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(54) Benævnelse: **Fremgangsmåde til afpasning af tidspunktet for en koloskopi, hvor der indgives en picosulfatsammensætning.**

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DESCRIPTION

[0001] Colorectal cancer (CRC) ranks third in incidence and second to third in case of cancer death for both men and women in the United States (US). Jackson-Thompson J, Ahmed F, German RR, et al. Cancer, Descriptive epidemiology of colorectal cancer in the United States, 1998-2001. 2006 Sep 1;107(5 Suppl):1103-11. The lifetime risk of being diagnosed with CRC is 5% to 6% with a 5-year survival rate of 60% to 70%. Regular screening, beginning at age 50 for average-risk individuals, is one of the keys to preventing colorectal cancer. Pignone M, Rich M, Teutsch SM, et al. Screening for colorectal cancer in adults at average risk: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Int Med 2002;137:132-141.

[0002] Several scientific organizations, including the US Preventive Services Task Force (USPSTF) and other federal agencies, recommend regular screening for all adults age 50 or older and at <45 years of age for African Americans. According to USPSTF, routine screening can reduce the number of people who die of colorectal cancer by as much as 60%. U.S. Preventive Services Task Force. Screening for Colorectal Cancer. Rockville, MD: Agency for Healthcare Research Quality; 2002.

[0003] One of the initial colorectal cancer screening procedures is a fecal occult blood test. Approximately 2 of 100 fecal occult blood results are expected to be abnormal, requiring further investigation, most frequently a colonoscopy.

[0004] A colonoscopy is a minimally invasive endoscopic examination of the colon. Colonoscopies may provide a visual diagnosis (e.g., ulceration, polyps) and allow the opportunity for biopsy and removal of suspected lesions. Colonoscopies are used not only for colorectal cancer screening procedures but also used to investigate possible causes of abdominal pain, rectal bleeding, chronic constipation, chronic diarrhea, and other intestinal problems.

[0005] Colonoscopies or colorectal surgery requires the bowel to be as clear as possible with good preparation of the bowel before such procedures. The safety and efficacy of the procedure can be related to the quality of the pre-investigational bowel preparation: contamination of the colon with fecal material can lead to incomplete examination of the colonic mucosa or hinder the surgical procedures. Thus, inadequate bowel cleansing can lead to inaccurate results, as well as increasing the time it may take to conduct procedures and increasing the risk of complications. Similarly, for computed tomography colonography, any fluid or residue retained in the colon reduces sensitivity and specificity. Thus, the success of a colonoscopy is dependent, in part, upon an empty bowel, which allows for clear visualization of the colonic mucosa (including reaching the caecum) and completion of the colonoscopy. If a clear bowel is not achieved, the examination may need to be repeated; this creates a disruptive timing and rescheduling process for all: the patient, physician, and endoscopy staff.

[0006] Ideally, bowel-cleansing should clear the colon of most, of not all, solid material and

cause no damage to the colonic mucosa. It should also be easy to administer, be well tolerated by the patient with few adverse events, and cause little shift in the patient's fluid and electrolyte balance. Bowel cleansing is not a pleasant procedure for the patient, yet compliance with any pre-treatment regimen is paramount. Therefore, pre-treatment with a bowel cleansing preparation should be suitable for the patient to self-administer with a minimum of inconvenience and of relatively short duration i.e., safe, simple, effective and pleasant tasting.

[0007] Prospective studies have reported that repeat colonoscopies due to the poor quality of bowel preparation are required in up to 6% of colonoscopy procedures. A more recent retrospective audit revealed a failure rate of 4.5%. Wexner SD, Garbus JE, Singh JJ, et al. A prospective analysis of 13,580 colonoscopies: reevaluation of credentialing guidelines. Surg Endosc 2001;15:251-61; Bowles CJA, Leicester R, Romaya C, et al. A prospective study of colonoscopy practice in the UK today: are we adequately prepared for national colorectal cancer screening tomorrow? Gut 2004;53:277-82; Thomas-Gibson S, Tharpar C, Shah SG, et al. Colonoscopy at a combined district general hospital and specialist endoscopy unit: lessons from 505 consecutive examinations. J R Soc Med 2002;95:194-97; Thomson J, Phull P. Audit of bowel preparation with Pico-Salax (sodium picosulfate plus magnesium citrate) for colonoscopy. Int J Clin Pract 2006;60(5):602-3. A retrospective review also showed that the scheduling of colonoscopies in the afternoon compared to morning may be a predictor of an incomplete colonoscopy and inadequate bowel preparation. Sanaka M et al., Afternoon colonoscopies have higher failure rates than morning colonoscopies, 101 Am. J. Gastroenerol. 2726-30 (2006).

