J Neurogastroenterol Motil, Vol. 20 No. 2 April, 2014
pISSN: 2093-0879 eISSN: 2093-0887
http://dx.doi.org/10.5056/jnm.2014.20.2.219
Journal of Neurogastroenterology and Motility

Original Article

Applying Novel Nutrient Drink to Clinical Trial of Functional Dyspepsia

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Background/Aims
The drink test has been regarded as a surrogate marker of gastric accommodation. The aims of this study were to develop a novel nutrient drink test (NDT) protocol and investigate its potential for application to a clinical trial of functional dyspepsia (FD).

Methods
A novel NDT was designed, involving drinking 125 mL of nutrient 4 times at 5-minute intervals or until maximal tolerability. Healthy volunteers and patients with FD rated their symptoms every 5 minutes for 20 minutes in a developmental study. Patients with FD were enrolled in an open trial of itopride for 4 weeks. NDT was performed before and after treatment. Improvement of integrative symptoms score during NDT after treatment for more than 50% compared with baseline was defined as responder.

Results
Total aggregate symptom scores, sum of symptom scores measured during NDT, were higher in FD patients (n = 40, 368.1 ± 245.3) than in controls (n = 19, 215.9 ± 171.2) (P = 0.018) in a developmental study. In an open trial of itopride, symptom scores measured during NDT decreased significantly at all time points after treatment in responders (n = 49), whereas did not in non-responders (n = 25). Total aggregate symptom score for NDT correlated significantly with integrative dyspeptic symptom score, sum of 8 symptom scores of NDI questionnaire, at baseline (r = 0.374, P = 0.001) and after treatment (r = 0.480, P < 0.001).

Conclusions
Our novel NDT can quantify dyspeptic symptoms and reflected therapeutic effects of itopride treatment in a clinical trial of FD patients. This NDT can be used as an effective parameter in clinical trials or drug development programs for assessing effects of novel therapies on postprandial symptoms.
(J Neurogastroenterol Motil 2014;20:219-227)

Key Words
Clinical Trial; Functional dyspepsia; Itopride; Nutrient drink test

Received: May 30, 2013 Revised: August 30, 2013 Accepted: October 1, 2013

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Financial support: This study was supported by research grant from JW Pharmaceutical Co., Ltd.
Conflicts of interest: None.
Author contributions: Myung-Gyu Choi designed the study; Chul-Hyun Lim and Myung-Gyu Choi enrolled patients, collected data, analyzed the results of the statistical analyses, wrote and edited the paper, and approved the final version; Myong Ki Baeg, Sung Jin Moon, Jin Su Kim, Yu Kyung Cho, Jae Myung Park, In Seok Lee, Sang Woo Kim and Kyu Yong Choi enrolled patients, collected data and revised, edited, and approved the paper.
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Introduction

Dyspeptic symptoms are a common problem in primary health care. No structural lesions cause these symptoms and there are no biological markers in most patients with functional dyspepsia (FD).[1] The difficulty in developing an effective therapeutic agent for FD is associated with the nonspecific symptoms and the diverse pathophysiology of this condition. The optimal clinical design for FD trials has not been established.[2] Challenges encountered in these trials include optimal patient selection and the lack of established and generally accepted endpoints for the evaluation of efficacy.[3] An integrated symptom questionnaire that incorporates the frequency and/or severity of multiple symptoms is commonly used in clinical FD trials. However, its disadvantages include the inclusion of non-FD symptoms and the assignment of equal weights to different symptoms.[4] The parameters of the gastric emptying test and accommodation measured with the barostat or single-photon emission computed tomography (SPECT) have been suggested as biomarkers for both research and clinical trials, but are limited in their reproducibility and in the evaluation of drug responses.[5]

The drink test is regarded as a surrogate marker of gastric accommodation and has the advantage of being simple to perform without complex equipment.[6,7] It has been performed with various protocols, using water or nutrients. Both water and nutrient drink tests (NDTs) can distinguish patients with FD from normal subjects[7-12] and have shown excellent reproducibility.[8,9,13] Recent studies have demonstrated that the results of these tests reflect pharmacological influences.[6,7,14,15] A NDT was used in a clinical trial of amitriptyline, although amitriptyline did not affect the drinking capacity of the subjects or the postprandial symptoms evoked by the drink test in FD patients.[16] It is not determined whether the results of drink tests can reflect response of prokinectic drug. Itopride is currently available in Korea and Japan, indicated for the treatment of FD. Administration of itopride 50 mg 3 times daily is used in standard practice. Itopride is thought to exert prokinetic effects by way of antidopaminergic and antiacetylcholinesterase actions[17] and probably to have effects on gastric accommodation and gastric hypersensitivity.

The aims of the study were to develop a novel NDT protocol and investigate its potential for application to a clinical trial of FD.

