



B



SAFETY AND LAXATIVE EFFECTS OF VISICOL® TABLETS (SODIUM PHOSPHATE) IN HEALTHY VOLUNTEERS

Martin Rose, MD^{1*}, Nancy Ettinger¹, Jeffrey Arcara¹ and William G Kramer, PhD².

¹InKine Pharmaceutical Co., Inc., Blue Bell, PA, United States and ²Kramer Consulting, LLC, North Potomac, MD, United States.

Time in hours to the first watery stool or the first loose or watery stool was significantly shorter with either NaP 8 tablets or NaP 12 tablets than with PEG 17 g (Wilcoxon rank sum test, $p \leq 0.0007$ for all comparisons, data not shown). In these normal subjects, time to the first bowel movement of any kind did not differ significantly among the groups by analysis of variance (data not shown).

SAFETY INFORMATION

Adverse events: No patient died, had a serious adverse event, or discontinued for an adverse event, although one subject in the PEG group was lost to follow-up after reporting vomiting and abdominal pain on Day 2. Minor and transient adverse events were reported by 2 additional subjects in the PEG 17 g group, 4 subjects in the NaP 8 tablets group, and 2 subjects in the NaP 12 tablets groups.

Information regarding the symptoms captured on the diary (cramping, flatus, and rectal irritation) is displayed in Table 5. For each symptom the number of subjects who reported none, mild, moderate, or severe symptoms is displayed for Day 1 and Day 7. For cramping and rectal irritation, symptoms tended to be worst in the NaP 12 tablet group on Day 1 but tended to resolve over time, suggesting a possible relationship to the degree of laxation experienced by the subjects. For flatus, the NaP 8 tablet group reported more symptoms than the other groups, with no clear temporal trends. For the data shown, only the differences at Day 1 for cramping were statistically significant.

Table 5 - Diary reports of cramping, flatus, and rectal irritation by group and severity on Day 1 and Day 7

Cramping / Day 1	8/2/0/0	4/1/5/0	8/3/0/0	0.0127
Cramping / Day 7	4/0/0/1	3/2/0/0	8/2/0/0	0.3997
Flatus / Day 1	2/4/4/0	4/1/4/1	3/3/3/0	0.5155
Flatus / Day 7	1/2/2/0	3/1/0/1	6/2/1/1	0.3590
Rectal Irritation / Day 1	5/0/1/0	3/2/1/2	10/1/0/0	0.1847
Rectal Irritation / Day 7	3/0/0/0	6/0/1/0	9/1/0/0	0.4917

* Comparison between groups by Chi square

Data for changes in electrolyte levels are shown in Table 6. Blood was drawn in the morning before dosing, so that, for example, the data for Day 2 show changes after the first day of dosing. Data for sodium, phosphate, calcium, and potassium levels following the first and last treatment days are displayed. In this study, there were no notable changes in sodium or phosphate in any study group. On Day 2, there were significant differences in changes from baseline in serum calcium (with the greatest reductions in the NaP 8 tablets group) and in serum potassium (with the greatest reductions in the NaP 12 tablets group). There were no differences between the groups in changes in bicarbonate, chloride, magnesium, glucose, AST, ALT, creatinine, or BUN (data not shown).

Table 6 - Change from baseline in serum electrolytes on Day 2* and last treatment day

Parameter / Day	Treatment	Mean ± SD	p-value	Significance
Sodium / Day 2 (mEq/L)	NaP 8 Table (N=10)	1.30 ± 1.77	0.4513	—
	NaP 12 Table (N=10)	1.80 ± 1.43	—	—
	PEG 17 g (N=11)	0.85 ± 0.99	—	—
Sodium / Last Day	NaP 8 Table (N=10)	0.30 ± 2.79	0.9184	—
	NaP 12 Table (N=10)	0.40 ± 2.12	—	—
	PEG 17 g (N=10)	0.90 ± 3.85	—	—
Phosphate / Day 2 (mg/dL)	NaP 8 Table (N=10)	0.22 ± 0.91	0.7358	—
	NaP 12 Table (N=10)	0.35 ± 0.37	—	—
	PEG 17 g (N=11)	0.19 ± 0.56	—	—
Phosphate / Last Day	NaP 8 Table (N=10)	0.07 ± 0.88	0.8772	—
	NaP 12 Table (N=10)	0.09 ± 0.45	—	—
	PEG 17 g (N=10)	0.17 ± 0.40	—	—
Calcium / Day 2 (mg/dL)	NaP 8 Table (N=10)	-0.40 ± 0.37	0.0001	< 0.05
	NaP 12 Table (N=10)	-0.09 ± 0.20	—	< 0.05
	PEG 17 g (N=11)	0.19 ± 0.30	—	—
Calcium / Last Day	NaP 8 Table (N=10)	-0.18 ± 0.40	0.3619	—
	NaP 12 Table (N=10)	-0.17 ± 0.32	—	—
	PEG 17 g (N=10)	0.05 ± 0.45	—	—
Potassium / Day 2 (mEq/L)	NaP 8 Table (N=10)	-0.01 ± 0.34	0.0481	NS
	NaP 12 Table (N=10)	-0.26 ± 0.23	—	< 0.05
	PEG 17 g (N=11)	0.11 ± 0.39	—	—
Potassium / Last Day	NaP 8 Table (N=10)	-0.17 ± 0.29	0.0912	—
	NaP 12 Table (N=10)	-0.28 ± 0.27	—	—
	PEG 17 g (N=11)	0.02 ± 0.35	—	—

* Blood was drawn on Day 2 before dosing and reflects changes resulting from dosing on Day 1

† Last diary day during treatment with study drug

‡ p value for treatment effect from an analysis of variance (ANOVA)

CONCLUSIONS

NaP tablets, at an initial dose of either 8 or 12 tablets daily, provided significantly greater and more prompt laxative effects than PEG 17 g daily in healthy volunteers. All subjects taking NaP tablets required 1 or more dose reductions for excess laxative effects, vs. none in the PEG group. There were no dropouts for adverse events, but one subject taking PEG was lost to follow-up after reporting vomiting and abdominal pain on Day 2. The data suggested that laxative effects were accompanied by cramping and possibly rectal irritation in some subjects; these symptoms tended to resolve over time and did not lead to discontinuation. Other adverse events were infrequent, not medically important, and did not lead to discontinuation. On Day 2, there were significant differences in changes from baseline in serum calcium (with the greatest reductions in the NaP 8 tablets group) and in serum potassium (with the greatest reductions in the NaP 12 tablets group). By the last treatment day, the differences were no longer significant. NaP tablets, like the widely used NaP solution, appears to be a safe and effective laxative. Additional studies in various populations of constipated patients are warranted.

ABSTRACT

Purpose: This study was intended to assess the safety and laxative effects of one week of therapy with sodium phosphate (NaP) tablets. Miralax (polyethylene glycol (PEG)) was used as a comparator.

Methods: After a 7 day screening period, 31 healthy volunteers were randomized to receive either 8 NaP tablets (1.5 g/tablet), 12 NaP tablets daily, or PEG 17 g (the dose recommended for constipation). Study drugs were given each morning for 7 days. NaP tablets were taken 4 at a time every 15 minutes with 8 oz of any beverage. PEG was dissolved in 8 oz water. Subjects ate their usual diets. Laxatives other than stable doses of fiber supplements were prohibited. Patients kept a diary of their bowel movements (time, consistency and ease of passage of each BM) and GI symptoms (cramps, flatus, and rectal irritation). Subjects who met defined criteria for excess laxative effects had mandatory reductions in their dose of study drug. Serum electrolytes (Na, K, Cl, HCO₃, Ca, P, Mg) were measured at baseline and 4 times during treatment.

Results: Each dose level of NaP was associated with a significantly greater increase in mean daily bowel movements than Miralax after one day of dosing and after the last dosing day for each patient (Table 1). Changes in the stool consistency score were significantly greater with NaP after the first and last dosing day. Every subject randomized to either NaP dose required at least one dose reduction, compared to none of the subjects taking PEG ($p < 0.01$). The time to the first soft or liquid BM was significantly shorter with NaP than with PEG. No subject was discontinued for an adverse event, but one subject in the PEG group was lost to follow-up after vomiting on the second day of dosing. Changes from baseline in electrolytes did not differ significantly among the treatment groups following completion of dosing.

Conclusion: NaP tablets taken for one week were well tolerated by volunteers, and produced significantly greater and more prompt laxative effects than PEG. Changes from baseline in electrolytes did not differ significantly among the treatment groups at the end of dosing. NaP tablets show promise as a treatment for constipation, and further studies in patients with constipation are planned.

Disclosure: This presentation will include discussion of commercial products or services.

Dr. Rose is an employee, corporate officer, and shareholder of InKine Pharmaceutical Co., Inc., the manufacturer of Visicol Tablets (sodium phosphate).

The study and travel arrangements for Dr. Rose were supported by InKine Pharmaceutical Co., Inc.

Background: Sodium phosphate solution has been marketed in the US as a laxative for over one hundred years. In 2000, InKine Pharmaceutical Co. obtained US approval of Visicol Tablets (1.102 g of sodium phosphate monobasic monohydrate, USP and 0.398 g of sodium phosphate dibasic anhydrous, USP, total of 1.5 g NaP), the first tablet purgative, for use in cleansing of the bowel prior to colonoscopy in adults. The approved dose for colon cleansing is 40 tablets (60 g). After approval, the company began to receive anecdotal reports of successful use of Visicol in the treatment of constipation, including patients with severely compromised gut motility secondary to such conditions as spinal stenosis and multiple sclerosis. As an initial study in a possible constipation program, we undertook a randomized, open study in healthy volunteers comparing the safety and laxative effects of two doses of Visicol tablets with those of Miralax (polyethylene glycol, PEG 3500) solution, the leading prescription laxative.

Methods: Thirty healthy volunteers (10/group) were intended to be randomized into one of three treatment groups. Subjects were men or non-pregnant, non-lactating women over the age of 18 who could swallow tablets, communicate with study staff, and gave informed consent. Major exclusion criteria included serum creatinine >2.0 mg/dL, clinically significant abnormalities, CHF, unstable angina pectoris, chronic constipation, or multiple loose stools or severe cramping during the screening period.

Subjects completed a one week screening and baseline period during which they kept a bowel movement diary (see below). Screening procedures included a chemistry panel, serum magnesium, ECG, and pregnancy test for women of child bearing potential.

Treatments: Subjects were randomized to one of three treatment groups: NaP 8 tablets (12 g) daily, NaP 12 tablets (18 g) daily, taken as 4 tablets every 15 minutes with 8 oz of any non-alcoholic beverage in the morning. Subjects taking PEG were instructed to stir one dispenser (17 g, about a heaping tablespoon) of PEG granules into 8 oz of any non-alcoholic beverage, stir, and drink. Study drugs were taken for 7 days. Treatment was open label.

Subjects taking NaP tablets had mandatory dose reductions for excessive laxative effect if they had any one of the following complaints or diary entries: Two stools rated as "loose" on any single day; any stool rated as "watery"; or two days of cramping rated as "moderate" or one day of cramping rated as "severe".

In the event of dose reduction, the daily dose of NaP Tablets was reduced by 4 tablets (from 12 to 8 or from 8 to 4). Subjects could have one or more subsequent dose reductions if they had qualifying symptoms again after a previous dose reduction (i.e., first, from 12 to 8 tablets and then from 8 to 4 tablets). Subjects taking 4 NaP Tablets daily who qualified for a dose reduction had their dose reduced to zero tablets but continued to be followed in the study. Any patient taking PEG who met the criteria for a dose reduction was to have their dose reduced to zero but continued to be followed in the study.

Subject Diary: During the screening/baseline and treatment periods, subjects kept a daily diary of bowel habits and GI symptoms. For each bowel movement, the following information was recorded: time of day; stool consistency on a scale from 1 to 5 (hard to watery); and difficulty of passage was rated on a scale from 1 to 5 (strain to very urgent). Subjects also recorded information on 3 GI symptoms commonly associated with laxative use: cramping, rectal irritation, and flatus. Patients recorded each symptom as absent ("none") or recorded the most severe symptom of the day as mild, moderate, or severe.

Patient Follow-up and Safety Information: After the screening/baseline period, subjects were seen on dosing days 1 (the first day of dosing), 2, 4, 6, and 8. The last dose of study drug was given on the morning of dosing day 7. At each visit (except on day 1, just before dosing), diary data were collected, subjects were queried about adverse events, and a blood chemistry panel was drawn (sodium, chloride, bicarbonate, potassium, calcium, inorganic phosphorous, BUN, creatinine, alkaline phosphatase, ALT, AST and glucose). In addition, serum magnesium was drawn at baseline and on the day following the last treatment day.

Endpoints and statistical analyses: The primary endpoint was the mean change in the mean number of stools per day from baseline. Other efficacy analyses included the number of patients needing a dose reduction, changes from baseline in stool consistency and ease of passage, the time to the first bowel movement or first watery or loose bowel movement.

RESULTS

Baseline information: Summary statistics for the demographics of the study groups are displayed in Table 1. No statistical comparisons were performed on demographic parameters. Age, gender, and height were very similar between the study groups. Females predominated in all 3 treatment groups. The NaP 12 tablet group had comparatively more African

Americans than the other two groups, while the NaP 8 tablet had somewhat heavier subjects. Summary statistics for baseline stool habits are played in Table 2. There were no significant differences in mean number of stools/day, stool consistency, or stool ease of passage among the treatment groups. Electrolyte levels at baseline were similar in the treatment groups (data not shown).

Table 1 - Demographic Information by Treatment

Treatment	Number of Subjects	Age (yr) Mean ± SD (Range)	Height (in) Mean ± SD (Range)	Weight (lb) Mean ± SD (Range)	Gender		Ethnicity	
					Male N (%)	Female N (%)	Caucasian N (%)	African American N (%)
NaP 8 Tabs	10	28 (21-48)	68.5 ± 4.06	160 ± 55.1	3 (30.0)	7 (70.0)	7 (70.0)	3 (30.0)
NaP 12 Tabs	10	28 (20-43)	67.2 ± 3.77	161 ± 41.3	2 (20.0)	8 (80.0)	3 (30.0)	7 (70.0)
PEG 17 g	11	27 (20-47)	67.3 ± 3.47	168 ± 61.5	3 (27.3)	8 (72.7)	8 (72.7)	3 (27.3)

Table 2 - Summary Statistics for Baseline Efficacy Parameters by Treatment

Treatment	N	Mean ± SD	p-value
Stools/day			
NaP 8 Tabs	10	1.63 ± 0.70	0.2018
NaP 12 Tabs	10	1.11 ± 0.48	
PEG 17 g	11	1.55 ± 0.79	
Consistency			
NaP 8 Tabs	10	2.42 ± 0.28	0.7709
NaP 12 Tabs	10	2.47 ± 0.57	
PEG 17 g	11	2.56 ± 0.43	
Ease of Passage			
NaP 8 Tabs	10	2.74 ± 0.81	0.8630
NaP 12 Tabs	10	2.73 ± 0.38	
PEG 17 g	11	2.75 ± 0.41	

^a Mean over 7-day screening period

^b p-value for treatment effect from an analysis of variance

Subject Disposition and Dosing: Ten subjects were initially randomized each study group; one subject who was lost to follow-up in the PEG group was replaced. Table 3 shows subject disposition data along with information on dose reductions for excess laxative effects. The proportion of completing subjects requiring dose reduction in each of the 2 NaP groups (10 of 10 in each group) was significantly greater than in the PEG group (0 of 10, p=<0.011 for each comparison).

