Randomized, Double-Blind, Placebo-Controlled Pilot Study Assessing the Ability of Inositol Hexaniacinate (Hexanicotinate) to Reduce Symptoms of Non-Ulcer Dyspepsia Possibly Due to Insufficient Hydrochloric Acid Production

Jonathan E. Prousky, MSc, ND[1,2] and Dugald Seely, MSc, ND[3,4]

[1] Chief Naturopathic Medical Officer, Professor, Canadian College of Naturopathic Medicine, 1255 Sheppard Avenue East, Toronto, Ontario, M2K 1E2, Tel: 416-498-1255 ext. 235, email: jprousky@ccnm.edu
[2]Editor, Journal of Orthomolecular Medicine, email: editor@orthomed.org
[3]Department of Research & Clinical Epidemiology, Canadian College of Naturopathic Medicine, Toronto, ON
[4]Editor, International Journal of Naturopathic Medicine

Abstract

Background: *No specific etiology can be identified in patients with a form of dyspepsia known as functional or nonulcer dyspepsia (NUD). One of the "unidentified" causes of NUD might be insufficient gastric hydrochloric acid (HCl) secretion.*

Objective: *To test the ability of inositol hexaniacinate (IHN) to reduce symptoms of NUD among subjects with insufficient gastric hydrochloric acid (HCl), as determined by Gastro-Test® pH measurements above 3.*

Design: *Double-blind, placebo-controlled trial.*

Setting: *The Robert Schad Naturopathic Clinic, the outpatient clinic of the Canadian College of Naturopathic Medicine (North York, Ontario).*

Intervention: *Twenty-three subjects with Gastro-Test® pH results above 3 were randomly allocated to either IHN (1782 mg/day) or placebo groups.*

Main Outcome Measures: *Gastrointestinal Symptom Questionnaire, Gastro-Test® pH measurements, compliance with the study protocol, and adverse events related to taking IHN and/or placebo capsules.*

Results: *There was a non-significant (i.e., non-statistical) trend towards a total Gastrointestinal Symptom Questionnaire score decrease in the treatment group compared to the control group as evaluated by a random effect models ($p = 0.08$). Using a multivariate linear regression model adjusting for potential confounders, no significant interactions were found between fasting gastric pH levels and the intervention ($p > 0.20$).*

Conclusion: *IHN might be a promising treatment for NUD, but further investigation is required. The total Gastrointestinal Symptom Questionnaire score did not correlate with gastric pH as measured by the Gastro-Test®. This finding was potentially the result of operator inexperience with the Gastro-Test® procedure.*

Trial Registration: *Approved and conducted before the Natural Health Products Directorate of Canada, Bureau of Clinical Trials and Health Science, required trial registration involving natural health products.*

Background

Dyspepsia is defined as chronic or recurrent discomfort concentrated in the upper abdomen and associated with belching, bloating, heartburn, nausea, and vomiting.[1] It affects approximately twenty-five percent of the population each year, even though most affected people do not seek medical care for the condition.[2,3] Fifty to sixty percent of patients with dyspepsia have functional or non-ulcer dyspepsia (NUD) where no specific aetiology can be identified.[4-6] Up to forty percent of cases of dyspepsia are caused by peptic ulcer disease and reflux esophagitis, with less than two percent of cases due to gastric or oesophageal cancer.[4] A contributing factor in the symptoms of NUD might be insufficient gastric hydrochloric acid (HCl) secretion, a condition known as either achlorhydria or hypochlorhydria depending on the severity of gastric HCl deficiency. Hypochlorhydria is a condition in which the parietal cells of the stomach secrete insufficient amounts of HCl when stimulated by the presence of food or other mediators. Achlorhydria is much more severe and occurs when parietal cells no longer function and acid secretion ceases. Common signs and symptoms of insufficient HCl production can be found in **Table 1** (below). Regardless of whether the term 'achlorhydria' or 'hypochlorhydria' is used, the symptoms associated with either can produce the symptoms that characterize NUD.