[0008] A general procedure is to take a picosulfate solution the day before and at least four hours before the colonoscopy, see Jennifer A Flemming: "Split-Dose Picosalax is Superior to Traditional Dosing for Colonoscopy Preparation - A Randomized Control Trial",Gastroenterology, 1 May 2011, page S-529, and JOE J TJANDRA ET AL: "Oral Sodium Phosphate (Fleet(R)) is a Superior Colonoscopy Preparation to Picoprep(R)(Sodium Picosulfate-Based Preparation)", DISEASES OF THE COLON & RECTUM, vol. 49, no. 5, 9 March 2006, pages 616-620.

[0009] In order to obtain consistently high quality colonoscopy examinations, one needs adequate colon cleansing. Enhancing the colonoscopy experience should also encourage more people to pursue examinations; consistent with public health goals of early polyp detection and removal of and accuracy of mucosal diagnosis. Currently available formulations can be improved, particularly regarding the timing requirements with complicated patient instructions leading to noncompliance and decreased incidences of lesion detection and therefore, repeat colonoscopies.

[0010] According to the present invention there is provided a picosulfate bowel composition for use in a method of timing a colonoscopy procedure, the method comprising:

administering, to the patient, a first picosulfate bowel composition the day before the procedure;

administering, to the patient the day of the procedure, a second picosulfate bowel composition; and

performing the procedure from 3 hours to 1 hour after the administration of the second bowel composition;

wherein the first and the second bowel compositions comprise sodium picosulfate, magnesium oxide, and citric acid.

DESCRIPTION

[0011] Particular aspects of the disclosure are described in greater detail below. The terms and definitions as used in the present application and as clarified herein are intended to represent the meaning within the present disclosure.

Terms and Definitions

[0012] The singular forms "a," "an," and "the" include plural reference unless the context dictates otherwise.

[0013] The terms "approximately" and "about" mean to be nearly the same as a referenced number or value. As used herein, the terms "approximately" and "about" should be generally understood to encompass ± 10% of a specified amount, frequency or value. With regard to specific values, it should be understood that specific values described herein for subject populations (e.g., the subject of the described clinical trial) represent median values, unless otherwise indicated as, e.g., mean values. Accordingly, aspects of the present disclosure requiring a particular value in a subject are substantially supported herein by population data in which the relevant value is assessed to be a meaningful delimitation of the subject population.

Example - Clinical Study

I.Split-Dose Study: PicoPrep™ and HalfLytely® Comparison

[0014] Overall Clinical Study and Design: A clinical study comprising a randomized, assessor-blinded, multi-centered study investigating the efficacy, safety and tolerability of "Split-Dose" sodium picosulfate, magnesium oxide, and citric acid, for example PicoPrep™, for oral administration versus bisacodyl, polyethylene glycol 3350, sodium chloride, sodium bicarbonate, and potassium chloride, for example HalfLytely® for oral administration, for colon

cleansing in preparation for colonoscopy. In addition to "split dose" administration of PicoPrep™ over Visit 1 and Visit 2, the PicoPrep™ administration also included where the first and second sachets of PicoPrep™ were both administered the day before the colonoscopy. The data presented in Table 4 includes the data obtained from both "split dose" administration methods.

[0015] This was planned to be 7-month, phase III, randomized, multi-center, assessor-blinded, parallel-group, active-control, non-inferiority study investigating the efficacy, safety, and tolerability of split-dose PicoPrep™ versus HalfLytely® for oral administration in adult subjects for colon cleansing in preparation for colonoscopy. The study was completed in 6 months.

[0016] The study was conducted at 10 investigative sites in the United States. It was planned that a sufficient number of subjects would be screened to ensure up to 600 randomized subjects (300 subjects to each treatment group). There were 608 subjects enrolled, 307 to the PicoPrep™ arm and 301 to the HalfLytely® arm; 599 subjects completed the study.

