

Real-life conditions of use of sodium phosphate tablets for colon cleansing before colonoscopy

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Background and study aims: The purpose of this study was to describe the real-life conditions of use, efficacy, safety, and acceptability of sodium phosphate (NaP) tablets for colon cleansing in routine medical practice in France.

Patients and methods: A total of 996 patients undergoing bowel preparation were enrolled by 108 gastroenterologists in this observational, longitudinal, prospective, multicenter study. The conditions of use of NaP tablets were assessed with a composite endpoint, which included six criteria for patient compliance with the recommended administration scheme and a criterion for the absence of contraindications to NaP use.

Results: Adequate use of NaP was reported for 75.1% of the patients. The main reasons for misuse were a smaller fluid intake than expected with a dose of 4 tablets and noncompliance with age-related contraindications. The quality of cleansing was satisfactory: the Boston Bowel

Preparation Scale (BBPS) total score was 7 or higher in 75.4% of the patients. Gastroscopy associated with colonoscopy in 38.9% of the patients revealed gastric lesions, which were considered as possibly related to the use of NaP tablets in 10.3% of them. Vomiting occurred in 9.8% of the patients, and 0.6% discontinued bowel preparation after an adverse event. No electrolyte disorders or renal impairment was reported, even if not systematically sought. The acceptability of the NaP tablets was high, particularly among patients who previously had undergone other methods of bowel preparation.

Conclusions: Despite being defined according to strict criteria, adequate use of NaP tablets was observed in a high percentage of patients. The quality of colon cleansing and the safety and acceptability of NaP tablets were satisfactory and consistent with data from randomized clinical studies.

Introduction

Colonoscopy is an important tool for the visual diagnosis of colonic mucosal lesions, especially colonic tumors; it is widely used for cancer screening and allows biopsy or removal of neoplastic lesions [1,2]. However, most patients find the bowel preparation before colonoscopy an unpleasant experience because of the large volumes of liquid to be taken, nasty taste of the preparation, and purgative effect or side effects. Successful colonoscopy requires adequate bowel preparation [3,4], and it is important to improve patient compliance to avoid imperfect preparation, which results in repeated examinations and increased costs [5]. Three main classes of oral bowel cleansing preparations are available: polyethylene glycol (PEG), sodium phosphate, and more recently sodium picosulphate [6].

Previous experience with sodium phosphate (NaP) in the United States as an over-the-counter drug and in the treatment of constipation highlighted serious safety concerns, such as kidney failure and electrolyte disturbances. The safety, efficacy, and acceptability of NaP tablets were evaluated in randomized clinical trials, in which they were compared with other preparations [6,7–10]. However, no study has assessed the use and safety of NaP tablets in a real-life context. In this observational study, we evaluated patient compliance in the conditions of use of NaP tablets in current medical practice and the consequences of these conditions on the safety and quality of colon cleansing, results of colonoscopy, and patient acceptability.

License terms



Patients and methods

Study design

USCOL (Study on the Conditions of Use and Safety of COLokit) is an observational, longitudinal, prospective, national study conducted in 108 centers in France. It was initiated in the context of a risk management plan for NaP tablets (Colokit) after Colokit became available on the French market in 2010. French health authorities approved the protocol and the administration scheme information sheet intended for patients.

The primary objective was to describe the conditions of use of NaP tablets in current medical practice based on available information given by physicians to patients in France. The secondary endpoints were assessments of safety, quality of colon cleansing, result of colonoscopy, and patient's acceptability.

Hospital-based or private physicians were recruited from a professional French database (Cegedim) including 3720 gastroenterologists. In order to limit selection bias, the entire group of physicians was contacted and given information on the study. Gastroenterologists interested in the study were selected according to the chronologic order of their agreement. Gastroenterologists became investigators if they were NaP prescribers and were able to enroll 10 outpatients consecutively within 2 months.

To be included in the study, patients had to be 18 years of age or older, be prescribed a colonoscopy at the end of a visit, and be eligible for bowel preparation with NaP tablets according to the Colokit summary of product characteristics [11]. According to French regulations, this study was considered to be observational, not requiring approval from a regional ethical committee. All patients were informed and gave their oral consent to participate. Patients received an information sheet describing the use of NaP tablets for bowel preparation, which, as part of the risk management plan for NaP tablets, had been validated by the French health authorities.