A potential therapeutic approach for the treatment of NUD, when insufficient gastric HCl is suspected or has been measured objectively, is to provide HCl supplementation. Many naturopathic doctors use HCl supplementation to palliate the symptoms of NUD. An alternative to HCl supplementation is to attempt the stimulation of HCl production by parietal cells and thus more directly treat the condition. Prousky and Seely reported some evidence of a therapeutic effect in which a patient was given inositol hexaniacinate/hexanicotinate (IHN), a specific form of vitamin B_3. In this case, the IHN appeared to lower fasting gastric pH (i.e., increased gastric HCl secretion) and reduce symptoms of achlorhydria.[7] It was hypothesized that IHN might have reduced symptoms of NUD by facilitating gastric HCl secretion.[7] To evaluate whether IHN has the ability to reduce symptoms of NUD we conducted a randomized, placebo-controlled trial to test this hypothesis. Herein we describe a trial on subjects with insufficient fasting gastric HCl production, as determined by Gastro-Test® pH measurements above 3. The results of this study should help elucidate whether IHN

Table 1. Common signs and symptoms of insufficient HCl production

- A sense of fullness after eating
- Acne
- Bloating, belching, burning, and flatulence immediately after eating
- Chronic candida infections
- Chronic intestinal parasites or abnormal flora
- Dilated blood vessels in the cheeks and nose
- Indigestion, diarrhoea, or constipation
- Iron deficiency
- Itching around the rectum
- Multiple food allergies
- Nausea after taking supplements
- Undigested food in stool
- Upper digestive tract 'gassiness'
- Weak, peeling, and cracked fingernails

(Adapted from: Murray M: Indigestion, antacids, achlorhydria and H. pylori. *Am J Nat Med*, 1997;4(1):11-14, 16-17)

can effectively reduce symptoms of NUD and/or stimulate fasting gastric HCl secretion.

Methods

Ethics

The institutional review board of the Canadian College of Naturopathic Medicine (CCNM) approved the study protocol. All subjects gave written informed consent prior to study inclusion. We adhered to the Declaration of Helsinki during all phases of study and this report follows the guidelines of the International Committee of Medical Journal Editors (available at www.icmje.org).

Setting

The pilot trial took place at the Robert Schad Naturopathic Clinic (RSNC), the outpatient clinic of CCNM. Recruitment of 62 participants was achieved in two groups comprising 36 and 26 people. For the first group of 36 subjects, the study commenced on October 17, 2003, and ended on November 17, 2003. For the second group of 26 subjects, the study commenced on October 21, 2004, and ended on November 18, 2004.

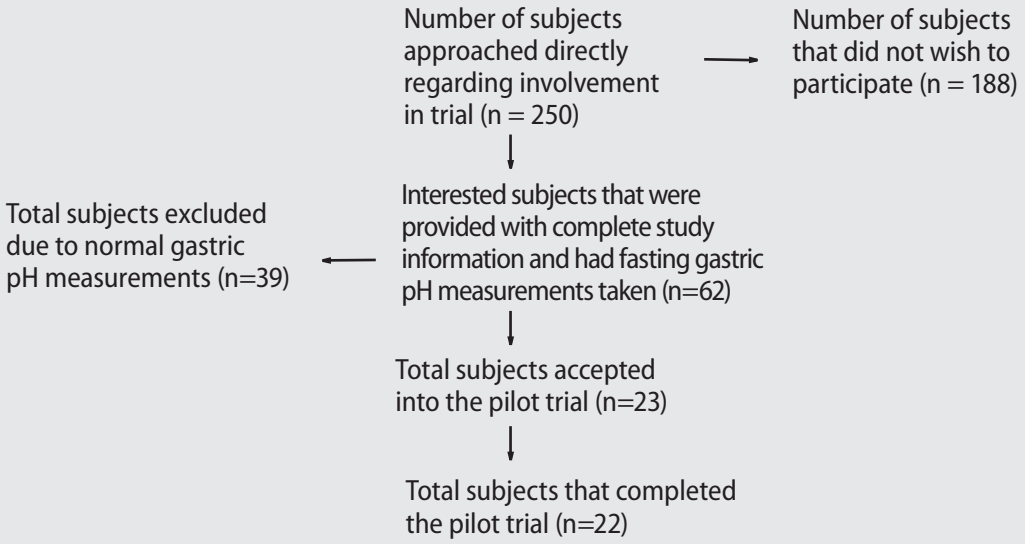
Participants

We recruited healthy volunteers from a student population. To be eligible for the study, participants had to be 20-40 years of age and able to comprehend and complete the intake and informed consent forms. In addition, they had to agree to complete a 10-12 hour pre-trial fast (water only) and to abstain from using any additional natural health products during the study. Participants were not asked to avoid caffeine, alcohol, or make any dietary changes during the duration of the study, except when fasting. Key criteria for inclusion required that participants had a fasting gastric pH above 3 on the Gastro-Test®. Participants were excluded if they were pregnant or attempting to become pregnant, or had a history of liver disease, gout, peptic ulcer disease, inflammatory bowel disease, diabetes mellitus, intolerance to caffeine, and intolerance to niacin. Participants did not receive remuneration for participation.