Treatment Administered

[0017] Subjects who fulfilled all inclusion and no exclusion criteria were randomized to one of the 2 preparations (PicoPrep™ or HalfLytely®) at Visit 2. On the day before the procedure (24 hours before), all subjects were limited to a liquid diet only; they received a list of clear liquids they were permitted to consume during the treatment. All assessments were performed at Visit 3. Subjects returned to the investigative site for 3 follow-up visits: within 24 to 48 hours (Visit 4), in 7 days (Visit 5), and in 4 weeks (Visit 6) after the colonoscopy procedure.

[0018] Only the subject and the sites' designated unblinded coordinator knew the treatment group to which each subject was randomized; the designated unblinded coordinator instructed the subject in use of the bowel preparation at Visit 2. It is important to note that treatment was also blinded to the gastroenterologist who assessed the efficacy of the 2 tested preparations.

PicoPrep™

[0019] PicoPrep™ powder for oral solution consisted of 2-sachets administered in divided doses (i.e., a picosulfate bowel composition kit). PicoPrep™ was reconstituted by mixing the contents of a sachet in a cup with 5 oz. of cold water. Subjects randomized to the PicoPrep™ treatment group began receiving treatment (first reconstituted sachet) between 5:00 PM and 9:00 PM 1 day before colonoscopy (Visit 2). Following the first administration of PicoPrep™, subjects consumed five 8 oz. glasses of clear liquids and following the second administration, subjects consumed three 8 oz. glasses of clear liquids. Subjects completed receiving treatment (second reconstituted sachet) the next day (Visit 3) at least 5 hours prior to but no later than 9

hours prior to colonoscopy.

HalfLytely®

[0020] HalfLytely® powder form for oral solution consisted of powder for oral solution (two 5 mg bisacodyl tablets + 2 liters polyethylene glycol PEG-EL). HalfLytely® in powder form for oral solution was reconstituted by adding water in the container provided, producing 2 liters of liquid. Subjects randomized to the HalfLytely®, a bisacodyl composition, treatment group began their treatment by taking two 5 mg bisacodyl tablets (according to approved labeled instruction) in the afternoon on the day prior to colonoscopy (Visit 2). After the first bowel movement or after 6 hours, whichever occurred first, subjects began to drink HalfLytely® at a rate of one 8 oz glass every 10 minutes. The HalfLytely® treatment group completed treatment 1 day before colonoscopy (Visit 2).

[0021] Compliance with treatment was documented in the case report form (CRF). Subjects were considered compliant if the dosing occurred within 30 minutes of the specified times. The following diet requirements and restrictions were followed for subjects enrolled in the study, regardless of treatment group: On the day before procedure, subjects were limited to a liquid diet only. Subjects received a subject diary card. For subjects with diabetes, special dietary instructions were provided.

Identity of Investigational Product(s)

PicoPrep™

[0022] PicoPrep™ powder for oral solution consisting of 2 sachets reconstituted and administered in divided doses. PicoPrep™ is a white crystalline powder for oral solution. Each sachet of PicoPrep™ contains: Sodium Picosulfate 10.0 mg, Magnesium Oxide, Light 3.5 gm, and Citric Acid, Anhydrous 12.0 gm. Magnesium oxide and citric acid react in solution to form magnesium citrate. PicoPrep™ was supplied in boxes containing 2 sachets each.

Physical Characteristics

[0023] PicoPrep™ exists in a white crystalline powder for oral solution. Each sachet consists of 4 layers: paper-polyethylene-aluminium-surlyn. Each pack contains a pair of sachets that can be separated by tearing apart the perforated strip. The weight of each sachet contents is 16.1g.

Chemical Characteristics

[0024] Sodium picosulfate (an ingredient of PicoPrep™) is a bisphenol derivative, with the chemical name 4,4'-(2-pyridinylmethelene)-bisphenol-bis (hydrogen sulphate)(ester) disodium salt. The chemical formula is $C_{18}H_{13}NNa_2O_8S_2$ and the molar weight is 481.409 g/mol. The Systematic International Union of Pure and Applied Chemistry name of sodium picosulfate is: disodium 2-[bis(4-sulfonatooxyphenyl)methyl]pyridine.

[0025] The chemical formula of magnesium citrate (an ingredient of PicoPrep™ achieved during reconstitution of magnesium oxide and citric acid) is $C_{12}H_{10}$ Mg_3O_{14} and the molecular weight is 451.1 g/mol. Magnesium oxide has a solubility of 1 in 50 in water and is not soluble in alcohol.

Pharmaceutical Characteristics

[0026] The PicoPrep™ product sachets contain 10 mg sodium picosulfate, 3.5 g light magnesium oxide, and 12 g anhydrous citric acid. The second two active ingredients are widely used in pharmaceutical and food products, and both are USP grade ingredients. Magnesium citrate is listed as a saline laxative in the Food and Drug Administration (FDA) tentative over-the-counter (OTC) Monograph for laxatives (last update August 2006). Other excipients in the sachet are widely used in pharmaceutical and food products, and the majority also listed in the FDA database of Inactive Ingredients for Approved Drug Products.

[0027] The contents of each sachet are dissolved in approximately 150 ml water before taking. When added to water the magnesium oxide and citric acid combine to form magnesium citrate; this is an exothermic reaction and if the liquid becomes hot the patient is instructed to wait until it cools sufficiently to drink.

[0028] The drug substances are dissolved in solution before administration to the patient. They act locally within the intestinal tract and systemic absorption is minimal.

Summary

[0029] PicoPrep™ is a cathartic agent used to clean the bowel prior to X-ray examination, endoscopy or surgery. It is available as white crystalline powder with a faint odor of orange for oral solution. The active ingredients in PicoPrep™ are sodium picosulfate, a bisphenol derivative with the chemical name 4,4'-(2-pyridinylmethylene)-bisphenol-bis (hydrogen sulphate)(ester) disodium salt, and also light magnesium oxide and anhydrous citric acid. When the product is dispersed in water, the magnesium oxide and citric acid interact to form magnesium citrate, which is an osmotic laxative with a powerful cathartic effect. Citric acid is included in excess to ensure a complete effervescence reaction with potassium bicarbonate

when dispersed in water. PicoPrep™ is provided in sachets containing 10 mg sodium picosulphate, 3.5 g light magnesium oxide, and 12 g anhydrous citric acid. PicoPrep™ treatment is administered as two doses taken 6 to 8 hours apart in the 24 hours prior to the hospital procedure.

[0030] The picosulfate the bowel composition comprises sodium picosulfate, magnesium oxide, and citric acid. In some embodiments, the picosulfate bowel composition further comprises at least one additive. The at least one additive is chosen from pharmaceutically acceptable excipients, other active ingredients, flavors, sweeteners, colorings, and combinations thereof.

HalfLytely®

[0031] HalfLytely® powder form for oral solution consisting of powder reconstituted for oral solution administered with two 5 mg bisacodyl tablets (according to approved labeled instruction). HalfLytely® is composed of 2 pink, round, enteric coated 5 mg bisacodyl delayed release tablets, stamped "BRA," and one 2-liter HalfLytely® bottle with powder for reconstitution (two 5 mg bisacodyl tablets + 2 liters polyethylene glycol PEG-EL). HalfLytely® contains the active ingredients PEG-3350 (polyethylene glycol 3350) 210 gm, sodium chloride 5.6 gm, sodium bicarbonate 2.86 gm, and potassium chloride 0.74 gm. After adding 2 liters of water, the reconstituted HalfLytely® solution (clear and colorless) contains PEG-3350 31.3 mmol/L, sodium 65 mmol/L, chloride 53 mmol/L, bicarbonate 17 mmol/L, and potassium 5 mmol/L.

[0032] Lemon-lime HalfLytely® and Bisacodyl Tablets Bowel Prep Kit contains 1 gm lemon-lime flavoring ingredient. HalfLytely® is manufactured and supplied by Braintree Laboratories, Inc. Braintree, MA. It is an approved GI lavage product indicated for cleansing of the colon as a preparation for colonoscopy in adults.

[0033] HalfLytely® is currently supplied to the US markets in one 2-liter bottle with powder for reconstitution and 2 bisacodyl tablets (two 5 mg bisacodyl tablets + 2 liters polyethylene glycol PEG-EL). The HalfLytely® arm of this trial used the product commercially available in the United States.