Bowel preparation and quality of colon cleansing

The dosing regimen consisted of 32 tablets taken orally: a first sequence of 20 tablets (4 tablets every 15 minutes with 250 mL of any clear liquid) on the evening before colonoscopy and a second sequence of 12 tablets (taken in the same manner) on the evening before colonoscopy (with at least a 4-hour interval between the 2 sequences) or on the morning of the procedure, depending on the scheduled time of the procedure.

The quality of the bowel preparation was assessed with the Boston Bowel Preparation Scale (BBPS) [12, 13]. The bowel preparation was considered good if the global BBPS score was 7 or higher because a score of 7 or higher is known to allow the detection of polyps 6 mm or larger in 88% of cases [14].

Questionnaire data

Physicians and patients completed dedicated questionnaires. The physicians recorded the following data for each patient at the inclusion visit and on the day of the colonoscopy: demographics, medical and surgical history, concomitant diseases and treatments, clinical examination findings, details of the procedure, laboratory tests when requested, result of gastroscopy if performed, quality of colon cleansing, result of colonoscopy, and adverse effects.

In the self-administered questionnaire that each patient was given by the gastroenterologist, the patient assessed the oral and written information received regarding the administration of NaP tablets and indicated the following: number of tablets taken

Table 1 Assessment of gastric lesions and their imputability to NaP tablets based on total score, according to the safety committee.¹

| Patient/lesion characteristics | Score | |
|---|-------|----|
| | Yes | No |
| Blackish color | 3 | 0 |
| Fundic localization | 2 | 0 |
| Multiple lesions | 1 | 0 |
| No gastrotoxic drug intake | 1 | 0 |
| No gastric symptoms ² | 1 | 0 |
| Negative <i>Helicobacter pylori</i> search result | 3 | 0 |

¹ Imputability based on total score: 0 to 2 points, doubtful; 3 to 5 points, possible; 6 to 7 points, likely; 8 to 9 points, very likely.

² Epigastralgia, dyspepsia, gastric pain.

with the time of administration; amounts of clear liquids taken; use of a low-fiber diet and, if applicable, its duration; adverse effects; and preparation acceptability.

Safety

Mild to severe adverse effects were reported in the questionnaires of both the patients and the physicians. Patient follow-up consisted of a telephone call 1 week after the colonoscopy.

Gastric lesions possibly related to bowel preparation were assessed in the subgroup of patients who simultaneously underwent gastroscopy.

An independent safety committee consisting of five gastroenterologists (none of them investigators) and one nephrologist assessed the adverse effects and their relationship to the NaP tablets. To investigate any relationship between adverse effects and the preparation, during their first meeting the safety committee members designed a specific grid with criteria weighted in favor of drug-induced gastric lesions, calculating a total score to assess relationship (Table 1). Each member of the safety committee reviewed and assessed all gastric lesions with this dedicated grid. During a second meeting, each adverse effect received a final assessment of relationship to the study drug based on collegial decision.

Endpoints and statistical analysis

The primary endpoint was a description of the conditions of use of NaP tablets, with both the conditions of use by the patients and the conditions of prescribing by the physicians taken into account. The conditions of use were considered adequate if the patient took the NaP tablets in compliance with all required terms (Table 2a). The conditions of use were considered inadequate if one or more term was not fulfilled. To achieve an accuracy of 3% for qualitative variables by using the formula of the confidence interval and taking into account missing data, the total number of patients to be included was 1000. The number of physicians was based (1) on their type of practice, in order to have a balance of physicians based at public hospitals and in private practice, and (2) their capacity to enroll patients within a 2-month inclusion period. To take into account patients who could not be analyzed and inactive centers, 120 physicians had to be selected.

The primary endpoint analysis was performed on the population of patients without missing data regarding the conditions of use. The secondary endpoints were quality of colon cleansing, lesions of the colon, safety, and acceptability.