Sampling and Recruitment

Participant flow is illustrated in **Figure 1** (below). Students from CCNM were invited to participate and posters were placed on bulle-

Figure 1. Participant recruitment flow diagram



tin boards throughout the college campus to encourage recruitment. In addition, several brief information sessions were held at the beginning of lectures to provide basic information about the study. Interested parties contacted the lead investigator (Prousky) directly, either by phone or e-mail and provided their name, telephone number, preferred time of contact, and mailing address. Interested subjects were given the complete study information, including the standard medical intake and consent forms. Of the 250 subjects that were informed of the study, 62 completed the required forms and had their fasting gastric pH measurements taken. Twenty-three subjects that had fasting gastric pH measurements greater than 3 were randomly allocated to either treatment (i.e., IHN) or placebo groups. All participants had to provide informed consent and indicate a high level of commitment to the trial and agree to be compliant with the study procedures. One patient from the placebo group had to stop involvement in the trial soon after commencement due to an unplanned pregnancy, thus reducing the placebo total to 11 subjects. Twenty-two subjects completed the trial.

Pilot Study Design

A randomized, double-blind, placebo-controlled clinical trial design was used. Upon acceptance to participate in the trial, all 62 subjects were given the dates of trial commencement and instructions. All 62 subjects attended the trial commencement dates (36 on October 17, 2003 and 26 on October 21, 2004), and were administered the Gastro-Test® according to the published procedure between the hours of 8:00AM and 9:00AM.[8] The Gastro-Test® is thought to provide an accurate measurement of gastric pH, and can identify gastroesophageal reflux disease and gastroesophageal bleeding.[8] Each subject also completed the Gastrointestinal Symptom Questionnaire (See Appendix A, p. 31). The questionnaire, developed by Prousky, identifies 15 symptoms that reflect insufficient HCl production, and assesses their presence and frequency on a 3-point (0-3) Likert-type scale. The symptoms included in the questionnaire were adapted from two prior publications that reported on the most common clinical signs and symptoms of insufficient HCl production.[9,10] Prousky identified 15 similar (i.e., overlapping) symptoms from both publications and used them to develop the questionnaire.

Of the 62 students that completed the fasting Gastro-Test®, 39 (63%) were not eligible for the trial since they had normal gastric pH readings (pH ≤ 3), whereas 23 (37%) of the students were eligible since they had gastric pH values greater than 3, suggesting either hypo- or achlorhydria. Several different investigators have used fasting pH values above 3.5,[11,12] 6.0,[13,14] 7.0,[15] or 8.2[16] to establish a diagnosis of achlorhydria. This has created confusion as to the exact pH that clearly defines the diagnosis, and the pH that would help to differentiate achlorhydria from hypochlorhydria. Fasting pH was found to be a sensitive method for diagnosing "true" hypochlorhydria in a study by Feldman and Barnett,[17] but these investigators failed to distinguish between hypochlorhydria from achlorhydria. As there seems to be no consensus on the pH value that defines hypo- and achlorhydria, we set a pH value greater than 3 as suggestive of insufficient gastric HCl secretion for purposes of this trial.

Randomization was facilitated by a computer generated list with each subject assigned to the treatment or placebo group in a blinded fashion by the trial coordinator (Seely) according to the allocation list. Eleven subjects in total were assigned to the treatment group and 11 subjects were assigned to the placebo group. Participant characteristics are noted in **Table 2**, (p. 25). Twenty-two subjects returned after the 30 days to redo the Gastro-Test®. Each subject was also asked to complete the Gastrointestinal Symptom Questionnaire at baseline and following 30 days of treatment with either IHN or placebo. To provide a measure of compliance, subjects were also asked to complete a medication diary and return any remaining pills at the time of their second Gastro-Test® for pill count.