Treatment Compliance

[0034] Preparations were given at the direction of the unblinded coordinator. The exact hour of administration varied according to the time of the procedure; therefore the coordinator who dispensed the drug instructed the subject about the exact time of administration during Visit 2.

[0035] Compliance with study drug was documented in the case report form. Subjects were

considered compliant if dosing occurred within 30 minutes of the following specified timings:

Day before colonoscopy procedure:

first reconstituted sachet: between 5:00 PM - 9:00 PM

Day of colonoscopy procedure:

second reconstituted sachet: 5 hours prior to but no later than 9 hours prior to procedure

Assessments, Endpoints, and Appropriateness of Measurements

Assessments

[0036] The primary variable was: The Aronchick Scale for demonstration of non-inferiority of PicoPrep™ to HalfLytely® in efficacy of overall colon cleansing in preparation for colonoscopy.

[0037] The secondary variables were: (1) The Ottawa Scale for demonstration of non-inferior of PicoPrep™ to HalfLytely® in efficacy of ascending colon cleansing. (2) Fluid assessment. (3) A standardized subject questionnaire for determination of tolerability and satisfaction of the preparation. (4) Monitoring of AEs, collection of concomitant medications, physical examination including weight and orthostatic vital signs (blood pressure and pulse rate), ECG findings, and clinical laboratory tests including change from baseline, for determination of safety.

Efficacy Assessments

Aronchick Scale

[0038] Using the Aronchick Scale for the primary efficacy assessment of the preparation, the gastroenterologist performing the evaluation of overall colon cleansing was blinded to treatment. Table 1 provides grades of overall colon cleansing and their definitions. A subject was considered a "responder" if overall colon cleansing was excellent or good on this 4-point scale.

Table 1 Aronchick Scale

Grade	Description
Excellent	>90% of mucosa seen, mostly liquid stool, minimal suctioning needed for adequate visualization

Grade	Description
Good	>90% of mucosa seen, mostly liquid stool, significant suctioning needed for adequate visualization
Fair	>90% of mucosa seen, mixture of liquid and semisolid stool, could be suctioned and/or washed
Inadequate	<90% of mucosa seen, mixture of semisolid and solid stool which could not be suctioned or washed

Ottawa Scale

[0039] Using the Ottawa Scale for the secondary efficacy assessment of the preparation, the gastroenterologist performing the evaluation of cleansing of the ascending colon was blinded to treatment. In addition to the ascending colon, data for the mid (transverse, descending) colon, and the descending (recto-sigmoid) colon were graded 0, 1, 2, 3 or 4 according to the definitions in Table 2.

Table 2 Ottawa Scale (Cleanliness)

Grade	Description
0	**Excellent:** Mucosal detail clearly visible. If fluid is present, it is clear. Almost no stool residue.
1	**Good:** Some turbid fluid or stool residue but mucosal detail still visible. Washing and suctioning not necessary.
2	**Fair:** Turbid fluid or stool residue obscuring mucosal detail. However, mucosal detail becomes visible with suctioning. Washing not necessary
3	**Poor:** Presence of stool obscuring mucosal detail and contour. However, with suctioning and washing, a reasonable view is obtained.
4	**Inadequate:** Solid stool obscuring mucosal detail and contour despite aggressive washing and suctioning.

[0040] The score of all colon segments was evaluated as

Clinical Success:	0, 1, or 2 score in the ascending colon
Not a Clinical Success:	Presence of 3 or 4 score in the ascending colon

Subject's Tolerability and Satisfaction Questionnaire

[0041] A standard questionnaire was used to assess subjects' tolerability and satisfaction and compared the treatment groups. This questionnaire was administered to subjects by the study

site coordinator at Visit 3 prior to sedation for the colonoscopy.

[0042] The questions were:

1. 1. How easy or difficult was it to consume the study drug?
2. 2. Were you able to consume the entire prep as instructed?
3. 3. Please describe your overall experience of the study preparation:
4. 4. The taste of this study preparation was:
5. 5. Would you ask your doctor for this preparation again if you need another colonoscopy in the future?
6. 6. Would you refuse the same preparation again if it were to be prescribed to you in the future?
7. 7. Have you had a colonoscopy before (within the past 3 years)?

