Serial monitoring of the physiological effects of the standard Pico-Salax® regimen for colon cleansing in healthy volunteers

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BACKGROUND: Sodium picosulfate/magnesium oxide/citric acid (Pico-Salax, Ferring Inc, Canada) is used widely in Canada and other countries for colon cleansing before colonoscopy. It is a low-volume osmotic/stimulant agent with the potential to deplete intravascular volume and alter electrolyte balance, yet there are little data regarding its effects on these clinically important end points.

OBJECTIVE: To serially measure parameters of intravascular volume and electrolyte status in healthy volunteers over a 24 h period using the standard two-sachet dosing.

METHODS: Twenty volunteers were given one sachet of Pico-Salax at time 0 h and another sachet 5 h later, as per usual bowel cleansing protocol. Subjects were continually monitored during the first 12 h of the study with postural vital signs, serum electrolytes and electrocardiograms obtained at intervals throughout this initial period and again at 24 h post-ingestion.

RESULTS: No adverse events were reported nor were there any signs of intravascular volume depletion observed. There were decreases in potassium and calcium levels from baseline to 12 h, but these appeared minor and were corrected by 24 h. The proportions of patients with hypermagnesemia at 0 h, 5 h, 12 h and 24 h were 5%, 35%, 35% and 20%, respectively ($P < 0.05$). However, the maximal values were only minimally elevated. Mean serum sodium, phosphate and creatinine levels remained within their respective reference ranges. There was a trend toward an increase in maximum corrected QT intervals from time 0 h (418 ms) to 5 h (430 ms) ($P = 0.06$), but no significant change was seen subsequently at 12 h (419 ms). The subjects tolerated the medication well. The mean number of bowel movements per subject was 8.15 (range four to 15). Subjects consumed a mean ($\pm$ SD) of 3.49 $\pm$ 1.53 L of fluids during the observation period.

CONCLUSIONS: The proportion of individuals with hypokalemia, hypocalcemia and hypermagnesemia following two sachets of Pico-Salax is significant, but the magnitude of the changes was not clinically relevant in this relatively small group, and both calcium and potassium levels normalized at 24 h. Nonetheless, this could have implications in patients with pre-existing electrolyte abnormalities and the safety of dosing with more than two sachets.

Key Words: Colon cleansing; Colonoscopy; Electrolyte changes

Colon cleansing before colonoscopy must be efficacious, safe and well tolerated to ensure effective colon screening. Polyethylene glycol electrolyte (PEG) solutions are iso-osmotic lavage preparations with a good safety profile with respect to dehydration and intravascular volume shifts. On the other hand, they are hindered by the large volume

La surveillance sérielle des effets physiologiques du régime Pico-Salax® standard d'irrigation du côlon chez des volontaires en santé

HISTORIQUE : Le picosulfate sodique, associé à l'oxyde de magnésium et à l'acide citrique (Pico-Salax, Ferring Inc., Canada) est largement utilisé au Canada et dans d'autres pays pour irriguer le côlon avant la coloscopie. C'est un agent osmotique et stimulant à faible volume qui a le potentiel d'épuiser le volume intravasculaire et de nuire à l'équilibre électrolytique, mais il existe peu de données quant à ses effets sur ces paramètres ultimes, qui sont importants sur le plan clinique.

OBJECTIF : Procéder à la mesure sérielle des paramètres liés au volume intravasculaire et au statut électrolytique chez des volontaires en santé pendant une période de 24 heures, à l'aide de la dose standard en deux sachets.

MÉTHODOLOGIE : Vingt volontaires ont reçu un sachet de Pico-Salax à l'heure 0 et un deuxième sachet cinq heures plus tard, conformément au protocole d'irrigation intestinale habituel. Les sujets faisaient l'objet d'un suivi continu pendant les 12 premières heures de l'étude, au moyen des signes vitaux posturaux, des électrolytes sériques et des électrocardiogrammes obtenus à des intervalles donnés tout au long de cette période initiale, puis 24 heures après l'ingestion.