Table 2. Participant Characteristics

Groups	Gender	Average Age (years)	Average Weight (lbs)
Placebo (n=11)	9 females and 2 males	26.91 ± 3.45	146.36 ± 27.79
Intervention (n=11)	10 females and 1 male	25.55 ± 3.38	146.45 ± 29.20

Study Intervention

Douglas Laboratories® Canada provided the IHN and placebo capsules. Sealed bags containing 100 pills were provided to each of the subjects, containing 594 mg of IHN (540 mg of crystalline niacin and 54 mg of inositol in a gelatine capsule) for the treatment group and 100 placebo pills identically matched for size, smell, and look in the placebo group. The placebo contained microcrystalline cellulose, silicon dioxide, dicalcium phosphate, magnesium stearate, and stearic acid in a gelatin capsule. Each person was instructed to take three capsules first thing in the morning with or without breakfast for the next 30 consecutive days. We chose this dose of IHN (1782 mg) since it approximated a dose used in published case report demonstrating improvement in a subject's NUD symptoms and gastric pH following IHN supplementation.[7]

Outcome Measures

Our primary objective was to determine if IHN can reduce symptoms associated with insufficient HCl production (in subjects presumed to have NUD) as determined by a reduction in their total Gastrointestinal Symptom Questionnaire scores. Our secondary objective was to assess if IHN was capable of stimulating gastric HCl secretion, and therefore lowering the fasting gastric pH measurements of the subjects in the treatment group. Other objectives included compliance with the study protocol, adverse reactions related to the Gastro-Test® procedure, and adverse events related to taking IHN and/or placebo capsules.

Statistical Analyses

Effects of the intervention on Gastrointestinal Symptom Questionnaire scores and fasting gastric pH levels were studied using the student's t-test. Interaction between fasting gastric pH levels and intervention effects on Gastrointestinal Symptom Questionnaire scores was evaluated using linear regression models controlling gender, weight, and age effects. Statistical analysis was conducted using SAS v.9.

Results

There was a non-significant (i.e., non-statistical) trend towards a total Gastrointestinal Symptom Questionnaire score decrease in the treatment group compared to the control group (**Table 3**, p. 26), as evaluated by a random effects model ($p = 0.08$, **Figure 2**, p. 26).

Gastric pH levels did not interact with intervention effects on total Gastrointestinal Symptom Questionnaire score

In a multivariate linear regression model evaluating factors affecting total Gastrointestinal Symptom Questionnaire score alterations, we found no significant interactions between fasting gastric pH levels and interventions ($p > 0.20$). Factors of age, weight, gender, and treatment compliance also showed no significant effects ($p > 0.20$).

Fasting gastric pH measurements decreased (independent of the intervention) in both placebo and treatment groups

There was a highly significant decrease ($p<0.01$) in fasting gastric pH levels (independent of the intervention) in the second