A logistic regression model (Cox model) was used for multivariate analyses (backward selection method with $P < 0.20$ for the se-

Table 2a Definitions of conditions of use.

| |
|--|
| Adequate use: patient compliant with all items listed below |
| First sequence taken on day before colonoscopy |
| Second sequence taken either on day before colonoscopy or on day of colonoscopy |
| First sequence with 20 tablets taken in 5 doses and second sequence with 12 tablets taken in 3 doses |
| Four tablets taken per dose |
| Volume of liquid with each dose \geq 250 mL |
| Interval of at least 4 hours between the 2 sequences |
| Absence of contraindications |
| Misuse: patient not compliant with at least one item listed above |

Table 2b Conditions of use and reasons for misuse in 926 patients.

| Conditions of use, n (%) | |
|--|------------|
| Adequate use | 607 (75.1) |
| Misuse | 201 (24.9) |
| Data missing ¹ | 118 (12.8) |
| Reasons for misuse (noncompliance with items listed below), n (%) ² | |
| First sequence taken on day before colonoscopy | 3 (0.4%) |
| Second sequence taken either on day before colonoscopy or on day of colonoscopy | 1 (0.1%) |
| First sequence with 20 tablets taken in 5 doses and second sequence with 12 tablets taken in 3 doses | 62 (7.7%) |
| Four tablets taken per dose | 23 (2.8%) |
| Volume of liquid with each dose \geq 250 mL | 105 (13%) |
| Interval of at least 4 hours between the 2 sequences | 71 (8.8%) |
| Absence of contraindications | 23 (2.8%) |

¹ Patients with data missing on at least one of the criteria for adequate use.

² More than one reason for misuse was possible.

lection of variables in univariate analysis and $P < 0.15$ in multivariate analysis) of independent predictive factors of adequate use of NaP tablets and quality of colon cleansing.

The data were analyzed with SAS 9.1.3 software (SAS Institute, Cary, North Carolina, USA).

Results

Physician characteristics

The 120 investigators planned for in the protocol were selected from the 343 gastroenterologists who agreed to participate according to the chronologic order of their agreement. Among them, 108 were active investigators; 27% of the patients were enrolled by gastroenterologists with a public hospital-based practice and 73% by gastroenterologists with a private practice.

Patient characteristics

From September 2011 to March 2012, 1048 patients were included and 996 were analyzed; 926 were included in the population analysis for the primary endpoint (Fig. 1). The patients' characteristics are described in Table 3. The most frequent concomitant diseases were related to the cardiovascular system (15.8%); endocrine system/metabolism (15.8%), including hypothyroidism (5.8%) and diabetes mellitus (3.7%); and gastrointestinal system (7.5%). Furthermore, 56.7% of the patients were receiving at least one concomitant treatment, the most frequent of which were cardiovascular treatments (39.3%) and cholesterol-lowering agents (26.9%).

Contraindications to NaP use were reported for 3.3% of the patients, with age older than 75 years the most frequent contrain-

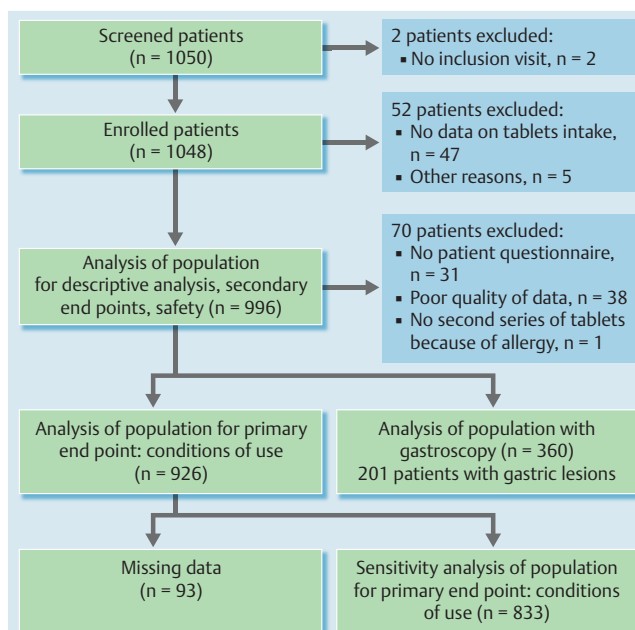


Fig. 1 Flow chart of the population analysis of patients in a study of the real-life conditions of use of sodium phosphate tablets for colon cleansing before colonoscopy.

dication ($n=20$; 2.1%). Concomitant treatments requiring precautions for use according to the Colokit summary of product characteristics were reported for 16.5% of patients. The factors requiring precautions of use are listed in Table 3.

Conditions of use of sodium phosphate tablets

Adequate use based on the composite endpoint, including appropriate intake by the patient and absence of contraindication, was reported in 75.1% of patients (Table 2b). The main reason for misuse was the consumption of an insufficient volume of liquid with at least one of the doses of NaP tablets ($n=105$), despite the fact that 59 of the patients (55.7%) had drunk more than 2000 mL of clear liquids over the 2 sequences, with a mean (SD) total volume of 2825 (\pm 1033) mL (Table 2b). In addition, the adequate use rate based on the conditions of use by the patients was 77.3%. High percentages of the patients complied with the number of tablets and number of intakes: 93% took 32 tablets and 3.6% took 28 tablets (2.5% took fewer than 28 tablets, and 0.7% took between 28 and 32 tablets); 92.5% of patients complied with the 8 intakes. A high percentage of patients (98.0%) complied with the intake of tablets in 2 sequences; 71 patients did not comply with the interval of 4 hours between the 2 sequences, and 18 took all the tablets in a single sequence.

In a multivariate analysis, the factors associated with adequate use of NaP tablets were previous colonoscopy (first vs. previous colonoscopy: odds ratio [OR] 0.569; 95% confidence interval [CI] 0.404–0.802; $P=0.0012$), a rural place of residence (urban vs. rural: OR 0.579; 95%CI 0.394–0.851; $P=0.0054$), information data sheet received from the investigator (received vs. not received: OR 1.951; 95%CI 0.959–3.967; $P=0.0650$), and lack of information on the need of large volumes of liquids to drink (informed vs. not informed: OR 0.267; 95%CI 0.079–0.898; $P=0.0328$).

Quality of colon cleansing

The BBPS score was 2 or higher (good to excellent cleansing) for the right, transverse, and left colon in 86.2%, 94.2%, and 94.0%

Table 3 Characteristics of the patients enrolled in a study of the real-life conditions of use of sodium phosphate tablets for colon cleansing before colonoscopy.

| | |
|---|----------------|
| Age, y | |
| Mean (standard deviation [SD]) | 54.6 (11.8) |
| Range | 18–81 |
| Female gender, n/N (%) | 556/996 (55.8) |
| Body mass index (BMI), kg/m ² | |
| Mean (SD) | 25.3 (4.3) |
| BMI > 25, n/N (%) | 470/960 (48.9) |
| Place of residence, n/N (%) | |
| Urban | 649/953 (68.1) |
| Rural | 304/953 (31.9) |
| Contraindications to sodium phosphate, n/N (%) ¹ | |
| At least one contraindication | 32/968 (3.3) |
| Age > 75 y | 20/968 (2.1) |
| Inflammatory bowel disease | 9/968 (0.9) |
| Congestive cardiac failure | 2/968 (0.2) |
| Renal insufficiency | 1/968 (0.1) |
| Precautions for use, n/N (%) ¹ | |
| At least one precaution | 153/928 (16.5) |
| Angiotensin II receptor antagonist | 85/928 (9.2) |
| Angiotensin converting enzyme inhibitor | 39/928 (4.2) |
| Diuretic | 25/928 (2.7) |
| Nonsteroidal anti-inflammatory drug | 19/928 (2.0) |

¹ According to the summary of product characteristics for Colokit (sodium phosphate tablets).

of patients, respectively (Table 4). A total score of 7 or higher was reported for 75.4% (743/986) of the patients. Insufficient cleansing (total BBPS score ≤ 5) was reported for 101 patients (10.2%). An additional lavage was performed during colonoscopy in 17.7% (131/740) of the patients with a BBPS score of 7 or higher and in 68.3% (166/243) of the patients with a BBPS score below 7.

Only 6 patients had a total BBPS score below 3. Colonoscopy was considered a failure (cecum not reached) in 1.7% (17/996), including 7 patients with poor preparation, 5 patients with an ana-

tomical obstacle, 4 patients with dolichocolon, and 1 patient with no cause specified.

Lesions were reported in 550 patients (56.5%): polyps in 403 patients (41.8%), suspected cancer in 5 patients (0.6%), diverticula in 219 patients (23.2%), ulcers in 29 patients (3.2%), and other abnormalities in 60 patients (6.9%).

Overall, 801 polyps were revealed in 401 patients: 521 sessile, 80 pedunculated, and 69 flat; the type was missing for 131 patients. The polyp detection rate (PDR) was 41.8%.

Safety

The most frequent predefined adverse effects (moderate or severe) reported in the self-administered patient questionnaires were bloating (26.2%), digestive discomfort (23.0%), and anal irritation (24.4%) (Table 5). Vomiting was reported in 9.8% of the patients, although severe vomiting was reported in only 1.9%. Adverse effects not predefined in the questionnaire were reported by 130 patients (13.4%); the most frequent were chills and headache in 5.9% and 3.2% of patients, respectively. No patients had an electrolyte disorder or acute renal failure during the 7 days of follow-up after the colonoscopy. However, it is important to remember that, as is usual in an observational study, blood tests, electrolyte measurements, and renal tests were not systematically performed. It is possible that missing data on the patient questionnaires could have caused the rate of adverse effects to be overstated because it is likely that patients did not fill in their questionnaires if no adverse effects occurred.

According to the investigators, 31.4% (310/986) of the patients reported at least one adverse effect (438 adverse effects). Of these, 92.4% (328/438) were designated as mild or moderate. The most frequent adverse effects (gastritis, gastric ulceration, nausea, esophagitis, vomiting, and abdominal pain) are common (Table 6); 54.5% of all adverse effects were considered to be related to the preparation and resulted in drug discontinuation in 6 patients (0.6%), who reported 9 adverse reactions (3 nausea, 3 vomiting, 2 abdominal pain, 1 headache). In 1 patient, 3 serious adverse effects (thoracic pain, atrial fibrillation, decrease of

Table 4 Efficacy of sodium phosphate tablets in colon cleansing in 986 patients.¹

| Boston Bowel Preparation Scale (BBPS) score | Right colon, n (%) | Transverse colon, n (%) | Left colon, n (%) |
|---|--------------------|-------------------------|-------------------|
| 0 (inadequate) | 15 (1.5) | 4 (0.4) | 5 (0.5) |
| 1 (fair) | 121 (12.3) | 53 (5.4) | 54 (5.5) |
| 2 (good) | 385 (39.1) | 227 (23.0) | 236 (23.9) |
| 3 (excellent) | 463 (47.1) | 701 (71.2) | 691 (70.1) |
| Data missing | 2 | 1 | 0 |

¹ A total of 10 patients were excluded from the population analyzed for quality of colon cleansing because the total BBPS score could not be calculated: anatomical obstacle, n = 5; bowel preparation discontinued because of adverse event, n = 1; bowel preparation with both polyethylene glycol and sodium phosphate tablets, n = 2; case report form corresponding to visit for colonoscopy not returned, n = 2.

Table 5 Adverse effects reported in the questionnaire sent to 996 patients.

| Adverse effect | None, n (%) | Mild, n (%) | Moderate, n (%) | Severe, n (%) | Data missing, n |
|----------------------|-------------|-------------|-----------------|---------------|-----------------|
| Bloating | 294 (33.1) | 361 (40.7) | 148 (16.7) | 84 (9.5) | 109 |
| Digestive discomfort | 333 (37.6) | 349 (39.4) | 144 (16.3) | 59 (6.7) | 111 |
| Anal irritation | 407 (46.4) | 256 (29.2) | 112 (12.8) | 102 (11.6) | 119 |
| Abdominal pain | 465 (52.8) | 287 (32.6) | 84 (9.5) | 45 (5.1) | 115 |
| Fatigue | 465 (55.0) | 261 (30.9) | 78 (9.2) | 41 (4.9) | 151 |
| Nausea | 512 (57.4) | 253 (28.4) | 75 (8.4) | 52 (5.8) | 104 |
| Dizziness | 687 (80.0) | 129 (15.0) | 32 (3.7) | 11 (1.3) | 137 |
| Vomiting | 760 (90.2) | 50 (5.9) | 17 (2.0) | 16 (1.9) | 153 |

Table 6 Adverse effects occurring in more than 1% of 986 patients during bowel preparation with sodium phosphate tablets.

| Event | Number | Percentage |
|--|--------|------------|
| Data missing | 10 | |
| Patients with at least one adverse event | 310 | 31.4 |
| Gastritis | 170 | 17.2 |
| Gastric ulceration ± gastritis | 39 | 4.0 |
| Nausea | 33 | 3.3 |
| Esophagitis | 24 | 2.4 |
| Vomiting | 21 | 2.1 |
| Abdominal pain | 13 | 1.3 |
| Headache | 17 | 1.7 |

ventricular ejection fraction) were reported, whose relationship to the preparation was considered doubtful (favorable outcome). A gastroscopy was performed in association with the colonoscopy in 360 patients. Gastric lesions, most frequently antral lesions, were revealed in 201 patients: isolated gastritis in 45.0% (162/360) and gastric ulcerations with or without gastritis in 10.8% (39/360). Analysis according to the presence ($n=201$) or absence ($n=159$) of lesions in the subgroup of 360 patients who underwent gastroscopy showed that 7.4% of the patients with gastric lesions had received nonsteroidal anti-inflammatory drugs, whereas only 0.7% of the patients without gastric lesions had received such drugs ($P=0.003$). No significant difference was observed for the other treatments. Of the patients with gastric lesions, 176 (87.6%) were tested for *Helicobacter pylori*, and the test result was positive in 27 (15.3%).

The relationship of gastric lesions to the preparation was assessed by the safety committee, which considered 0 of 157 cases of nonerosive gastritis, 4 of 5 cases of erosive gastritis, 15 of 16 cases of gastric ulcerations, and 18 of 23 cases of gastric ulcerations with gastritis as possibly likely or very likely related to the preparation, corresponding to 10.3% of the patients who had undergone gastroscopy at the same time as colonoscopy.

Acceptability of bowel preparation with sodium phosphate tablets

The oral and written information that patients received was considered to be “clear” or “very clear” by 98.1% of them. Patients reported that they experienced little or no difficulty in swallowing the 32 tablets (85.2%) or in drinking the recommended volume of liquid (88.1%).

Of the patients who had previously undergone a colonoscopy, 75.8% (394/520) preferred the NaP tablets to other bowel preparations. The main reasons for that preference were no taste (34.2%), more acceptable (57.8%), and easier to take (68.9%). Overall, 71.9% of the patients (635/883) said they would be willing to take NaP tablets for a future colonoscopy.

Discussion

Following the introduction of a new pharmaceutical form and specific administration scheme, this study formed part of a risk management plan for the product and was conducted at the request of French health authorities from September 2011 to March 2012.

We believe that this study, which assessed the conditions of use of a bowel preparation in a real-life setting, is the first of its kind to be conducted in Europe. With this preparation, as with any

drug, it was also important to evaluate in routine practice the understanding of the administration scheme and whether contraindications and precautions for use were observed and could contribute to an improved benefit-to-risk ratio.

The gastroenterologists in our sample were representative of the overall population of French gastroenterologists in terms of geographic area, activity, and type of practice; their geographic distribution was not statistically significantly different ($P=0.10$) from the one from the professional database. This distribution matches the results of an endoscopy survey conducted in France in 2008, which reported that 72% of colonoscopies were performed by physicians in private practice [15]. Because the current clinical practice was not modified in this observational study, the study population is likely representative of outpatients undergoing colonoscopy and eligible for preparation with NaP tablets.

The conditions of use of NaP tablets, the primary objective of the study, identified “adequate use” when the patient complied with all the criteria for adequate conditions of use. We found that 3 of every 4 patients (75.1%) were in compliance with all these criteria, including the absence of contraindications. Of the patients with misuse ($n=105$), half ($n=59$) ingested less than 250 mL of clear liquids on at least one occasion; however, it must be emphasized that these patients drank a total of more than 2 L of clear liquids over the 2 sequences and as such consumed the total amount of liquid required in the prescribing information. This is consistent with the fact that the oral and written information about preparation with the NaP tablets was considered clear or very clear by 98% of patients, as recommended by the European Society of Gastrointestinal Endoscopy (ESGE) guideline [16].

In this real-life study, contraindications to the use of NaP tablets were reported for 3.3% of patients ($n=32$); according to the French prescribing information, the most frequent contraindication was age older than 75 years ($n=20$; 2.1%) (Table 3). This same characteristic is labelled as a precaution in the United Kingdom summary of product characteristics [17] and the U.S. prescribing information for this drug [18].

At least one concomitant treatment possibly interacting with NaP was reported for 16.5% of the patients: angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors were the most frequent, in 9.2% and 4.2% of the patients, respectively (Table 3). Although no cases of an electrolyte disorder or acute renal failure were reported, and although no patient required blood, electrolyte, or renal tests following NaP tablet intake, it is important that special care be taken when this preparation is prescribed because ARBs and ACE inhibitors are known to decrease the glomerular filtration rate.

The rates of good quality of bowel preparation were high: an 84.2% rate of good to excellent cleansing for each colonic segment, with a total BBPS score above 6. It should be noted that the quality of cleansing was good in the right colon, where the potential for missed neoplastic lesions is known to be high [19]. The high rate of successful cleansing in this study may be partly linked to the observed compliance with the NaP tablets preparation [6, 7, 8, 10]. A failure of colonoscopy was reported for 17 patients (2%), who included 7 with poor preparation. In comparison with French observational data, the rate of colonoscopy failure was slightly lower than expected, irrespective of whether or not this was due to poor preparation: 2% vs. 10% and 0.7% vs. 2%, respectively [20, 21].

The PDR, which included all sizes and types, was above 41%, which is slightly higher than expected compared with the literature data for similar observational studies [20, 22]. This result

confirms that in routine practice, the use of NaP tablets improves the quality of bowel cleansing, with a positive impact on the PDR. Secondary endpoints on colon cleansing with NaP tablets were consistent with the results previously reported in controlled clinical trials and in a meta-analysis [10].

The adverse effects reported by physicians and patients were mainly similar to those associated with other bowel preparations. Vomiting is a frequent cause of poor compliance, and it is important to emphasize the low rate of vomiting (9.8%) associated with NaP tablets compared with other preparations (Table 5). Kasztenberg et al. reported vomiting in 18.5% of patients after bowel preparation with 4L of PEG [22].

No serious adverse reaction related to the bowel preparation was reported over the 7 days of follow-up after the procedure, and in anticipation of this result, no blood tests were planned in our observational study. Only 6 patients discontinued the preparation because of adverse reactions.

These safety results are not consistent with the recent ESGE guidelines, which advised against the routine use of oral NaP because of safety concerns, including kidney injury and electrolyte disturbances [16]. However, the evidence to support this statement was limited, and the quality of the data included in the paper was questionable [16]. The data presented related only to the use of oral over-the-counter NaP products or oral NaP solutions and were based mainly on case series and most often collected retrospectively. In contrast, a recently published study by Layton et al., which analyzed a large U.S. database, found no evidence of an increased risk of acute kidney injury in the general population or in high-risk subgroups of patients undergoing colonoscopy and using NaP or PEG for bowel cleansing [23]. More controlled and prospective studies are needed to investigate these findings further.

Gastric lesions were mainly erythematous gastritis-like lesions, erosive gastritis, or superficial gastric ulcerations with a blackish base, most often asymptomatic and spontaneously regressive, in agreement with post-marketing pharmacovigilance data [24]. Of the gastric lesions, only erosive gastritis and gastric ulcerations were considered very likely to be related to NaP tablets by the safety committee (10.3% of all gastric lesions).

It is common practice in France to perform gastroscopy at the same time as colonoscopy, and consequently gastric findings have been reported in this study. Such adverse effects are not reported in the United States, where performing gastroscopy with colonoscopy is unusual in clinical practice, although NaP tablets have been marketed in the United States since 2006. The fact that these lesions have never been observed in the United States provides evidence for their benign character and the absence of risk of progression. Furthermore, in an attempt to reproduce the gastric lesions observed in humans, Coron et al. developed a pig model to determine the effects of NaP tablets on the gastric mucosa. They found that after the direct and prolonged gastric application of NaP tablets, gastric injuries were acute, superficial, and reversible within 72 hours [25]. The only issue related to the gastric lesions was that they could interfere with the interpretation of the gastroscopy results. However, the appearance of these lesions is quite typical, and gastroenterologists should be aware of their possible occurrence and appearance.

The degree of acceptability of the NaP tablets was high; 75.8% of the patients who had previously undergone colon cleansing with other preparations preferred NaP tablets, and 71.9% were willing to take NaP tablets again for a future colonoscopy. This high degree of acceptability confirmed the data from controlled clinical

studies. In meta-analyses, it was found that 97.2% of patients who used NaP tablets completed bowel preparation and that NaP preparation was better accepted than PEG preparation; the unpleasant taste and the requirement to drink a large volume of liquid (3–4L for PEG) were the most frequent reasons for the poor acceptability of PEG [10,24].

Our study has some limitations. First, a sampling bias among the population of gastroenterologists should be mentioned; this was caused by the type of selection, which was sequential on a first come–first served basis. The relatively small number of participating gastroenterologists should nonetheless be representative of all types of practice and activity because our results are consistent with the data of the French National Health Insurance [19]. Second, because of the eligibility criteria used, the recruited population could not reflect the population of all patients undergoing colonoscopy; instead, it included the majority of outpatients scheduled for colonoscopy with bowel preparation. It must be acknowledged that only a gastroenterologist could assess patient eligibility, and the patient's agreement to participate was also required. We must emphasize that this study was conducted at the request of the French health authorities. Therefore, the choice of methodology may not accurately reflect the real-life situation because of the small number of participating gastroenterologists proposed and endorsed by the health authorities.

Third, we were unable to identify predictive factors of misuse after multivariate analysis because of the small size of the sample of patients with inadequate use.

Fourth, because of a lack of data in the literature [26] that could be used to assess the imputability of NaP preparations in the induction of gastric lesions, a grid was empirically developed by experienced endoscopists in the safety committee. It takes into account factors beyond endoscopic appearance, such as patient history, *H. pylori* status, and gastrototoxic drug intake. This imputability grid is not yet a standardized and validated tool for assessing a causal relationship between gastric lesions and the drug but has been designed to facilitate and coordinate decision making regarding the imputability of the preparation in relation to gastric lesions.

Fifth, in this study, in which the polyp detection rate was slightly higher than that in the literature data, it would have been appropriate to know the adenoma detection rate. It should be taken into account that in an observational study, it is impossible to perform a histologic analysis for each polyp or lesion of each patient systematically.

Sixth, despite the excellent rate of completion of the questionnaires by the patients, there may be some bias due to missing or incomplete data. In an observational study conducted in routine clinical practice, it is not possible to enforce rigorously the completion of online questionnaires, in which all items have to be recorded before validation, and therefore it is unlikely that 100% of data collection was reached.

Finally, because the patients were followed up for only 1 week after the procedure and no blood testing was planned, it is premature to draw conclusions on electrolyte disturbances and renal failure, which can occur several weeks later. In this context, the results of an interventional prospective phase IV study (NCT 01427296), set up in the United States in 2011 to assess the safety of NaP tablets vs. PEG and bisacodyl in 2154 patients until 180 days after colonoscopy, are expected and will contribute to the debate.

In conclusion, this observational, longitudinal, prospective study of a representative sample of gastroenterologists and 996 pa-

tients, conducted at the request of French health authorities, highlights the good rate of adequate use (75%) according to stringent criteria and excellent acceptability of NaP tablets (>85%) for bowel preparation in routine practice.

The quality of the preparation was rated as good to excellent (BBPS score ≥ 2 in all segments) in 84% of patients. These data, generated in real practice, demonstrate the safety of NaP tablets, with no short-term electrolyte disorder or acute kidney injury observed. Some gastric lesions were found if gastroscopy was performed with colonoscopy. All of these had favorable outcomes and were quoted by the safety committee as possibly related to NaP tablets in only 37 cases (10.3%).

It should be noted that the results of this observational study in routine clinical practice clearly reinforce the data for NaP tablets obtained in controlled clinical trials.

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