RÉSULTATS : Les chercheurs n'ont constaté aucun effet indésirable et observé aucuns signes d'épuisement du volume intravasculaire. Ils ont remarqué une diminution des taux de potassium et de calcium entre le point de départ et la douzième heure, mais elle semblait mineure et s'était rétablie au bout de 24 heures. La proportion de patients présentant une hypermagnésémie au bout de 0 heure, 5 heures, 12 heures et 24 heures s'élevait à 5 %, 35 %, 35 % et 20 %, respectivement ($P < 0,05$). Cependant, les valeurs maximales étaient peu élevées. Le sodium sérique moyen ainsi que les taux de phosphate et de créatinine sont demeurés dans leur plage de référence respective. On a remarqué une tendance vers une augmentation des intervalles QT corrigés maximaux entre l'heure 0 (418 ms) et la cinquième heure (430 ms) ($P = 0,06$), mais aucun changement significatif au bout de 12 heures (419 ms). Les sujets toléraient bien le médicament. Ils présentaient un nombre moyen de 8,15 mouvements péristaltiques (plage de quatre à 15). Ils avaient ingéré une moyenne ($\pm$ ÉT) de 3,49 $\pm$ 1,53 L de liquide pendant la période d'observation.

CONCLUSIONS : La proportion de personnes ayant une hypokaliémie, une hypocalcémie et une hypermagnésémie après la prise de deux sachets de Pico-Salax est significative, mais la magnitude des changements n'était pas pertinente sur le plan clinique dans ce groupe relativement restreint, et tant le taux de calcium que de potassium est redevenu normal au bout de 24 heures. Néanmoins, ces changements pourraient avoir des effets chez les patients présentant déjà des anomalies électrolytiques ainsi que sur l'innocuité d'une dose de plus de deux sachets.

(4 L) required for ingestion over a short period of time (2 h to 3 h). Hence, most adverse events related to PEG are secondary to vomiting (1). The tolerability of low-volume colonic preparation for patients undergoing colonoscopy is an attractive alternative compared with high-volume colonic preparations (2-4). However, there are significant

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TABLE 1
Timeline of data collection

	Baseline (08:00)	2h (10:00)	4h (12:00)	5 h (13:00)	7 h (15:00)	9 h (17:00)	12 h (20:00)	24 h (08:00 day 2)
Study medication	X			X				
Assessment of adverse events	X	X	X	X	X	X	X	X
Weight	X			X			X	X
Electrocardiogram	X			X			X	X
Hematology panel	X			X			X	X
Serum electrolytes	X	X	X	X	X	X	X	X
Total liquid intake							X	
Urinalysis	X			X			X	
Vital signs	X	X	X	X	X	X	X	

safety concerns regarding low-volume colon cleansing preparations, particularly, sodium phosphate-based preparations (1,5,6). Electrolyte shifts and intravascular depletion may occur in patients with or without risk factors for electrolyte shifts and hypovolemia. Hypocalcemia, hyperphosphatemia, hyponatremia, hypokalemia and acidosis have occurred with the use of oral sodium phosphate solutions. The product is contraindicated in patients with impaired renal function, heart disease, acute myocardial infarction, unstable angina, pre-existing electrolyte imbalances and in patients taking drugs that may affect electrolyte levels, elderly and debilitated patients (7). Although most adverse events with sodium phosphate preparations are associated with patient selection or dosing errors, recent reports of idiosyncratic nephrocalcinosis further reduced its attractiveness (8) and have led to its withdrawal from clinical practice in North America.

Pico-Salax (Ferring Inc, Canada) has recently been introduced in Canada and is being widely used in outpatient colonoscopy. This is despite minimal evidence regarding its safety profile (6), although it has been used for several decades in the United Kingdom and Australia. Each sachet of Pico-Salax contains the following active ingredients: sodium picosulfate 10.0 mg, magnesium oxide 3.5 g and citric acid 12.0 g. Pico-Salax has been evaluated before colonoscopy in only a few studies. Furthermore, while published data suggest a favourable safety profile intravascular depletion can occur and asymptomatic hypermagnesemia has been reported (9).

Recently, we performed a large, randomized control trial using Pico-Salax with or without the addition of bisacodyl (9) and demonstrated that these preparations were safe, well tolerated and effective regimens for colon cleansing before colonoscopy. While the study did not demonstrate evidence of intravascular depletion, there was a slight increase in serum magnesium levels (maximal value 1.21 mmol/L), which has been reported elsewhere (10). These recent results suggest that Pico-Salax has a favourable safety profile but the data are restricted to time points 10 h to 16 h hours postingestion of the second dose of the medication. Given this limitation, the maximal changes in intravascular volume, electrolyte values and corrected QT (QTc) intervals may not have been detected.

The primary objective of the present study was to evaluate the magnitude and time course of serum electrolyte shifts and intravascular depletion following administration of two sachets of Pico-Salax in a manner that mirrors the bowel preparation regimen commonly used before colonoscopy, including a clear liquid diet, timing of Pico-Salax doses and proper hydration. In addition, the population was selected in a manner designed to produce demographic characteristics typical of patients undergoing elective colonoscopy.