Figure 2. Alterations of Total Gastrointestinal Symptom Questionnaire Score

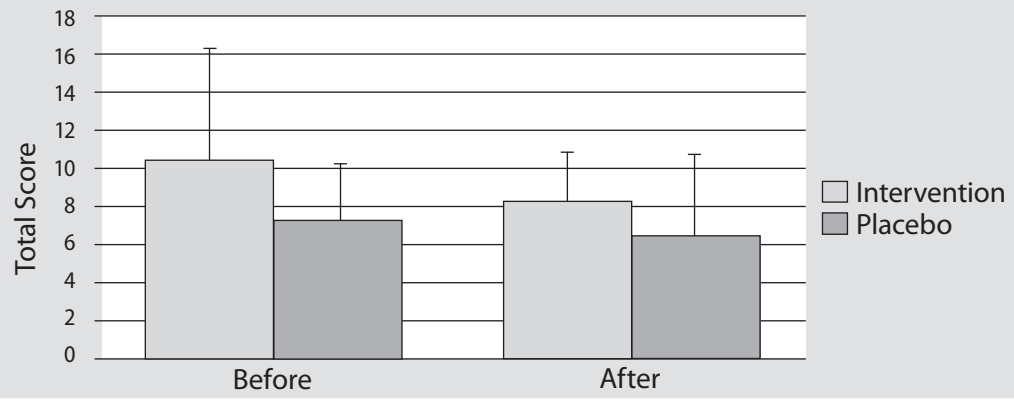


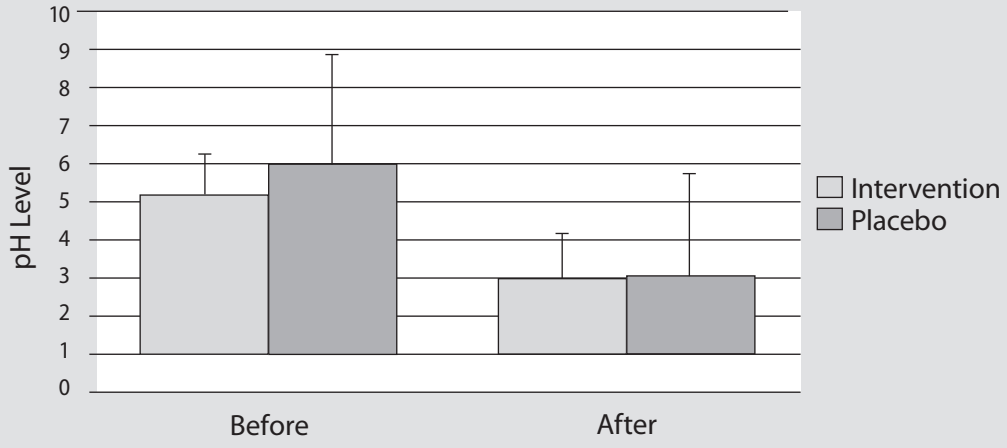
Table 3. Alterations of Total Gastrointestinal Symptom Questionnaire Score

Groups	Average Baseline Gastrointestinal Symptom	Average Final Gastrointestinal Symptom Questionnaire Score	Total Gastrointestinal Symptom Questionnaire Score Alteration
Placebo (n=11)	7.40 ± 2.56	6.55 ± 4.39	-0.64 ± 2.91
Intervention (n=11)	10.73 ± 5.55	8.45 ± 2.91	-2.27 ± 4.50

Table 4. Recorded adverse during the 30-day trial period

IHN (n = 6)	**Placebo (n = 7)**
• Acid reflux and stomach upset	• Acid reflux
• Daily nausea	• Constipation
• Constipation	• Bloating
• Flatus	• Burning sensation in the throat, increased bloating and flatus, and nausea and vomiting
• Increased bloating and flatus	• Nausea
• Bloating and flatus	• Flatus and constipation
	• Abdominal discomfort and stool changes

Figure 3. Alterations of Fasting Gastric pH Level



visit over the first visit in both placebo and treatment groups (**Figure 3**, above).

Treatment compliance was suboptimal

The medication diaries of all 22 subjects were evaluated for compliance with the trial protocol. Ten subjects reported days in which they neglected to take the allocated intervention. This amounted to a total of 27 days from a possible 300 intervention days in which IHN or placebo were not taken. Four subjects from the placebo group missed a combined total of 6 intervention days. Six subjects from the treatment group missed a combined total of 21 intervention days. For the remaining 12 subjects or 360 intervention days treatment compliance was reported to be 100 percent. It cannot be ascertained from this data if the 27 missed days had any influence (i.e., negative or positive) on the reported results, but compliance with the trial protocol was suboptimal.

Adverse Reactions from IHN and Placebo were almost identical

All 22 subjects that completed the pilot clinical trial recorded adverse reactions in a medication diary. None of the recorded adverse reactions were considered serious. **Table 4** (p. 26) lists adverse reactions that were recorded by 13 subjects (6 from the IHN group and 7 from the placebo group).

Adverse Reactions from the Gastro-Test® were virtually absent

Eighty-four Gastro-Tests® were administered during the course of this study. Only 2 subjects gagged excessively from undergoing the testing procedure, but were otherwise capable of completing it. No other adverse reactions were reported from the administration of the Gastro-Test®.

Fasting Gastric pH levels did not correlate with total Gastrointestinal Symptom Questionnaire score

There was no significant correlation between fasting gastric pH levels and the total Gastrointestinal Symptom Questionnaire scores among the 62 subjects that were evaluated ($r = -0.1142$, $p = 0.33$). We were expecting to see a correlation between total Gastrointestinal Symptom Questionnaire scores and fasting gastric pH measurements, in that, high questionnaire scores would correlate with higher (i.e., basic) fasting gastric pH measurements.