   7a. If yes, which type of colon cleansing medication(s) did you receive?

   7b. If yes, provide the name of the colon cleansing medication used in most recent colonoscopy:

   7c. If yes, do you remember if you were able to complete as instructed the entire colon cleansing medication you used in you most recent colonoscopy?

   7d. If yes, would you describe the colon cleansing medications you received for this colonoscopy as? (1: Much better --- 5: Much worse)

Safety Assessments

[0043] Safety variables included:

- Medical history and demographic data
- Physical examination
- Weight and orthostatic vital signs (including blood pressure and pulse rate)
- 12-lead ECGs
- Clinical laboratory tests including urinalysis
- Incidence, severity, and causality of AEs/serious adverse events (SAEs)
- Concomitant medication reporting

Efficacy Results and Tabulations of Individual Subject Data

Primary Efficacy Variable: Aronchick Scale

[0044] The primary efficacy variable was the percentage of subjects classified as responders (successes), where responder is a subject who had a rating of Excellent or Good on the Aronchick scale at Visit 3 during colonoscopy.

[0045] The percentage of responders was similar in both the intent-to-treat and the per protocol analysis sets and consistently greater in the PicoPrep™ than the HalfLytely® treatment group in both analysis sets.

[0046] In both analysis sets, the difference between PicoPrep™ and HalfLytely® satisfied the criteria for non-inferior of PicoPrep™ versus HalfLytely® in response rates; subsequently, the lower bound of the CI was determined, and the superiority of PicoPrep™ was declared.

Secondary Efficacy Endpoints

[0047] The secondary efficacy variables were the percentage of subjects classified as responders (successes), where responder is a subject who had a rating of Excellent, Good, or Fair on the Ottawa Scale at Visit 3 during colonoscopy by section of the colon (ascending colon, mid colon, and recto-sigmoid colon) and overall, as well as fluid assessment (small, moderate, or large amount), and a standardized subject questionnaire for determination of tolerability and satisfaction of the preparation.

[0048] The secondary analyses using the Ottawa Scale for ascending colon cleansing were consistent with the results of the primary analysis; PicoPrep™ was found to be non-inferior to HalfLytely®. Additionally, in all sections of the colon, PicoPrep™ was found to be superior to HalfLytely®. Further, in the fluid assessment and across the subject questionnaire for the determination of tolerability and satisfaction of the preparation, PicoPrep™ demonstrated statistically "better" results when compared with HalfLytely®.

Colonoscopy Timing

[0049] The Study's primary and secondary objectives sought to demonstrate non-inferiority and assess safety, efficacy, and tolerability. Additionally, it was discovered that with the picosulfate composition (i.e., PicoPrep™), a minimal time interval could be achieved between the last ingestion of the picosulfate composition and the performance of the colonoscopy.

[0050] Although the study protocol for PicoPrep™ proscribed administration of the second reconstituted sachet at least 5 hours prior to but no later than 9 hours prior to colonoscopy, deviations in time administration occurred. Those deviations included the administration of PicoPrep™ less than 5 hours prior to the colonoscopy procedure.

[0051] In some instances, administration occurred less than or equal to 4 hours prior to the colonoscopy procedure, e.g., less than about 4 hours, less than about 3 hours, less than about 2 hours and further for example, a time interval ranging from about 4 hours to about 1 hour, from about 3 hours to about 1 hour, from about 2 hours to about 1 hour, from about 3 hours to about 2 hours, prior to the colonoscopy, or any half hour interval in between. Despite the deviations in time from administration, patients still responded with PicoPrep™ under the Aronchick scale. Table 3 below provides the data for those patients that were administered PicoPrep™ less than or equal to 4 hours prior to the colonoscopy procedure. Table 4 below summaries the data for those patients that were administered PicoPrep™ at time intervals according to the protocol.