METHODS

The present study used a single treatment design with 20 healthy male and female volunteers >45 years of age. Exclusion criteria included evidence of dehydration, abnormal serum electrolytes, renal insufficiency (estimated glomerular filtration rate greater than the upper limit of normal for age and sex), liver disease, congestive heart failure,

unstable angina and uncontrolled hypertension. The study was approved by the Queen's University Health Sciences and Affiliated Hospitals Research Ethics Board (Kingston, Ontario) and registered in an international clinical trials registry (NCT00885430).

Subjects consumed clear fluids for 12 h before arriving at the study site (Hotel Dieu Hospital, Kingston, Ontario) where they were monitored in a clinic area, with each participant assigned a private room with bathroom. One sachet of Pico-Salax was administered at 08:00 (time 0 h) and one at 13:00 (time 5 h). Participants were encouraged to consume fluids ad libitum. Fluids provided included carbohydrate electrolyte drink (Gatorade, Quaker Inc, Canada), popsicles, water, Jell-O (Kraft Canada, Inc), chicken broth and coffee. The self-reported quantity of fluid consumption was recorded. Weight, postural vital signs, hematocrit, serum and urine chemistry and surface 12-lead electrocardiograms (ECGs) were performed at baseline (time 0 h) and several time points throughout the day including just before ingestion of the second sachet of Pico-Salax (time 5 h) (Table 1). Weight was recorded on a calibrated scale used for all patients. Postural vitals were taken after the subject was resting supine for 5 min, with the second measurement taken with the subject standing for 1 min (11). Serum chemistry included measurement of serum sodium, chloride, potassium, magnesium, ionized calcium, blood sugar, urea and creatinine levels. Urine chemistry measurements included pH, specific gravity, osmolality, protein, glucose, ketones, urobilinogen and blood.

ECGs were analyzed by a blinded investigator (AB). The QT interval was measured, and QTc intervals were analyzed in all leads by scanning the traces at 300 dpi. To measure the ECGs, a semi-automatic caliper (Iconico, USA) was used amplifying the ECG $\times 8$. QT measurement was performed from the beginning of the QRS interval to the intersection of the downslope of the T-wave on the isoelectric line. The maximum QTc interval was calculated using Bazett's formula and used for the analysis.

Adverse events were recorded on both a self-reported basis and on questioning during physical data collection at each time point.

Outcomes

For postural vitals, clinically significant postural changes in blood pressure were defined as any of the following: decrease in systolic blood pressure by 20 mmHg, a decrease in diastolic pressure by 10 mmHg or an increase in heart rate by 20 beats/min in the standing position (12). Maximum QTc intervals were measured and compared against baseline at time 5 h, 12 h and 24 h. The concentration of serum sodium, chloride, potassium, magnesium, calcium, creatinine, glucose and urine osmolality were measured at baseline and compared with subsequent time points.

Statistical analysis

Data were initially analyzed using Student's *t* test for means between time points. $P < 0.05$ was considered to be statistically significant without correction for multiple testing. Where significant changes were observed in electrolyte values, further analysis was then pursued that included parametric and nonparametric testing.

TABLE 2
Mean serum electrolyte levels over the course of observation period

Time, h	Sodium*, mmol/L (133 mmol/L–145 mmol/L)	Chloride*, mmol/L (95 mmol/L–107 mmol/L)	Creatinine*, μ mol/L (0 μ mol/L–80 μ mol/L)	Phosphate*, mmol/L (0.90 mmol/L–1.30 mmol/L)	Glucose*, mmol/L (3.5 mmol/L–10.0 mmol/L)
0	139 $\pm$ 2	104 $\pm$ 3	73 $\pm$ 18	1.02 $\pm$ 0.15	4.7 $\pm$ 1.2
2	139 $\pm$ 2	102 $\pm$ 4 [†]	71 $\pm$ 17	1.02 $\pm$ 0.17	4.3 $\pm$ 1.3
4	139 $\pm$ 2	102 $\pm$ 2	73 $\pm$ 15	1.01 $\pm$ 0.13	4.6 $\pm$ 1.1
5	138 $\pm$ 2	102 $\pm$ 2	72 $\pm$ 17	1.06 $\pm$ 0.17	4.7 $\pm$ 1.0
7	138 $\pm$ 2	101 $\pm$ 3 [†]	71 $\pm$ 15	1.09 $\pm$ 0.17 [†]	4.4 $\pm$ 0.8
9	138 $\pm$ 2	102 $\pm$ 2 [†]	70 $\pm$ 15	1.06 $\pm$ 0.15	4.5 $\pm$ 1.0
12	138 $\pm$ 2	101 $\pm$ 2 [†]	74 $\pm$ 14	1.14 $\pm$ 0.17 [†]	4.7 $\pm$ 0.6
24	139 $\pm$ 1	103 $\pm$ 2	74 $\pm$ 14	1.15 $\pm$ 0.29 [†]	5.3 $\pm$ 1.3