Discussion

The results of this pilot trial showed that gastrointestinal symptoms, as reflected in the Gastrointestinal Symptom Questionnaire, had no correlation with fasting gastric pH measurements. There was, however, a

non-significant trend towards symptomatic improvement with IHN over placebo in reducing the total Gastrointestinal Symptom Questionnaire score. Since there were no requirements about taking IHN with or without food, we cannot ascertain the influence the presence or absence of stomach contents had upon the results. We also did not test the IHN and placebo tablets for their gastric pH buffering capacities. The disintegration times (as furnished by the manufacturer) for the IHN and placebo tablets were 12 minutes and 10 respectively. It was not possible, therefore, to statistically analyze the impact disintegration times and pH buffering capacities had on gastric pH measurements and the total Gastrointestinal Symptom Questionnaire score.

Treatment compliance was suboptimal since there were differences in compliance rates between subjects on placebo and subjects on IHN. Since these differences were not considered in our statistical analysis, it is uncertain if these differences impacted the results.

With respect to mechanism of action, our hypothesis (which requires further study) is that IHN might help by influencing the central nervous system (CNS). IHN is composed of six niacin molecules ester bonded to one central inositol molecule. The IHN is absorbed essentially intact, and, unlike niacin, it does not act as an acid in the stomach.[7] Therefore, there is no mechanism by which IHN can directly acidify the stomach. Studies have delineated the role of the CNS in conducting and processing visceral signals and suggest that alteration in brain processes involving perception and affective responses play key factors in the pathogenesis of functional gastrointestinal symptoms.[18,19] The niacin, contained within the larger IHN molecule, converts to the nicotinamide nucleotide coenzymes within the liver and also converts to niacinamide, the amide form of niacin.[20] Anecdotal reports have demonstrated reductions in anxiety among several patients given niacinamide for therapeutic purposes.[21,22] The inositol part of the IHN molecule also has beneficial effects upon the CNS as suggested in previous double-blind studies on depression,[23,24] panic disorder,[25] and obsessive-compulsive disorder.[26] IHN might, therefore, facilitate improved gastric function by stimulating and/or normalizing parasympathetic tone. IHN might also moderate afferent neuronal transmissions from the gastric mucosa itself. The overall net effect of these possible CNS (i.e., brain-gut) altering interactions would be improved gastric function (and fewer symptoms) since a relaxed state facilitates better gastrointestinal function.

With respect to safety, 1,782 mg/day of oral IHN over the course of one month was well tolerated and not associated with any serious adverse outcomes. The subjects in the treatment and placebo groups reported very similar side effects, mostly involving the gastrointestinal system. In clinical studies evaluating the therapeutic uses of IHN, doses up to 4 g daily have been shown to be safe and relatively free of side effects.[27]

The other aspects of this clinical study involved the use of the Gastro-Test®. We used the Gastro-Test® to exclude subjects with normal gastric acidity, and identify subjects with insufficient fasting gastric pH so that they could be included in our pilot clinical trial. This was the only practical way in which we were able to assess gastric acidity because direct gastric intubation would have been very expensive, invasive, and impractical. Our results showed that both the treatment and placebo groups had substantial declines in fasting gastric pH measurements at trial conclusion. Of the 62 participants, 23 were randomized to either placebo or treatment groups. Thirty-seven percent [(23/62) x 100)] had fasting gastric pH values that were above 3, which is unusually high. The mean age of all participants was 26.97 ± 3.72. (One participant neglected to record his/her age, so the mean age was calculated from 61 instead of 62 participants). All participants were healthy and met the inclusion criteria, and therefore most of their fasting gastric pH measurements should have been normal. In addition, the actual testing of gastric pH was done following the published procedure that included fasting and the ingestion of 200

mg caffeine alkaloid pills;[8] known simulators of gastric HCl secretion. Based on previous published studies evaluating the prevalence of insufficient gastric HCl secretion among both young (mean age, 30 years) and elderly subjects aged 65 and older,[28, 29] we estimate that the prevalence of insufficient gastric HCl secretion in our study should have been somewhere between 11% and 14%. Approximately, 7 to 9 subjects from our sample should have had fasting gastric pH measurements above 3. Most of subjects from the 23 enrolled should not have been randomized. Our unusual results were most likely due to operator inexperience in properly conducting the Gastro-Test®. When the Gastro-Test® was administered following trial completion, the results were uniformly normal. This large regression to the mean makes logical sense because the operators were more skilled at conducting the test. We should have had several trained operators administer the Gastro-Test® to all subjects.