Table 3 - Time from Last Dose of Treatment to Start of Colonoscopy and Response

Patient Identification	Treatment	Time From Last Dose of Treatment to Start of Colonoscopy (hours)	Response
150 (Not of this invention)	PicoPrep™	3.67	Responder
461 (Example of Invention)	PicoPrep™	1.78	Responder
Responder = If "Good" or "Excellent" designation of overall colon cleansing, based on the Aronchick Scale			

Table 4 - Summary of Responders and Non-responders for Various Time Intervals with PicoPrep™

Response (Responder or Non-responders)	Time Interval	Number of Patients
Responders	<= 4 hours	2
Responders	>4 hours	490
Responders	<=6 hours	74
Responders	> 6 hours	418
Non-responders	<=4 hours	0
Non-responders	> 4 hours	96
Non-responders	<=6 hours	10
Non-responders	> 6 hours	86
Responder = If "Good" or "Excellent" designation of overall colon cleansing, based on the Aronchick Scale		

II. PicoPrep™ Split-Dose v. PicoPrep™ Day Before Dose Study

[0052] Overall Clinical Study and Design: A randomized, assessor-blinded, multi-centered study investigated the efficacy, safety and tolerability of "Split-Dose" sodium picosulfate,

magnesium oxide, and citric acid for oral administration, for example PicoPrep™ or Pico-Salax®, versus "Day Before" of the same product for colon cleansing in preparation for colonoscopy.

[0053] The study was conducted at one investigative site in Canada. It was planned that a sufficient number of subjects would be screened to ensure up to 16 randomized subjects (8 subjects to each treatment group).

[0054] Subjects having elective colonoscopy who fulfilled all inclusion and no exclusion criteria were randomized to one of two treatment groups ((1)split-dose group or (2) day-before group) at Visit 2. On the day before the procedure (24 hours before), all subjects were limited to a liquid diet only. All assessments were performed at Visit 3 occurring less than 5 days from Visit 2.

1. (1) Split-Dose Group: Subjects randomized to the split-dose group began treatment (1st reconstituted sachet) on the day before colonoscopy between 5:00 and 9:00 PM, and completed the treatment (2nd reconstituted sachet) the next day, at least 2 hours, but no later than 4 hours, prior to colonoscopy.
2. (2) Day-Before Group: Subjects randomized to the day-before group began treatment (1st reconstituted sachet) one day before colonoscopy between 4:00 and 6:00 PM, and completed the treatment (2nd reconstituted sachet) at least 6 hours later, between 10:00 PM and 12:00 AM.

[0055] Sachets were reconstituted by mixing the contents of the sachet in a cup with approximately 5 oz. of cold water. Following each administration subjects consumed five 8 oz. glasses of clear liquids after the first administration and three 8 oz. glasses of clear liquids after the second administration.

Treatment Compliance

[0056] As in the study discussed above, preparations were given at the direction of the unblinded coordinator. The exact hour of administration varied according to the time of the procedure; therefore the coordinator who dispensed the drug instructed the subject about the exact time of administration during Visit 2.

[0057] Compliance with study drug was documented in the case report form. Subjects were considered compliant if dosing occurred within 30 minutes of the specified times.

Assessments, Endpoints, and Appropriateness of Measurements

[0058] Assessments, endpoints, and appropriateness of measurements were the same as discussed above.

Colonoscopy Timing

[0059] The Study's primary and secondary objectives sought to demonstrate non-inferiority and assess safety, efficacy, and tolerability with regard to the minimal time interval achieved between the last ingestion of the picosulfate composition and the performance of the colonoscopy discussed above.

Efficacy Conclusions

[0060] This study examined the efficacy, patient tolerability, and safety of sodium picosulfate, magnesium oxide, and citric acid for oral administration, for example PicoPrep™ or Pico-Salax®, when given as two doses the "Day Before" compared to a "Split Dose" regimen where the second dose was given less than 4 hours to the scheduled time of colonoscopy. The study demonstrated that both dosing regimens were feasible and effective.

[0061] The Study enrolled 16 subjects between the ages of 47 and 74 comprising 11 males and 5 females, all of which completed the study. There were no major protocol deviations. One patient took his second dose at a 4 hour interval as opposed to 6 hours. All patients were included in the analysis.

[0062] The primary efficacy variable was the percentage of subjects classified as responders (successes), where responder is a subject who had a rating of Excellent or Good on the Aronchick scale at Visit 3 during colonoscopy. See Table 5.

Table 5 - Summary of Responders and Non-responders

Treatment Group	Total Patients	No. of Responders	No. of Non-Responders
Split-Dose	8	5	3
Day Before	8	4	4
Responder = If "Good" or "Excellent" designation of overall colon cleansing, based on the Aronchick Scale			

[0063] Of the eight patients randomized to the "Split Dose" group, five patients were classified as responders, four of which were rated as excellent and one as good on the Aronchick scale. Of eight patients randomized to the "Day Before" group, four were classified as responders, all which were classified as good on the Aronchick scale and none as excellent.

[0064] The evaluation of the efficacy of the preparation using the Aronchick score showed that

there was a trend towards better cleansing with the "split dose" (4 preparations deemed excellent vs. 0 in the "day--before" dosing group) but this did not reach statistical significant. See Table 6. This may represent a type II error as the sample size is small. There was also a significant improvement in the right colon cleansing using the Ottawa Bowel Preparation Score which supports this contention. See Table 6. Previous studies showed that split dosing can provide improved cleansing, particularly if the colonoscopy is performed in the afternoon i.e. the procedure is further from the last dose of the cleansing agent. Nonetheless, none of the dosing schedules employed in the current study were scored as inadequate suggesting both regimens have efficacy.

Table 6 - Summary of Ottawa Bowel Preparation Scores and Aronchick scores.

Study ID #	Randomization	Procedure completed	OBP right colon	OBP mid colon	OBP recto-sigmoid	Fluid Score	Total OBP score	ABP Score
1	1	1	3	3	0	1	7	2
2	2	1	2	2	2	1	7	1
3	1	1	3	2	2	1	8	2
4	2	1	3	3	3	2	11	3
5	2	1	2	2	2	1	7	1
6	1	1	3	3	2	1	9	3
7	2	1	3	2	1	0	6	3
8	1	1	3	3	3	0	9	3
9	2	1	2	2	1	0	5	1
10	1	1	3	2	2	0	7	2
11	1	1	4	1	1	0	6	3
12	2	1	2	1	2	0	5	1
13	2	1	3	2	2	0	7	2
14	1	1	3	2	3	0	8	3
15	2	1	3	2	3	1	9	3
16	1	1	3	2	3	0	8	2

[0065] Table Designations: OBP=Ottawa Bowel Prep Scale; ABP=Aronchick Bowel Prep Scale; Randomization (1=day before 2=split dose); Procedure completed (1=yes; 2=no due to poor prep; and 3=no due to other reason); OBP right colon (0=excellent; 1=good; 2=fair; 3=poor; 4=inadequate); OBP mid colon (0=excellent; 1=good; 2=fair; 3=poor; 4=inadequate); OBP recto-sigmoid (0=excellent; 1=good; 2=fair: 3=poor: 4=inadequate); Fluid Score (0=small; 1=moderate: 2=large); ABP Score (1=excellent; 2=good; 3=fair; 4=inadequate)

Primary End Points

[0066] There was a trend towards a better Aronchick score for the split dose group mean and standard deviation (mean ± standard deviation = 1.88 ± 0.991; 4/8 reported as excellent); compared to the day before group (mean ± standard deviation = 2.5 ± 0.535; 0/8 reported excellent) but this was not significant when analyzed using a Mann Whitney test.

Secondary End Points

[0067] There was no difference in the overall Ottawa bowel preparation score for the "split dose" group compared to the "day-before" group. The right colon (ascending colon) scores were significantly better in the "split dose" group ($p = 0.015$).

Adverse Events

[0068] No serious adverse events were reported to nurse or physicians. There were no clinically significant changes in physiological (postural vital signs) or biochemical parameters, including changes in creatinine, sodium, potassium, or magnesium. There was no difference in the reporting of symptoms between the "day-before" group and the "split dose" group.

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

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P A T E N T K R A V

1. Picosulfattarmsammensætning til anvendelse i en fremgangsmåde til afpasning af tidspunktet for en koloskopiprocedure, hvilken fremgangsmåde omfatter:

at indgive en første picosulfattarmsammensætning til patienten dagen før proceduren;

at indgive en anden picosulfattarmsammensætning til patienten på dagen for proceduren; og

at udføre proceduren fra 3 timer til 1 time efter indgift af den anden tarmsammensætning;

hvor den første og den anden tarmsammensætning omfatter natriumpicosulfat, magnesiumoxid og citronsyre.