Data presented as mean $\pm$ SD. *Normal range given in parentheses; [†]P<0.05 compared with baseline

Figure 1 Parametric models of changes in potassium, calcium and magnesium levels over 24 h

For nonparametric analysis, observations were classified as normal if they fell within the reference range. For each element, the relative frequencies of normal and abnormal observations were calculated and subsequently analyzed for association between abnormal proportion and time. The Cochran-Mantel-Haenszel test, stratified according to patient, was used to test for global association. Strongly significant statistics suggest the presence of a pattern over time, which is consistent across patients. The patterns identified were further investigated with a parametric model. The observations were modelled as repeated measures over time. Because levels were expected to gradually worsen and then restore over time, a nonlinear model for the mean was proposed. To accommodate this possibility, the mean level was modelled as a quadratic function of time. Repeated measures for each patient were allowed to be correlated over time. This was realized by assuming that each patient had a random quadratic function to describe his/her level changes over time. The intercept and the linear term were random effects. The quadratic term was restricted to be equal for all patients. The resulting parabolas, which are the predicted mean levels, were plotted over the observed values.

ECG data were analyzed with paired samples *t* tests to compare the baseline data with the other three time points. Due to the small sample size, the nonparametric Wilcoxon signed-rank test was used to confirm the results.

RESULTS

Twenty subjects 45 to 64 years of age participated in the study with 12 h of observation on day 1 followed by a repeat visit at 24 h. Subjects ingested a mean ($\pm$ SD) liquid intake of 3.49 $\pm$ 1.53 L between 0 h and 12 h. No clinical adverse events were reported or observed. There were no significant changes in body weight or postural vital signs throughout the study period.

Mean serum sodium and glucose remained within the reference range at all time points through the study, with no significant change in mean levels. Although a statistically significant decrease in chloride and increase in phosphate levels were observed at several time points, there were no cases of these levels being outside the respective reference ranges, nor did serum creatinine change significantly (Table 2). Urine osmolality decreased from 416 mmol/kg at time 0 h to 289 mmol/kg at 5 h ($P=0.03$), and was 308 mmol/kg at 12 h. There were no episodes of thrombocytopenia or leukocytosis, and the mean hematocrit remained within the reference range throughout the study.

There was a significant decrease in mean potassium concentration from baseline (time 0 h) to the 9 h and 12 h points of the study, but this returned to near baseline levels by 24 h (Figure 1A). The mean concentrations at time 9 h and 12 h were below the lower limit of normal (3.4 mmol/L and 3.3 mmol/L, respectively [lower limit of normal 3.5 mmol/L]) (Table 3). The proportions of patients with hypokalemia at 0 h, 5 h, 12 h and 24 h were 25%, 35%, 75% and 15%, respectively. The proportions with potassium levels <3.0 mmol/L at the same time points were 3%, 0%, 6% and 0%, respectively.

Mean ionized calcium levels also decreased significantly from time 0 h at several time points throughout the day but had normalized by time 24 h (Figure 1B). The proportion of patients with low calcium

TABLE 3
Serum calcium, potassium and magnesium levels over the course of the observation period

	Ionized calcium* (1.19–1.31 mmol/L)	Potassium* (3.5–5.2 mmol/L)	Magnesium* (0.80–1.00 mmol/L)
0	1.24±0.06	3.8±0.6	0.90±0.06
2	1.22±0.07	3.7±0.4	1.00±0.08†
4	1.21±0.07†	3.6±0.5	0.98±0.07†
5	1.18±0.06†	3.7±0.5	0.97±0.07†
7	1.18±0.06†	3.6±0.6	1.02±0.07†
9	1.15±0.06†	3.4±0.3†	0.99±0.07†
12	1.17±0.05†	3.3±0.3†	0.99±0.08†
24	1.25±0.06	4.0±0.5	0.95±0.06†

Data presented as mean ± SD. *Normal range given in parentheses; †P<0.05 compared with baseline

levels at 0 h, 5 h, 12 h and 24 h were 10%, 50%, 70% and 15%, respectively. Compared with time 0 h, there was a significant increase in magnesium levels at all time points compared with baseline. The mean magnesium concentration was higher than the upper range of normal at 7 h (1.02 mmol/L). The proportion of patients with hypermagnesemia at 0 h, 5 h, 12 h and 24 h were 5%, 35%, 35% and 20% (Table 3).