Another novel aspect to our study involved the use of the Gastrointestinal Symptom Questionnaire to assess symptoms associated with insufficient HCl production, and therefore NUD. While this questionnaire had not been validated in previous clinical trials, and requires validation in future research studies, we believe that it adequately captured the breadth of gastrointestinal symptoms that characterize NUD. NUD is a condition in which the symptoms originate in the upper gastrointestinal tract and include epigastric pain or discomfort, heartburn, acid regurgitation, excessive burping and belching, upper abdominal bloating, early satiety and nausea.[30,31] Our questionnaire includes the majority of these dyspepsia symptoms, but also includes additional ones that are associated with insufficient gastric HCl production. Since insufficient gastric HCl production is an uncommon clinical condition among young healthy individuals, it is not surprising in hindsight that there were no correlations between gastric pH values and total questionnaire scores. While we believe that the "functional" pathology being studied in this pilot trial was NUD, we now realize that insufficient gastric HCl production had a minor role to play in the genesis of the participants' symptoms.

From a global perspective, the results of this trial hold some promise for a new treatment of NUD. In his review of dyspepsia, Greenbaum has delineated pertinent facts about the financial aspects of this condition.[32] An estimated 40% of adults in the Western world have repeated episodes of dyspepsia; 2-5% of all primary care visits in the United States are for this condition; and more than $1.3 billion is spent annually on prescription drugs for dyspepsia in the United States. This does not include the costs of over-the-counter (OTC) medications presumed to be at least equal to the annual prescription costs for the same condition. It is evident that there is a significant financial burden to the health care system with the conventional treatment of NUD. OTC medications for dyspepsia include antacids and histamine-type 2 receptor antagonists. These medications are associated with nutrient depletion. Antacids can induce copper defiency,[33] malabsorption of folic acid,[33] and depletion of phosphorus.[34] Histamine-type 2 receptor antagonists, such as cimetidine, can reduce the absorption of folic acid[35] and vitamin B_{12},[36] as well as hepatic vitamin D 25-hydroxylase activity.[37] Assuming that IHN has some potential therapeutic benefit, and if one considers the tremendous health care costs and nutrient depletion associated with the mainstream treatments for NUD, clearly the use of a cheap, safe, and promising alternative warrants further investigation.

Conclusions

In summary, there was a non-significant trend towards symptomatic improvement among participants taking IHN compared to those on placebo. IHN might be a promising treatment for NUD, but further investigation is required. The total Gastrointestinal Symptom Questionnaire score did not correlate with gastric pH as measured by the Gastro-Test®. This finding was potentially the result of operator inexperience with the Gastro-Test® procedure.

Acknowledgements

The study received no external funding. The authors thank the students for their participation in this trial; without their commitment, this trial would not have been possible. Our sincere gratitude to both Mr. Len Ross of HDC Corporation for supplying the Gastro-Test® kits and Dr. Victoria Coleman, President of Douglas Laboratories Canada, for supplying the IHN and identical placebo pills. We commend these individuals and their respective companies for their steadfast support.

Competing Interests

The authors declare that they have no competing interests.

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Appendix A: Gastrointestinal Symptom Questionnaire

Today's Date:
Name:
Date of Birth:
Age:
Ethnicity (Caucasian, Asian, Black, etc):
Weight:

Symptom Rating Scale: 0=Never 1=Occasionally 2= Frequently 3=Almost Always

___ Gas
___ Bloating
___ Heartburn
___ Upper abdominal heaviness after eating
___ Nausea after eating
___ Nausea when taking supplements
___ Diarrhoea
___ Constipation
___ Acne
___ Hair loss
___ Food allergies
___ Swollen tongue
___ Soreness, burning and/or dryness of the mouth
___ Weak, peeling and/or cracked fingernails
___ Itching around the rectum

TOTAL SCORE =

Did the subject fast for 10-12 hours? Yes/No (circle)

GASTRO-TEST® result:

Record any adverse reaction(s)/event(s) below: