THE TIME COURSE AND EFFECT ON SERUM ELECTROLYTES OF ORAL SODIUM PHOSPHATES SOLUTION IN HEALTHY MALE AND FEMALE VOLUNTEERS

Michael Caswell[1], William O Thompson[2], Joseph A Kanapka[1], Deborah JB Galt[1]

[1]C.B. Fleet Company, Inc., [2]Department of Biostatistics, Medical College of Georgia, USA

Corresponding Author: caswellm@cbfleet.com

_____

ABSTRACT

Background
Although oral sodium phosphates solution is used extensively for bowel preparation, the pharmacokinetic profile of 2 x 45 mL oral sodium phosphates solution has not been reported.

Objectives
The primary objective of this study was to evaluate the time course and degree of electrolyte shifts in two age groups and two gender groups following administration of oral sodium phosphates solution. Secondary objectives included evaluation of electrocardiograms, postural blood pressure, standard serum chemistry and hematology panels, and adverse experiences.

Methods
Twenty-four healthy adult volunteers were divided equally into groups based on age and gender. Each received 2×45 mL oral sodium phosphates solution at 7:00pm (hour 0) and at 7:00am (hour 12). Serum electrolytes were measured at sixteen different time points.

Results
Mean serum phosphate concentrations exceeded the upper normal limit within 1 hour following the first dose, peaking at 3 hours (6.26 mg/dL; $p < 0.0001$) before decreasing. Following the second dose at 12 hours, mean serum phosphate concentrations peaked at 14 hours (6.86 mg/dL; $p < 0.0001$), before decreasing to normal limits by hour 24. Mean serum sodium, potassium, and calcium concentrations fluctuated within the normal range. However, serum sodium concentrations peaked at 1 hour following the second dose of phosphate, showing a statistically significant ($p < 0.0001$) increase of 2.4% from baseline to 144.8 mmol/L. No clinically significant changes in ECG were observed. Mean reductions in supine and standing systolic blood pressure were not associated with postural change. No subject had postural decreases in systolic blood pressure of greater than 20 mmHg.

Conclusions
Administration of 2 x 45 mL oral sodium phosphates solution 12 hours apart with proper hydration caused transient serum electrolyte shifts, which were clinically insignificant and resolved within 24 hours.

Key Words: *Age, oral sodium phosphates solution, electrolytes, Phospho-soda*®

_____

Oral sodium phosphates solution (NaP; Phospho-soda®) has been sold in the United States since 1893 by C.B. Fleet Company, Inc., Lynchburg, VA, and in Canada since 1987. Since 1975, oral sodium phosphates solution has been included in the FDA's Tentative Final Monograph[1] on laxatives. It is currently tentatively recognized as safe and effective by the FDA, as an over-the-counter (OTC) laxative for the treatment of constipation at doses not to exceed 45 mL in a 24-hour period, and as an ingredient for bowel cleansing prior to medical

procedures. While Carrera[2] describes the transient hyperphosphatemia following a single 45-mL dose of NaP as a potential complication in serum phosphate analysis, formal pharmacokinetics was not conducted on the one-dose regimen for laxation.

Since the report by Vanner *et al.*, in 1990[3], physicians have used a NaP regimen of two 45-mL doses 5 to 12 hours apart as part of a bowel cleansing regimen in preparing the colon for surgery, X-ray, or endoscopic examination.[3-15] While electrolyte shifts have been described[15-21], formal pharmacokinetics have not been reported on the two-dose regimen for bowel preparation.

Because pharmacokinetic studies have not been reported on this OTC drug, this study was conducted to further evaluate the time course and magnitude of serum electrolyte shifts following administration of a 2 x 45-mL regimen of NaP; although, these data also provide pharmacokinetic information following a single 45-mL dose of NaP. Colonoscopy is normally recommended beginning at age 50, so this study examined electrolyte shifts in two groups, young males and females, aged 30-64, and elderly males and females, over age 64.

METHODS

This was an open-label study employing a single-treatment design in healthy male and female volunteers. Twenty-four subjects participated in this trial: six men and six women who were between 30 and 64 years of age; and six men and six women who were 65 years of age or older. Exclusion criteria included an abnormal 12-lead electrocardiogram upon screening, abnormal screening laboratory values, uncontrolled hypertension, known or suspected congestive heart failure, recent (within 6 months) myocardial infarction, known or suspected renal or hepatic insufficiency, unstable angina pectoris, clinical evidence of dehydration, or an inability to maintain adequate hydration. Female subjects had to have a negative urine pregnancy test, and each subject had screening for illicit drugs. Calcium or potassium supplements as well as phosphate-containing compounds or drugs that alter calcium, phosphate, or potassium serum concentrations were also discontinued beginning one week prior to, and continuing through, the study period.

STUDY DESIGN

Four subject groups were recruited by age and gender: 6 males age 30-64 years (YM); 6 males age ≥ 65 years (EM); 6 females age 30-64 years (YF); and 6 females age ≥ 65 years (EF).

Study medications were administered in a fashion that replicates the bowel cleansing procedure commonly used prior to colonoscopy starting with a clear liquids diet at hour 11 (8:00am) and continuing through to hour 12. The first dose of NaP was taken in the evening at hour 0 (7:00pm) and the second dose was taken the following morning at hour 12 (7:00am). Each 45-mL dose was diluted with 120 mL of cold clear liquid and followed by one large glass of clear liquid (360 mL). To assure adequate hydration, each sequestered subject was requested to drink additional clear liquids *ad libitum* throughout the evening with a minimum of three additional large glasses (3×360 mL for a total of 1605 mL in the evening). For their morning dose, the subjects were recommended to dilute 45 mL of OSPS into 120 mL of cold clear liquid and follow that with one large glass of clear liquid (360 mL). Each subject was recommended to then drink a minimum of three additional large glasses (3 x 360 mL for a total of 1605 in the morning). The total liquid requested for entire preparation regimen was ≥ 3210 mL. The mean (± SD) reported quantity of liquid consumed was 4175 (± 579) mL. Table 1 lists the schedule of treatment and the assessments made throughout the treatment period. All subjects were included in the data analysis. Safety was assessed through adverse event reports (only one), body weight changes, vital signs (including postural changes), electrocardiogram changes, and clinical laboratory tests including serum chemistry panels, serum electrolyte panels, serum haematology panels, and urinalysis. Blood pressure and pulse were measured with the study participant in both the supine (after resting for 5 minutes) and standing (after standing for 1 minute) positions. A standard 12-lead electrocardiogram and routine vital signs (including pulse, respiration, blood pressure, and temperature) were obtained during screening, at baseline (hour 0), and periodically throughout the study. The serum chemistry panel included evaluations for sodium, potassium, magnesium, calcium, phosphorus, chloride, carbon dioxide,

creatinine, BUN, total protein, albumin, total bilirubin, AST, ALT alkaline phosphatase, LDH, and glucose. A serum electrolyte panel was obtained at times independent from the chemistry panel and consisted of sodium, potassium, magnesium, calcium, and phosphorus. The haematology panel included: haemoglobin, haematocrit, RBC, WBC, platelets, and a WBC differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils). Urinalysis was conducted at screening and at hour 84 and included pH, specific gravity, protein, glucose, ketones, urobilinogen, and blood. Corning Clinical laboratories (Quest Diagnostics), 1300 E.

Newport Center Drive, Deerfield Beach, FL 33442, conducted the serum chemistry panel, the serum electrolyte panel, the haematology panel, and the urinalysis. The urinalysis was by dipstick, so the results are qualitative only. All subjects stayed at the study centre from hours 1 through 36, and then returned to the clinic for evaluations at hours 60 and 84.

The study design was reviewed and approved by the Southern Institutional Review Board, Inc., (Miami, FL), and each subject signed an approved Informed Consent form prior to enrolment in the study.

TABLE 1   Schedule of Treatments and Assessments

	Screen	Hours When Procedures Were Performed				
Study Medication		0	12			
Assessment of AEs	X	X	X	X	X	X
Body Weight	X	0	12, 16	36	60	84
Electrocardiogram		0, 1, 2, 4	13, 14, 16, 24	36	60	84
Hematology Panel	X					84
Physical Examination	X					X
Serum Chemistry Panel[‡]		0, 3	12, 15, 24	36	60	84
Serum Electrolytes[§]	X	1, 2, 4, 6	13, 14, 16, 18			
Total Liquid Intake		X	X			
Urinalysis	X					X
Vital Signs[†]	X	0, 4	12, 16, 24	36	60	84

[†] Measurement of supine and standing blood pressure and pulse.
[‡] Serum chemistry panel comprises all of the following: serum electrolyte panel, chloride, carbon dioxide, BUN, creatinine, phosphorus, total protein, albumin, total bilirubin, SGOT, SGPT, ALP, LDH, and glucose.
[§] Times listed pertain to gathering just the serum electrolyte panel data, which was a subset of the chemistry panel.

Statistical Methods

All statistical analyses were performed using SAS® (SAS Institute Inc., Cary, NC). Summary tables and data listings were prepared using SAS. Results were considered statistically significant when the statistical test yielded a two-tailed probability of 0.05 or less, and 0.10 for tests of interaction. The concentrations of serum sodium, phosphate, calcium, potassium, and magnesium were measured at baseline (hour 0) and selected

times thereafter. The one adverse experience (AE) was tabulated. Electrocardiographic (ECG) intervals were measured and analyzed over time against values obtained at baseline (hour 0). Correlations between shifts in serum potassium and serum calcium concentrations and changes in ST segment displacement, QTc interval, and T wave amplitude were examined. All clinical laboratory and vital sign measurements were

summarized by mean values for each of the four groups. The influence of body weight and liquid intake was explored with respect to clinical laboratory tests and vital signs. Clinically significant postural changes in blood pressure, defined as a systolic blood pressure decrease from baseline ≥ 20 mmHg or a diastolic blood pressure decrease from baseline ≥ 10 mmHg upon standing, were tabulated.

TABLE 2 Mean Weight and Body Mass Index

Mean Weight	Male (young)	Male (older)	Female (young)	Female (older)
Kg (SD)	79.2 (6.6)	70.8 (12.9)	70.8 (10.6)	73.6 (4.9)
BMI (SD)	26.4 (2.7)	26.4 (4.0)	27.9 (2.9)	28.0 (2.4)

RESULTS

The study groups were well matched for height and weight (Table 2). The mean age (min, max) for each of the four groups was as follows: YM (44.2; 34, 55); EM (74.5; 71, 79); YF (44.7; 31, 64); and EF (67.5; 65, 71).

The clinical effectiveness of bowel cleansing was not evaluated in this study, although the onset and duration of bowel evacuation was recorded. The median time to onset of bowel evacuation was 56 minutes (min: 30 minutes, max: 228 minutes) following administration of the first dose, and 38 minutes (min: 4 minutes, max: 125 minutes) following administration of the second dose. The median time from the first bowel evacuation to the last bowel evacuation was 383 minutes and 496 minutes for the first and second doses, respectively. Only one of the 24 subjects reported an adverse event (pharyngitis with lymph node enlargement that was mild in intensity), and the relationship to the study medication was listed as "unlikely" by the investigator. None of the subjects discontinued, reduced or interrupted their dosage.

Serum Phosphate and Sodium Concentrations
Serum phosphate concentrations rose and fell after each dose of NaP (Table 3). The mean serum phosphate concentration for all subjects peaked at 6.26 mg/dL at hour 3, decreased to 4.70 mg/dL just prior to the second dose (hour 12), and peaked again at 6.86 mg/dL at hour 14. The mean shift from baseline corresponding to the peak results were +2.93 and +3.53 mg/dL following the first and second doses, respectively. The mean serum phosphate concentration returned to normal limits by hour 24, and returned to baseline by hour 36. Twenty-three subjects (96%) had one or more values of serum phosphate concentration above the normal limit of 4.5 mg/dL following the first dose, and all 24 subjects (100%) had one or more values above the normal limit following the second dose. The highest recorded serum phosphate concentration after the first dose was 7.8 mg/dL (68 year-old female), and the highest recorded serum phosphate concentration after the second dose was 8.9 mg/dL (74 year-old male). By hour 36, all serum phosphate concentrations had returned to normal.
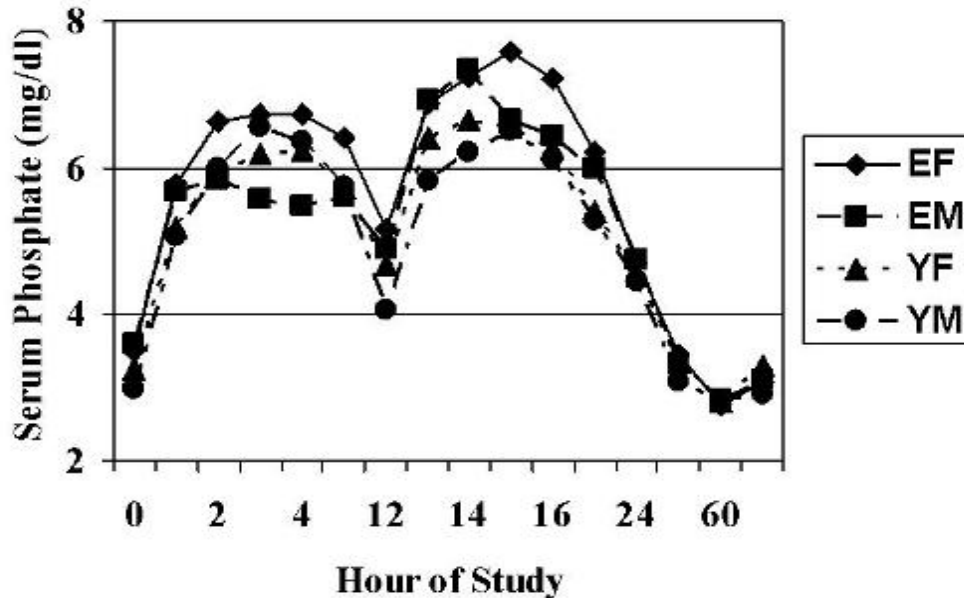
The time-course of mean serum phosphate concentration for each age-gender subgroup is shown in Figure 1. While there did not appear to be any clear age or gender-related differences, serum phosphate levels peaked slightly higher in the elderly female subgroup following the second NaP dose.