As described above, additional nonparametric and parametric analysis was performed for the observed potassium, calcium and magnesium changes. Cochran-Mantel-Haenszel testing with P<0.001 for each electrolyte suggested the presence of a pattern over time, which was consistent across patients. These patterns were further investigated with a parametric model with quadratic terms that were strongly significant. The resulting parabolas, which are the predicted mean levels, were plotted over the observed values in Figure 1.

Maximum QTc analysis

A surface 12-lead ECG was performed at screening, just before administration of the first dose at 0 h, and before administration of the second dose at 5 h and at 12 h. The normal QTc interval was defined as a maximum of 440 ms for men and 460 ms for women. The mean maximum QTc for the subjects in the present study at time 0 h was 418 ms. The mean maximum QTc interval increased to 430 ms at 5 h (P=0.06); however, at 12 h, there was no significant variations with respect to baseline (419 ms) (P>0.05) (Table 4). The absolute maximum QTc observed was 477 ms at 12 h in one subject.

DISCUSSION

The present study was the first to monitor the physiological effects of Pico-Salax over a 24 h period. Although the agent is new to North America, it has been used for several decades in the United Kingdom and Australia, with only rudimentary knowledge of its effects on electrolytes and fluid balance (6). Our study was designed to examine the typical bowel preparation regimen commonly used before colonoscopy including the clear liquid diet, the 5 h interval between doses and the instructions for hydration. Furthermore, the subjects were 45 to 64 years of age in an effort to reflect a demographic typical of patients undergoing elective colonoscopy. As expected – and seen in previous studies – we observed hypermagnesemia but also saw a substantial proportion of patients develop hypokalemia and hypocalcemia that returned to baseline levels at 24 h. The elevated magnesium level is at least partially attributable to the magnesium load delivered within the agent as well, whereas the hypokalemia likely resulted from the expected diarrhea from the purgative. The decreased urine osmolality likely reflects free water load from the consumption of clear fluids. We cannot attribute the decrease in urine osmolality to enhanced sodium retention because we did not observe the alteration in serum sodium that would be expected in this setting. Although PEG is purported to have an improved safety profile compared with lower volume preparation

TABLE 4
Mean patient maximum corrected QT (QTc) intervals, urine osmolality and hematocrit

Time, h	Maximum QTc, ms	Urine osmolality, mmol/kg (P)	Hematocrit (P)
0	418*††	416 (–)	0.418 (–)
5	430*	289 (0.03)	0.423 (0.11)
12	419†	308 (0.10)	0.413 (0.61)
24 (n=12)	428†		

*P=0.06 comparing time 0 h with 5 h; †P=0.86 comparing time 0 h with 12 h; ††P=0.34

agents, there are no published data investigating PEG because the present study examined Pico-Salax, thus comparisons are difficult. The available data with PEG are limited to before and after preparation (13). The introduction of low-volume PEG preparations make this question even more intriguing and an area for future research.

The present study was also one of the first to investigate potential QTc interval changes with this particular bowel preparation. No statistically or clinically significant changes were observed in this group. Although there was a trend toward an increase at 5 h, this was not seen at 12 h, the time point at which the subjects had ingested two sachets and, thus, when one could expect to see a maximal effect. It is worth noting that the methodology used (maximum QTc) is the most robust for finding potential changes.

CONCLUSION

Pico-Salax appears to be safe and well tolerated. The proportion of individuals with hypokalemia, hypocalcemia and hypermagnesemia within 12 h of administration of Pico-Salax in standard fashion is significant but the magnitude of the changes does not appear to be clinically relevant, at least in this relatively small group. Nonetheless, they could have implications in patients with pre-existing electrolyte abnormalities and when used in everyday practice with a much larger number of patients. Patients who are dehydrated or have difficulty maintaining hydration status may be prone to symptomatic volume depletion. We have previously demonstrated that complications with sodium phosphate, another low-volume preparation, occur most commonly in patients with comorbidities (1). At this point, the use of multiple sachet dosing of Pico-Salax (three sachets or more) cannot be recommended. Lengthening the dosing interval (potentially through split dosing) and encouraging prehydration may prove to be important strategies in at-risk patients. Future research should focus on the effects of this agent in the elderly, alternate dosing intervals, multiple sachet dosing and hydration status, and its use in patients with comorbidities.

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