Table 3 - Subject Disposition by Treatment

	NaP 8 Tablets	NaP 12 Tablets	PEG 17 g
Number randomized	10	10	11
Completed	0	0	1
Lost to follow-up	10	10	10
Completed with dose reduction	4	10	0
Completed without dose reduction	6	5	0
Completed with dose reduction	7	9	0
Completed without dose reduction	6	3	0
Completed with dose reduction	4	7	10

^a Lost to follow-up after reporting vomiting on treatment Day 2

^b Per protocol; subjects could have had the following number of dose reductions if they met the relevant criteria: NaP 8 tablet group - 2; NaP 12 tablet group - 3; PEG 17 g group - 1

^c With or without dose reduction(s).

Laxative Effects: Table 4 displays summary changes from baseline by group in the number of stools/day, stool consistency, and stool ease of passage on Day 1 and the last diary day during dosing with study drug (a dose > 0) for each patient. Patients taking either dose of NaP tablets marked changes in stool count, stool consistency, and ease of passage, in the direction of laxation, while patients in the PEG group had little, if any, change in laxation. The difference between both NaP groups and the PEG group were statistically significant on Day 1. On the last day of treatment (after 1 or more dose reductions for each patient taking NaP, differences between the groups were somewhat reduced, but still significant for most parameters. There appeared to be dose response between 8 and 12 NaP tablets daily, especially on Day 1. Data for the other treatment days were consistent with the ones displayed in Table 4 (data not shown).

Table 4 - Change from baseline in efficacy parameters on Day 1 and last treatment day

Parameter	Treatment	Mean ± SD	p-value	p-value
Stools/day (Day 1)	NaP 8 Tabs (N=10)	1.97 ± 1.53	0.0002	<0.05
	NaP 12 Tabs (N=10)	2.29 ± 2.40		<0.05
	PEG 17 g (N=11)	-0.18 ± 0.68		--
Stool consistency (Day 1)	NaP 8 Tabs (N=10)	1.15 ± 0.76	0.0004	<0.05
	NaP 12 Tabs (N=10)	1.56 ± 0.96		<0.05
	PEG 17 g (N=11)	0.13 ± 0.44		--
Ease of passage (Day 1)	NaP 8 Tabs (N=10)	1.36 ± 1.02	<0.0001	<0.05
	NaP 12 Tabs (N=10)	2.19 ± 0.62		<0.05
	PEG 17 g (N=11)	0.15 ± 0.48		--
Stools/day (Last Day)	NaP 8 Tabs (N=10)	1.18 ± 0.53	<0.0001	<0.05
	NaP 12 Tabs (N=10)	1.52 ± 0.72		<0.05
	PEG 17 g (N=11)	0.29 ± 0.31		--
Ease of passage (Last Day)	NaP 8 Tabs (N=10)	0.68 ± 0.77	0.0202	<0.05
	NaP 12 Tabs (N=10)	0.91 ± 0.74		<0.05
	PEG 17 g (N=11)	-0.16 ± 0.87		--
Ease of passage (Last Day)	NaP 8 Tabs (N=10)	0.54 ± 0.52	0.0257	NS
	NaP 12 Tabs (N=10)	0.63 ± 0.65		<0.05
	PEG 17 g (N=11)	0.12 ± 0.54		--

^a Last diary day during treatment with study drug

^b p-value for treatment effect from an analysis of variance