TABLE 3 Mean Serum Electrolyte Concentrations (standard deviation) and Statistical Significance from Baseline

	Phosphate mg/dL	Calcium mg/dL	Sodium mmol/L	Potassium mmol/L	Magnesium mg/dL
Normal Range	2.4 - 4.9	8.5 - 10.5	134 - 147	3.5 - 5.5	1.3 - 2.3
0 hr	3.33 (0.48)	8.98 (0.25)	141.4 (2.4)	4.43 (0.37)	1.87 (0.13)
1 hr	5.43 (0.84)***	9.07 (0.36)	144.4 (2.0)***	4.23 (0.42)*	2.01 (0.17)***
2 hr	6.10 (0.87)***	8.91 (0.24)	144.4 (1.6)***	4.20 (0.33)*	1.90 (0.14)
3 hr	6.26 (0.81)***	8.88 (0.27)	143.7 (2.2)***	4.35 (0.41)	1.88 (0.18)
4 hr	6.20 (0.83)***	8.79 (0.30)	142.7 (2.3)**	4.26 (0.37)	1.83 (0.20)
6 hr	5.88 (0.72)***	8.70 (0.33)**	142.2 (1.9)*	4.37 (0.33)	1.85 (0.14)
12 hr	4.70 (0.66)***	8.88 (0.29)*	142.1 (1.8)*	4.25 (0.31)*	1.85 (0.19)
13 hr	6.51 (0.91)***	9.22 (0.31)*	144.8 (1.9)***	4.25 (0.37)	1.94 (0.14)*
14 hr	6.86 (0.98)***	9.08 (0.33)	144.7 (2.4)***	4.30 (0.50)	1.88 (0.13)
15 hr	6.83 (0.89)***	8.96 (0.28)	143.8 (2.2)***	4.36 (0.39)	1.93 (0.17)*
16 hr	6.50 (0.88)***	8.85 (0.29)*	143.2 (2.1)*	4.38 (0.30)	1.90 (0.17)
18 hr	5.73 (0.68)***	8.70 (0.31)***	143.7 (2.2)***	3.99 (0.33)***	1.86 (0.20)
24 hr	4.60 (0.57)***	9.03 (0.38)	142.8 (2.0)**	4.43 (0.28)	1.91 (0.18)
36 hr	3.31 (0.39)	9.12 (0.30)*	141.5 (1.7)	4.47 (0.35)	1.92 (0.18)
60 hr	2.81 (0.34)***	9.28 (0.36)**	141.2 (1.9)	4.59 (0.29)	1.83 (0.17)
84 hr	3.09 (0.41)*	9.42 (0.35)***	140.7 (1.5)*	1.87 (0.13)***	1.86 (0.20)

* <0.05 - ≥ 0.001; ** <0.001 - ≥ 0.0001; *** <0.0001

FIG. 1 Mean serum phosphate concentrations versus time in elderly females (EF), elderly males (EM), young females (YF), and young males (YM). Serum phosphate levels peak slightly higher in the elderly female subgroup following the second NaP dose.
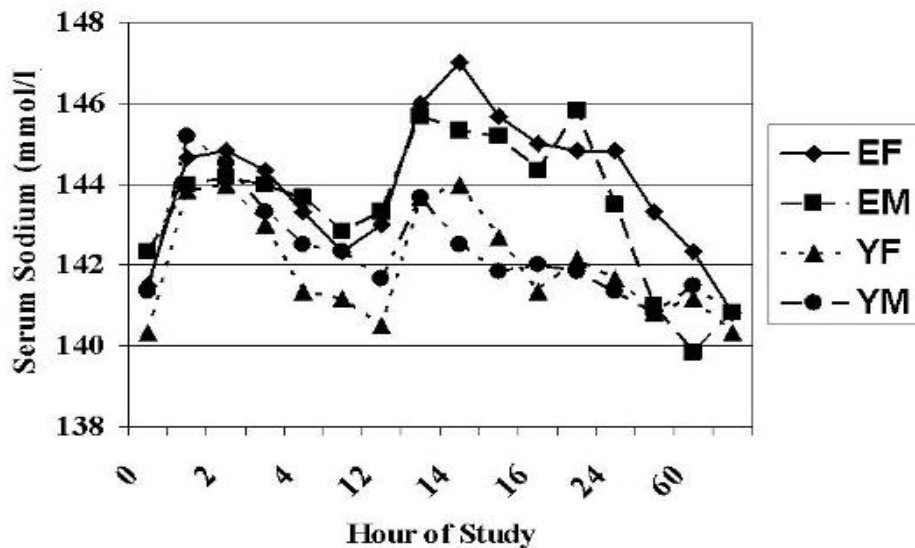

Mean serum sodium and phosphate concentrations followed the same time course, but the magnitude of shift was much smaller for serum sodium and the mean concentrations remained within the normal individual range at all time points.

The mean serum sodium concentration for all subjects rose from 141.4 mmol/L at baseline, peaked at 144.8 mmol/L at one hour following the second dose (hour 13), and returned to baseline by hour 36 (Figure 2). Mean serum sodium levels peaked slightly higher in the elderly subgroups (146.2 mg/dL) following the second dose of NaP, but this mean was still within the normal individual range.

Mean serum sodium concentrations were highest in the 13th and 14th hours for both the elderly and young groups, and both means were significantly different from their respective baseline means. However, the change in mean serum sodium concentration for the young group was 2 mmol/L less than the change in the elderly group.

Four subjects (17%) had one or more serum sodium values above the upper normal limit of 147 mmol/L. In three cases, this was a single, isolated observation. In all cases, the maximum values did not exceed 149 mmol/L. There were no instances of hyponatremia.

FIG. 2 Mean serum sodium concentrations versus time in elderly females (EF), elderly males (EM), young females (YF), and young males (YM). Serum sodium levels peak slightly higher in the elderly female and elderly male subgroups following the second NaP dose.

Serum Calcium, Potassium and Magnesium Concentrations

Serum concentrations of calcium, potassium and magnesium demonstrated a predictable inverse relationship with serum sodium and phosphate concentrations. All study subgroups followed the same inverse relationship with no clear age- or gender-related differences.

Mean serum calcium values declined briefly after each dose of NaP, as expected, reaching a nadir of 8.7 mg/dL six hours after each of the two doses at hour 6 ($p = 0.0003$) and hour 18 ($p < 0.0001$), with an average decline of -0.28 mg/dL. The mean serum calcium values then returned to pre-dose levels by hour 24, and then were slightly higher than pretreatment levels at hours 36, 60 and 84. The lack of parallel movement of the means at each time point from the four age groups (EM, EF, YM, and YF) does not have a ready explanation (Figure 3), as elderly males responded differently from elderly females. The data indicate that elderly males had lower mean serum levels of calcium than elderly females. Seven subjects (29%) had serum calcium values below the normal lower limit of 8.5 mg/dL on one or more occasions, with six subjects (25%) having one or more low serum calcium values following the first dose, and 4 subjects (17%) having one or more low serum calcium values following the second dose (67 year-old female, 39 year-old female, 37 year-old female, 75 year-old male, and 67 year-old female). The lowest observed serum calcium concentration reported was 8.0 mg/dL on a single, isolated occasion (67 year-old female, hour 18); no other subject exhibited serum calcium concentrations of < 8.2 mg/dL. There were no instances of clinically significant or symptomatic hypocalcaemia, and no instances of hypocalcaemia were observed at or beyond hour 48.

FIG. 3 Mean serum calcium concentrations versus time in elderly females (EF), elderly males (EM), young females (YF), and young males (YM). Serum calcium levels fluctuated inversely to serum phosphate concentrations.
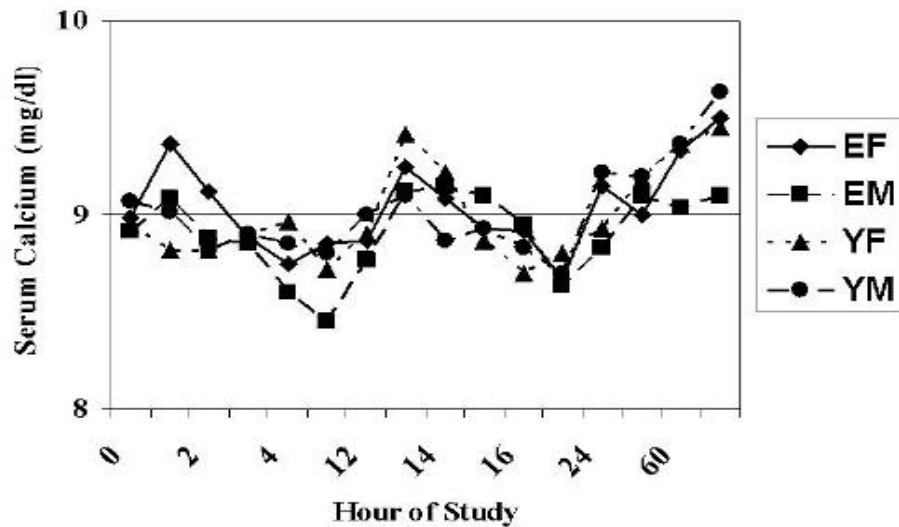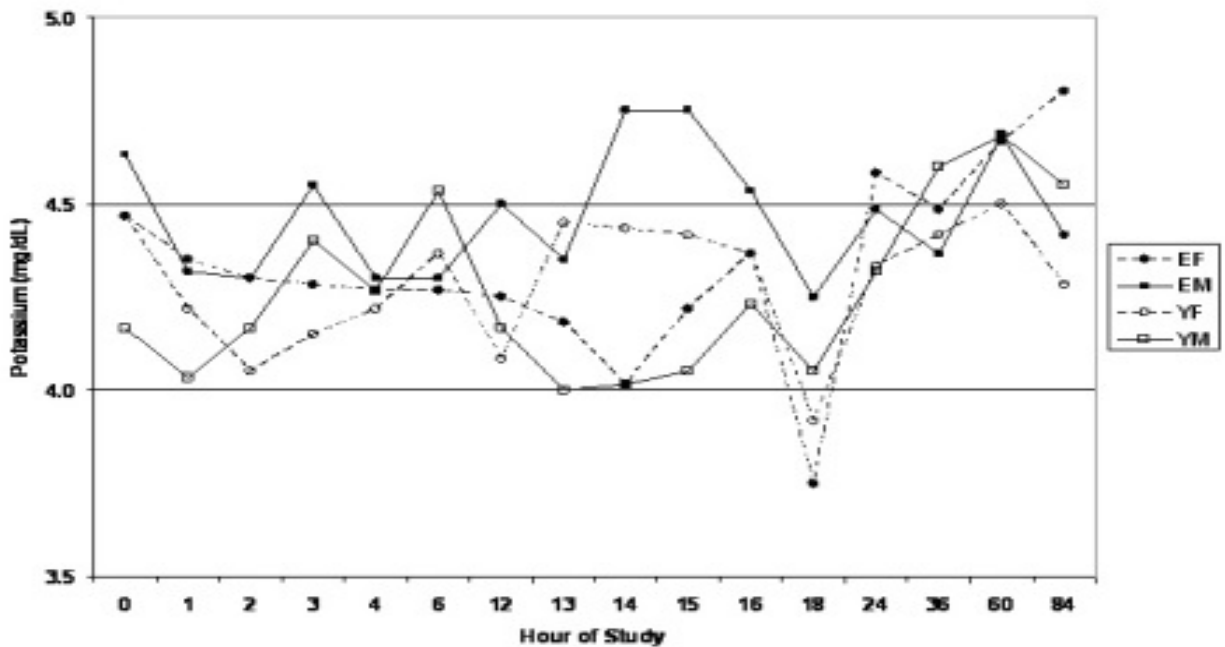

FIG. 4 Mean serum potassium concentrations versus time in elderly females (EF), elderly males (EM), young females (YF), and young males (YM).

Can J Clin Pharmacol Vol 14 (3) Fall 2007:e260-e274; November 1, 2007

Mean serum potassium concentrations fell slightly and transiently after each dose of NaP (Figure 4) except for YF. Following administration of the first dose, mean serum potassium concentration for all subjects reached a nadir of 4.2 mmol/L at two hours (mean shift:-0.23 mmol/L), but quickly returned to values within the range of baseline variability. A second nadir of 3.99 mmol/L (mean shift: -0.44 mmol/L) was reached six hours after administration of the second dose at hour 18, and then returned to baseline by hour 24. There was one report (4%) of hypokalemia, and one report of hyperkalemia (4%). The single incidence of hypokalemia (55 year-old male) recorded a serum potassium level of 3.4 mmol/L one hour after administration of the second NaP dose, at hour 13, although the preceding and subsequent values at hours 12 and 14 were each 3.8 mmol/L. The hyperkalemia report (71 year-old male) recorded a serum potassium level of 6.1 mmol/L two hours after the second dose, at hour 14, although the levels at hours 13 and 15 were each 4.8 mmol/L.

There was a transient increase above baseline level in mean serum magnesium concentration shortly after each dose administration (Figure 5). Three subjects (13%) had isolated elevations within normal limits in serum magnesium concentration (36 year-old male, 34 year-old male, and 67 year-old female); however, these transient shifts showed no consistent pattern. There were no instances of hypomagnesaemia. No significant shifts in other serum electrolyte concentrations, including chloride, were found.

FIG. 5 Mean serum magnesium concentrations versus time in elderly females (EF), elderly males (EM), young females (YF) and young males (YM). The mean serum magnesium concentration remains constant.
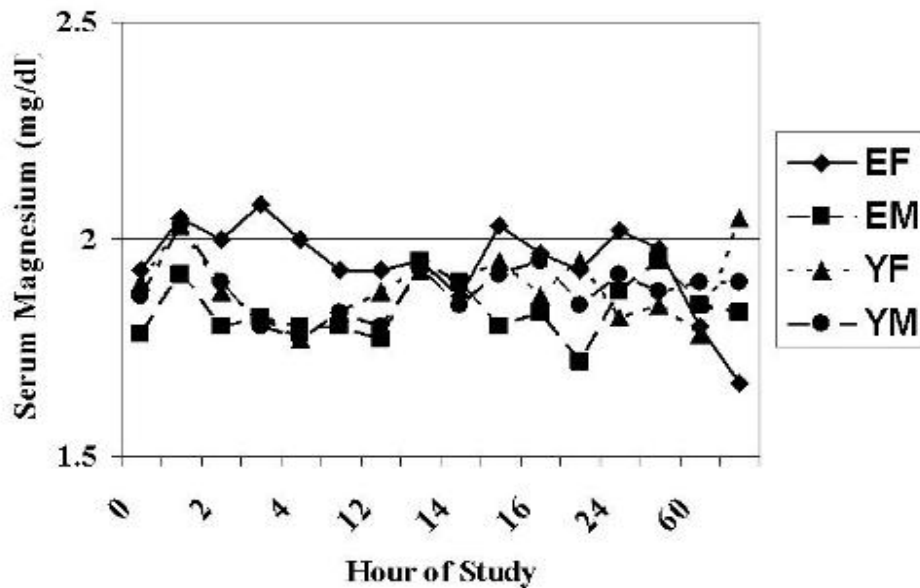
Electrocardiogram (ECG)

A 12-lead ECG was performed at screening, just prior to administration of the first dose at hour 0, after administration of the first dose at hours 1, 2, and 4, and then after administration of the second dose at hours 13, 14, 16, 24, 36, 60, and 84. The relationship between the primary serum electrolyte concentrations and ECG intervals, T wave amplitude, and ST segment displacement was statistically explored. The normal range for QTc was defined as 375 msec to 450 msec; the mean for the subjects in this study was 402 ± 20 msec at hour 0 (baseline). The mean QTc interval transiently increased 7.1 msec at hour 2 ($p = 0.11$) to 409 msec. Following the second dose, the mean QTc interval increased 11.3 msec ($p = 0.0073$) to 413 msec at hour 13 and to 412 msec ($p = 0.018$) at hour 14. Elderly males had lower QTc means, and with less change over time than elderly females, young males, or young females (Figure 6). The highest value observed in an individual subject was 475 msec (68 year-old female, hour 13), which is below the level (480 msec) that would classify this occurrence as an adverse event.[22] The ECGs were read by Dr. Arthur J. Moss, Director, Heart Research Follow-up Program, University of Rochester Medical Center, Rochester, NY, who concluded that "The change in QTc values were inversely related to the shift in serum potassium concentration, but the association was weak and not significant. There were no QTc outliers above 500 msec, and thus no real concern." (Letter on file, C.B. Fleet Company, Inc.).

FIG. 6 Mean change from baseline in QTc interval (msec) versus time in elderly females (EF), elderly males (EM), young females (YF), and young males (YM). The mean QTc interval remains constant.

Can J Clin Pharmacol Vol 14 (3) Fall 2007:e260-e274; November 1, 2007
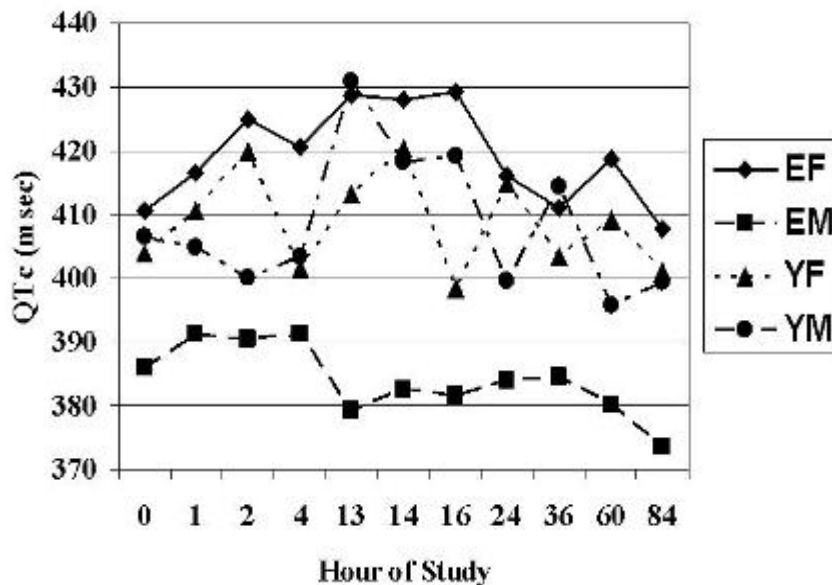
During the time interval between administration of the first dose until hour 36, fluctuation in the QTc interval generally demonstrated a positive relationship to serum calcium concentration and a negative relationship to serum potassium concentration. These findings were not unexpected, but the relationships were weak and in the case of serum calcium concentration this relationship reversed direction at hour 24. The correlation over the entire time course was not significant ($p = 0.14$ for calcium, and $p = 0.19$ for potassium).

Liquid Intake and Blood Pressure

There were no specific recommendations for clear liquid intake during the pre- and post-prep periods (other than *ad libitum* intake). Subjects were to have received a total liquid intake of approximately 3,120 mL during the preparation between hours 0 and 12 (120 mL for dilution plus 360 mL clear liquid for each dose), plus an additional three large glasses (~360 mL each) of clear liquid following each dose. Short-term shifts in body weight were examined for indirect evidence of a net fluid loss over the 84 hours.

At the start of the study, the mean body weight for all groups was 163.04 ± 20.02 pounds or 73.95 ± 9.08 kilograms. Body weight decreased by an average of 2.16 pounds or 0.98 kilograms at hour 16 to a minimum weight of 160.88 ± 20.44 pounds or 72.97 ± 9.27 kilograms. All subjects lost some weight (1 to 6 pounds or 0.45 to 2.72 kilograms) on at least one occasion with the exception of one subject (79 year-old male). At the end of the study, hour 84, the mean body weight was 162.08 ± 20.05 pounds or 73.52 ± 9.09 kilograms. The short-term decrease in body weight probably reflects a combination of eliminating the bowel contents and the net of liquid intake minus fluid loss. As a result, these findings suggest that with proper hydration, net fluid loss is minimized. There were no significant differences between the screening and end-of-study physical examination data, and there were no clinically significant changes in urinalysis results.

Blood pressure and heart rate were measured in the supine position and standing positions. Baseline means and standard deviations for SBP were 123.1 ± 11.8 mmHg and 125.8 ± 13.4 mmHg for supine and standing, respectively. Mean SBP

decreased significantly from baseline at both supine and standing, except that supine SBP was not significantly different at hour 84. The mean change from baseline while supine (-9.50 mmHg) and standing (-12.25 mmHg) was highest at hour 16. No subjects had postural decreases in systolic blood pressure ≥ 20 mmHg.

Baseline means and standard deviations for DBP were 70.3 ± 6.6 mmHg and 72.7 ± 6.5 mmHg for supine and standing, respectively. Supine mean DBP was significantly increased from baseline only at hour 36 and 84; mean standing DBP was not significantly different from baseline. There were no clear trends for change in diastolic blood pressure or pulse rate although two subjects had postural decreases in diastolic blood pressure ≥ 10 mmHg on a single occasion. The first subject (34 year-old male) had a fall in diastolic blood pressure from 78 mmHg supine to 62 mmHg upon standing at hour 4; and the second subject (64 year-old female) had a fall in diastolic blood pressure from 80 mmHg supine to 66 mmHg upon standing at hour 84; neither subject had a postural drop in systolic blood pressure. These changes in diastolic blood pressure were not associated with a fall in systolic blood pressure or a compensatory increase in heart rate (pulse: 62 supine, 64 standing; and 68 supine, 74 standing, respectively). The differences between supine and standing blood pressure and heart rate were within normal limits at all other observations for both subjects. Considering the isolated nature of the observations and the lack of decrease in systolic blood pressure or a compensatory increase in heart rate, neither of these findings appears to represent postural hypotension resulting from reduced intra-vascular volume.

There were no observations of hypertension, hypotension, or tachycardia in any of the study participants. A few isolated instances of bradycardia (pulse <60 beats per minute) were observed, but there were no apparent trends or clinically significant changes.

Chemistry Panel

The oral administration of NaP failed to have any apparent impact on the serum chemistry values at hours 0, 3, 12 15, 24, 36, 60, and 84 (aside from the primary serum electrolytes already noted). Serum chemistry panel evaluated serum sodium, potassium, magnesium, calcium, phosphate,

chloride, carbon dioxide, creatinine, BUN, total protein, albumin, total bilirubin, AST, ALT, alkaline phosphatase, LDH, and glucose. While small random fluctuations were observed for each of the mean parameters, there were no significant shifts in the mean results and no apparent pattern relative to dose administration, except for mean serum creatinine concentration, which showed a marked transient increase of 0.24 mg/dL in elderly

and young males only at hour 24 (Figure 7). This transient increase resulted in the mean creatinine value increasing statistically significantly ($p = 0.0002$) from baseline (0.90 ± 0.22 mg/dL) to 1.03 ± 0.29 mg/dL at hour 24. This is the only mean that was statistically significantly different from baseline.

FIG. 7 Mean serum creatinine concentration versus time in elderly females (EF), elderly males (EM), young females (YF) and young males (YM). Mean serum creatinine increased significantly from baseline only at the 24 hour timepoint.
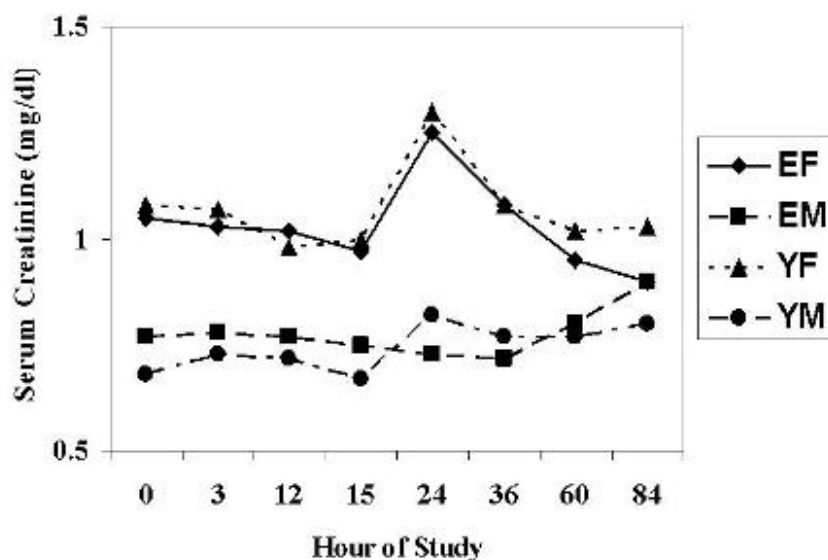
Haematology

Haematology panels were obtained at screening and upon discharge from the study and no significant shifts were found. Mean haemoglobin decreased from 13.70 ± 1.23 g/dL at baseline to 13.61 ± 1.20 g/dL at hour 84 ($p = 0.43$). Haematocrit decreased from $40.66 \pm 3.29\%$ at baseline to $40.28 \pm 3.29\%$ at hour 84 ($p = 0.29$). A few isolated deviations outside the normal ranges were observed, but none were considered to be clinically significant. There were no observations of thrombocytopenia.

Four subjects (17%) had small decreases in haemoglobin and haematocrit. One subject (65 year-old female) had a 4% decrease in white

blood cell count, from 5.8 to 3.7 x 10^3 cells/mm^3 and a corresponding decrease in neutrophil percentage from 50.7% to 23.4%.

DISCUSSION

The primary objective of this study was to evaluate the magnitude and time course of serum electrolyte shifts following administration of 2 x 45 mL of NaP. The study was designed to mimic the bowel preparation regimen commonly used prior to colonoscopy, including a clear liquid diet, timing of NaP doses and proper hydration. In addition, the population was selected in a manner

designed to produce demographic characteristics typical of patients having elective colonoscopy with one-half of the study participants aged 65 years or older. The study population was balanced for age and gender.

Our observations show that NaP given at a dose of 2 x 45 mL 12 hours apart was well tolerated and no subjects withdrew due to an adverse event. The regimen was associated with transient shifts in serum electrolytes typically reported following bowel cleansing with NaP.[16] Absorption of sodium and phosphate was associated with transient rises in the serum concentrations of these two ions[2] following each of the two doses. Mean serum sodium concentration fluctuated within the normal range, while serum phosphate concentrations exceeded the upper limits of normal, rising to a peak of 6.86 mg/dL following the second dose. Of the four age groups, elderly females exhibited the highest serum phosphate concentration after each dose. The serum sodium and phosphate concentrations returned to baseline values 24 hours after administration of the second dose.

Serum phosphate concentration is tightly controlled in the body by modulating the absorption in the small intestine, distribution in intercellular and bone storage pools, and renal excretion. The plot of serum phosphate concentration versus time (Figure 1) clearly shows increased hyperphosphatemia following the second dose of NaP, suggesting that phosphate absorption differs for the second dose. The increased hyperphosphatemia for the second dose implies increased intestinal absorption or increased proximal tubular reabsorption. Through a complex feedback mechanism involving parathyroid hormone, hyperphosphatemia is known to reduce the capacity of the NaPi-IIa cotransporter to reabsorb phosphate in the proximal tubule.[23-25] If proximal tubule reabsorption of phosphate is decreased, the other methods to account for the increased hyperphosphatemia following the second dose is increased intestinal absorption and increased distribution from intercellar storage pools. Stauber *et al.*[26] have recently reported that acidosis stimulates expression of NaPi-IIb cotransporter in the rat small intestine. However, the possibility of acidosis is not supported by the stable serum CO_2 concentrations. Acute phosphate nephropathy

associated with oral sodium phosphates solution was first described by Desmules *et al*[27] in a 71 year old woman. Additional reports of an association between oral sodium phosphates solution and acute phosphate nephropathy leading to impairment of renal function have been published.[28-30] The majority of these rare reports occurred in persons taking drugs to treat hypertension or other drug products such as diuretics or NSAIDs, which may result in dehydration. The transient rise in mean serum phosphate concentration observed in this study (Figure 1), results in a maximum mean serum calcium phosphate product of 67.8 mg^2/dL^2 which occurred at 15 hours in elderly females. While this value is only slightly above the currently recommended limit for dialysis patients of 55 mg^2/dL^2 [31], the significance of a transient elevation of the calcium phosphate product in healthy individuals has not been reported. There was no increase in creatinine concentration that mirrored the serum calcium phosphate product increase.

The shifts in mean serum sodium and phosphate concentrations were also associated with decreases in mean serum potassium and calcium concentrations. Both mean serum potassium and calcium concentrations fluctuated within the normal individual range and then returned to baseline range values by 12 hours after administration of the second dose. No individual subject had clinically significant hypocalcaemia or hypokalemia, and there were no significant age- or gender-related differences in the primary serum electrolyte response to NaP administration.

QT prolongation can be induced by drugs or by electrolyte abnormalities and can cause fatal arrhythmias. Therefore, understanding the electrolyte changes associated with Fleet Phospho-soda is important in understanding the risk of QT prolongation associated with the drug.[32-37] None of the slight increases in the QTc interval following each NaP dose were considered clinically significant by a referral cardiologist. These changes appeared to be negatively correlated with serum potassium concentration and positively correlated with serum calcium concentration. Elderly males consistently exhibited the lowest QTc interval.

Mean systolic blood pressure appeared to be slightly reduced following administration of NaP. The reductions in supine and standing systolic blood pressure were not associated with

episodes of postural change. There were no clear trends for change in diastolic blood pressure or pulse rate.

CONCLUSIONS

In conclusion, the transient serum electrolyte concentration shifts associated with the administration of 2 x 45 mL of NaP were clinically insignificant, were transient and resolved within 12 to 24 hours after completing the bowel preparation regimen. This study confirms other reports where proper patient selection, timing of dosages, and adequate hydration have been found to be essential elements for safe and effective bowel cleansing with NaP.[38-41]

REFERENCES

1. 50 Federal Register 2124, et seq., January 15, 1985 (Laxative Drug Products for Over-the-Counter Human Use; Tentative Final Monograph).
2. Carrera AE. Effect of oral administration of Fleet Phospho-soda on serum phosphorus concentration. Am J Clin Pathol 1968;49:739-741.
3. Vanner SJ, MacDonald PH, Paterson WG, et al. A randomized prospective trial comparing oral phosphate with standard polyethylene glycol-based lavage solution (Golytely) in the preparation of patients for colonoscopy. Am J Gastroenterol 1990;85:422-427.
4. Aronchick CA, Lipshutz WH, Wright SH, et al. A novel tableted purgative for colonoscopic preparation: efficacy and safety comparisons with Colyte and Fleet Phospho-Soda. Gastrointest Endosc 2000;52:346-352.
5. Frommer D. Cleansing ability and tolerance of three bowel preparations for colonoscopy. Dis Colon Rectum 1997;40:100-104.
6. Berkelhammer C, Ekambaram A, Silva RG. Low-volume oral colonoscopy bowel preparation: sodium phosphate and magnesium citrate. Gastrointest Endosc 2002;56:89-94.
7. Bujanda L, Muñoz C, Sánchez A, et al. Tolerance to and colon cleansing with two preparations. polyethylene glycol or sodium phosphate. Gastroenterol Hepatol 2001;24:9-12.
8. Poon CM, Lee DWH, Mak SK, et al. Two liters of polyethylene glycol-electrolyte lavage solution versus sodium phosphate as bowel cleansing regimen for colonoscopy: a prospective randomized controlled trial. Endoscopy 2002;34:560-563.
9. Parra-Blanco A, Nicolas D, Gimeno A-Z, et al. Timing of bowel cleansing solution administration before colonoscopy determines the quality of colonic preparation and the detection of flat polyps. Gastrointest Endosc 2003;57, AB103.
10. Canard JM. Fleet Phospho-soda: for greater acceptability of the colic preparation before colonoscopy. Randomized comparative single blind study versus polyethylene glycol. Acta Endoscopica 2001;31:703-708.
11. Cohen SM, Wexner SD, Binderow SR, et al. Prospective, randomized endoscopic-blinded trial comparing pre-colonoscopy bowel cleansing methods. Dis Colon Rectum 1994;37:689-696.
12. Pou Fernández JM, Munoz SR, Felis TS. Characterization of the safety, effectiveness and use of oral sodium phosphate. Rex Esp Enferm Dig 2001;93:220-225.
13. Balaban DH, Leavell BS, Oblinger MJ, Thompson WO, Bolton ND, Pambianco DJ. Low volume bowel preparation for colonoscopy: randomized, endoscopist-blinded trial of liquid sodium phosphate versus tablet sodium phosphate. Am J Gastroenterol 2003;98:827-832.
14. Young CJ, Simpson RR, King DW, Lubowski DZ. Oral sodium phosphate solution is a superior colonoscopy preparation to polyethylene glycol with bisacodyl. Dis Colon Rectum 2000;43:1568-1571.

15. Huynh T, Vanner S, Paterson W. Safety profile of 5-h oral sodium phosphate regimen for colonoscopy cleansing: lack of clinically significant hypocalcemia or hypovolemia. Am J Gastroenterol 1995;90:104-107.

16. DiPalma JA, Buckely SE, Warner BA, Culpepper RM. Biochemical effects of oral sodium phosphate. Dig Dis Sci 1996;41:749-753.

17. Brown AR, DiPalma JA. Bowel preparation for gastrointestinal procedures. Curr Gastroenterol Rep 2004;6:395-401.

18. Gumurdulu Y, Serin E, Ozer B, Gokcel A, Boyacioglu S. Age as a predictor of hyperphosphatemia after oral phosphosoda administration for colon preparation. J Gastroenterol Hepatol 2004;19:68-72.

19. Lieberman DA, Ghormley J, Flora K. Effect of oral sodium phosphate colon preparation on serum electrolytes in patients with normal serum creatinine. Gastrointest Endosc 1996;43:467-469.

20. Ma K, Ng C, Mui L, Chan K, Ng E. Severe hyperphosphatemia and hypocalcemia following sodium phosphate bowel preparation: a forgotten menace. Endoscopy 2003;35:717.

21. Tan HL, Liew QY, Loo S, Hawkins R. Severe hyperphosphataemia and associated electrolyte and metabolic derangement following the administration of sodium phosphate for bowel preparation. Anaesthesia 2002;57:478-483.

22. National Cancer Institute. Cancer Therapy Evaluation Program. Common Toxicity Criteria Manual. Common Toxicity Criteria, Version 2.0, Publish Date: April 30, 1999. Retrieved on June 27, 2005 from: http://ctep.cancer.gov/reporting/CTC-3.html

23. Murer H, Hernando N, Forster I, Biber J. Regulation of Na/Pi transporter in the proximal tubule. Ann Rev Physiol 2003;65:531-542.

24. Tenenhouse HS. Regulation of phosphorous homeostasis by the type IIa Na/phosphate cotransporter. Ann Rev Nutr 2005;25:197-214.

25. Forster IC, Hernando N, Biber J, Murer H. Proximal tubular handing of phosphate: A molecular perspective. Kidney International advance online publication, 6 September 2006; doi:10.1038/sj.ki.5001813.

26. Stauber A, Radanovic T, Stange G, Murer H, Wagner CA, Biber J. Regulation of intestinal phosphate transport. II. Metabolic acidosis stimulates Na+ -dependent phosphate absorption and expression of the Na+ -Pi cotransporter NaPi-IIb in small intestine. Am J Physiol Gastrointest Liver Physiol 2005;288:G501-G506.

27. Desmeules S, Bergeron MJ, Isenring P. Acute phosphate nephropathy and renal failure. N Engl J Med 2003;349:1006-1007.

28. Markowitz GS, Nasr SH, Klein P, et al. Renal Failure due to acute nephrocalcinosis following oral sodium phosphate bowel cleansing. Hum Pathol 2004;35:675-684.

29. Markowitz GS, Stokes MB, Radhakrishnan J, D'Agati VD. Acute phosphate nephropathy following oral sodium phosphate bowel purgative: an underrecognized cause of chronic renal failure. J Am Soc Nephrol 2005;16:3389-3396.

30. Gonlusen G, Akgun H, Ertan A, Olivero J, Truong LD. Renal failure and nephrocalcinosis associated with oral sodium phosphate bowel cleansing. Arch Pathol Lab Med 2006;130:101-106.

31. Block GA, Port FK. Re-evaluation of risks associated with hyperphosphatemia and hyperparathyroidism in dialysis patients: recommendation for a change in management. Am J Kidney Dis 2001;37:1331-1333.

32. Gamulka BD. Case 2: First do no harm. Paediatr Child Health 2003;8:573-575.

33. Hookey LC, Vanner S. Recognizing the clinical contraindications to the use of oral sodium phosphate for colon cleansing: A case study. Can J Gastroenterol 2004;18:455-458.

34. Geffner M, Opas L. Phosphate poisoning complicating treatment for iron ingestion. Am J Dis Child 1980;134:509-510.

35. Boivin M, Kahn S. Symptomatic hypocalcemia from oral sodium phosphate: A report of two cases. Am J Gasterenterol 1998;93:2577-2579.

36. Mishra R, Kaufman D, Mattern J, Dutta S. Severe hyperphosphataemia and hypocalcemia caused by bowel preparation for colonoscopy using oral sodium phosphate in end-stage renal disease. Endoscopy 2005;37:1259-1260

37. Patel M, Trigg N, Petropulos T, Berkelhammer C. Colonoscopy bowel preparation in patients with long QT syndrome. Am J Gastroenterol 2005;100:S226.

38. Barclay RL, Depew WT, Vanner SJ. Carbohydrate-electrolyte rehydration protects against intravascular volume contraction during colonic cleansing with orally administered sodium phosphate. Gastrointest Endosc 2002;56:633-638.

39. Tjandra JJ, Tagkalidis P. Carbohydrate-electrolyte (E-Lyte) solution enhances bowel preparation with oral Fleet Phospho-soda. Dis Colon Rectum 2004;47:1181-1186.

40. Love J. The appropriate use of sodium phosphates oral solutions. Can J Gastroenterol 2003;17:531.

41. Hookey LC, Vanner SJ. Recognizing the clinical contraindications to the use of oral sodium phosphate for colon cleansing: a case study. Can J Gastroenterol 2004;18:455-458.