hours after an ingested dose.<sup>48</sup> Thus, allowing 10–12 hours or more between doses permits increased phosphate levels to fall after the first dose but before the second dose is ingested. Split dosing, with 1 dose taken the day before colonoscopy and 1 dose taken the morning of the procedure, facilitates adequate dose separation, whereas administration of 2 doses the evening before colonoscopy usually necessitates a short interval between doses.

#### HYDRATION

Adequate hydration is an important component of the bowel preparation process, and maintaining proper hydration before, during, and after the preparation is critical to avoid dehydration-related complications and to minimize AEs associated with NaP purgatives.<sup>1,19</sup> Adherence to recommended fluid requirements (Table 1) promotes adequate filtration of excess phosphate,<sup>29,30</sup> increasing the likelihood of safe administration of NaP preparations. In my practice, we use prescribed volumes of hydration with NaP preparations (Table 4).

Carbohydrate/electrolyte rehydration solutions (eg, Gatorade, Quaker Tropicana Gatorade, Chicago, IL, and E-Lyte, CB Fleet Company, Inc., Lynchburg, VA) may be administered as a preferred clear liquid for hydration because they result in better bowel preparation and better hemodynamic status on presentation for colonoscopy.<sup>49,50</sup> Also, an intravenous line during colonoscopy provides an additional opportunity to hydrate.

#### Summary

Sodium phosphate preparations cause expected transient shifts in serum electrolyte levels due to their hyperosmotic nature and, for this reason, are contraindicated in patients with renal insufficiency and in patients at risk for dehydration. Given that NaP preparations are well tolerated and preferred by patients compared with PEG-ELS products, the ideal NaP purgative should minimize expected electrolyte shifts while maintaining effective bowel cleansing. The minimally effective doses are 75 mL of NaP solution or 32 NaP tablets. These doses reduce the phosphate load associated with administration of NaP purgatives, cause less-pronounced elevations in serum phosphate levels, and

<b>Table 4.</b> An Example of an Aggressive Hydration Regimenfor Use with NaP Bowel Preparation				
Timing	Regimen <sup>a</sup>			
Before preparation	8 oz clear liquid every hour for the 6 h preceding the first dose			
With and after the first dose	at least 48 oz of clear liquid			
With and after the second dose	at least 24 oz of clear liquid			
After the procedure and the patient is awake	8 oz of clear liquid every hour for 6 h or at least 6 times before retiring			

<sup>a</sup>Carbohydrate/electrolyte solutions are preferred as clear liquids.

achieve comparable colon cleansing compared with 90 mL or 40 tablet NaP preparations. Doses of NaP should be split, with 1 dose taken the day before colonoscopy and the second dose taken on the day of colonoscopy, 3–5 hours before the scheduled time of the procedure. The doses of NaP should be separated by at least 10–12 hours whenever possible. Specific volumes of clear liquid hydration, preferably carbohydrate/electrolyte solution, should be prescribed for the intervals before and during preparation and after the procedure. Intravenous hydration during the procedure is also generally advisable.

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Consideraciones de Dosificación en el Uso de Preparaciones Intestinales de Fosfato de Sodio para Colonoscopia DK Rex

Ann Pharmacother 2007;41:1466-75.

#### EXTRACTO

**OBJETIVO:** Repasar las consideraciones de dosificación y otras recomendaciones de tratamiento con el propósito de maximizar la eficacia, la tolerabilidad, y la seguridad de las preparaciones de fosfato de sodio (NaP).

FUENTES DE INFORMACIÓN: Se obtuvo acceso a la literatura a través de PubMed (1990-mayo 2007) y de abstractos de reuniones científicas.

SELECCIÓN DE FUENTES Y MÉTODO DE EXTRACCIÓN DE INFORMACIÓN: Se evaluaron publicaciones en el idioma inglés incluyendo ensayos clínicos y reportes de casos. Informes recientes evaluando preparaciones intestinales nuevas, conteniendo dosis reducidas de NaP fueron repasados para evaluar la eficacia, la tolerabilidad y, la seguridad.

SÍNTESIS: Entre las preparaciones intestinales usualmente administradas para colonoscopia, los preparados de NaP son generalmente más efectivos y mejor tolerados en comparación con los regimenes de una solución electrolitica de lavado de glicol polietilénico. Sin embargo, los preparados de NaP están contraindicados en poblaciones específicas de pacientes, y los médicos deben utilizar mecanismos de detección efectivos para seleccionar los pacientes apropiados a recibir una preparación de NaP para colonoscopia. En pacientes con una previa función renal normal, recientemente se han reportado casos de insuficiencia renal después de utilizar un preparado de NaP para colonoscopia, aumentando la preocupación sobre la seguridad de estos agentes. Los nuevos productos contienen dosis reducidas de NaP y pueden mejorar la seguridad y la tolerabilidad de los purgantes de NaP sin comprometer la eficacia de la limpieza del colon. En adición, los datos clínicos acumulados y/o la exposición razonada apoyan la división de la dosis de los productos de NaP, un amplio intervalo entre las dosis y, una hidratación agresiva antes y durante la preparación del intestino y después del procedimiento de colonoscopia.

CONCLUSIONES: La administración segura de los productos de NaP requiere una atención rigurosa a las consideraciones de dosificación y otras recomendaciones de tratamiento, incluyendo la administración de dosis mínimas efectivas, los horarios de dosis divididas, y la hidratación agresiva.

Traducido por Brenda R Morand

Eléments de Dosage dans l'Usage des Préparations Intestinales par Phosphate de Sodium pour Coloscopie

#### DK Rex

Ann Pharmacother 2007;41:1466-75.

#### RÉSUMÉ

**OBJECTIF:** Analyser les éléments du dosage et autres recommandations de traitement pour maximiser l'efficacité, la tolérance, et les précautions d'emploi des préparations de Phosphate de Sodium (NaP).

**REVUE DE LITTÉRATURE:** De 1990-mai 2007, une recherche bibliographique fut menée à l'aide de la base de donnée PubMed et des extraits de conférences scientifiques.

SÉLECTION DES ÉTUDES ET SÉLECTION DE L'INFORMATION: Des publications en langue anglaise rapportant des études cliniques et des observations ont été analysées. De récents rapports évaluant de nouvelles préparations intestinales contenant des doses réduites de NaP ont été analysés pour évaluer l'efficacité, la tolérance, et les précautions d'emploi.

RÉSUMÉ: Parmi les préparations intestinales les plus couramment administrées pour la coloscopie, les préparations NaP sont généralement plus efficaces et mieux tolérées en comparaison avec le schéma posologique des solutions de lavage d'électrolytes polyéthylène glycol. Cependant, les préparations de NaP sont contre-indiquées chez des

#### Sodium Phosphate Dosing in Colonoscopy

populations spécifiques de patients, et les cliniciens doivent utiliser des mécanismes de dépistage adaptés pour sélectionner les patients adaptés pour recevoir des préparations de NaP pour coloscopie. Récemment, des cas d'insuffisance rénale chez des patients qui auparavant avaient une fonction rénale normale ont été rapportés après une administration de préparations NaP pour coloscopie. Ceci suscite des préoccupations sur la tolérance de ces agents. De nouveaux produits possèdent des dosse réduites de NaP et pourraient améliorer les précautions d'emploi et la tolérance des purgatifs de NaP sans altérer l'efficacité de détersion du colon, et ce avec une accumulation des données cliniques et/ou un support rationnel d'administration fractionnée de doses des produits

NaP, de larges intervalles de doses et une agressive hydratation avant et après la préparation intestinale, et également après la procédure de coloscopie.

CONCLUSIONS: L'administration sûre de produits NaP nécessite une rigoureuse attention aux éléments de dosage et autres recommandations de traitement, y compris une administration de doses minimum efficaces de NaP, un schéma posologique par split doses fractionnées et une agressive hydratation.

Traduit par Thierry Youmbi

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