Materials and Methods

This study was approved by the Institutional Research Ethics Board of Seoul St Mary's Hospital (KCMC07MI177) and conformed to the Declaration of Helsinki. Informed consent was obtained from all patients. This study was composed of two parts. The aims of the first part were to develop a novel NDT protocol and to investigate its capacity to discriminate between healthy volunteers and patients with FD. The second part was an open trial of itopride in patients with FD, used to assess the responsiveness of the NDT.

Developmental Study

Healthy asymptomatic volunteers and patients with FD over 18 years of age were enrolled to develop a novel NDT protocol between December 2006 and October 2007. Patients with FD had symptoms of FD in accordance with the Rome II criteria. They had to fulfill 3 or more score for intensity (0 [not at all] to 5 [very severe]) or bothersomeness (0 [not at all] to 4 [extremely bothersome]) about one or more of 8 dyspeptic symptoms (upper-abdominal pain, upper-abdominal discomfort, upper-abdominal soreness, early satiety, postprandial fullness, upper-abdominal pressure, upper-abdominal bloating and nausea). The participants had negative upper endoscopy results and normal laboratory tests for one month preceding enrollment.

The participants were required to refrain from treatment with antibiotics, steroids, or nonsteroidal anti-inflammatory drugs in the four weeks preceding the study. Any medication that affected gastrointestinal motility or secretion, including prokinetics, histamine 2 receptor antagonists, proton pump inhibitors, antispasmodics and antidepressants, were discontinued at least 14 days before enrollment. Women of childbearing age were required to practice proper contraception. The patients who met the following criteria were excluded: those who had undergone major abdominal surgery, except laparoscopic cholecystectomy or appendectomy; pregnant or lactating women; those with any clinically relevant electrocardiographic abnormalities, inflammatory bowel disease, irritable bowel syndrome, or severe hepatic, renal, cardiac, pulmonary, metabolic, hematological or malignant disease; those with alcoholism, drug abuse or an active psychiatric disease.

A novel NDT was designed, involving the ingestion of 500 mL of nutrient liquid meal (Ensure^{TM}; Abbott Laboratories, Abbott Park, IL, USA; 1.06 kcal per mL, 22% fat, 64% carbo-

hydrate and 14% protein) in 20 minutes. The participants were asked to ingest 125 mL of the liquid meal four times at 5-minute intervals or until they could tolerate no more. The participants rated their symptoms of satiety, postprandial discomfort, and nausea on 100 mm visual analogue scales every 5 minutes for 20 minutes. The total aggregate symptom score was defined as the sum of the symptom scores measured during the NDT.

Open Trial of Itopride

Patients with FD over 18 years of age were enrolled in an open trial of itopride (50 mg; JW Pharmaceutical Co., Ltd., Seoul, Korea) taken three times daily for four weeks between May 2008 and September 2011. The patients had symptoms of FD according to the Rome III criteria. The other inclusion and exclusion criteria were the same as in the developmental study.

The patients were classified into postprandial distress syndrome (PDS), epigastric pain syndrome (EPS), PDS + EPS and neither PDS nor EPS groups. The patients with dyspeptic symptoms which did not fulfill the frequency of dyspeptic symptoms (several times per week in PDS or once per week in EPS) were classified as neither PDS nor EPS reflecting mild symptoms.

After screening, the participants completed the Nepean Dyspepsia Index (NDI) questionnaire, which included 25 questions assessing their disease-specific quality of life and a separate symptom checklist that measured the frequency, intensity and bothersomeness of 15 upper-gastrointestinal symptoms,[18] on scales of 0 (not at all) to 4 (daily) for frequency, 0 (not at all) to 5 (very severe) for intensity and 0 (not at all) to 4 (extremely bothersome) for bothersomeness. The scores were summed over the 3 groups of symptoms. The impact of the study medication on the patients' health-related quality of life (HRQoL) was assessed using the NDI questionnaire, a validated, disease-specific HRQoL measure. The NDI is comprised of 25 items in 5 domains (tension, interference with daily activities, eating/drinking, knowledge/control and work/study). The patients rated each item for the previous 2 weeks on a 5-point Likert scale, providing individual domain scores ranging from 1 to 100. The NDI was administered at baseline and at the end of treatment. A previous validation study of the Korean version of the NDI revealed excellent test-retest reproducibility and internal consistency, expressed by Cronbach's α of 0.92. The construct was validated by comparison with the short form 36 health survey, a global rating scale for quality of life, anxiety, and intrusiveness. The responsiveness of the NDI instrument was assessed as part of the cross-cultural validation.[19]

The NDT protocol described above was performed. Because some participants complained of bloating and abdominal pain during the developmental study, these symptoms were incorporated into the total aggregate symptom score. We also measured five dyspeptic symptoms 30 minutes after the nutrient drink was ingested to quantify the changes in postprandial symptoms.

The NDI questionnaire and the NDT were checked after screening and at the end of the 4-week itopride trial. The following outcome parameters were measured. (1) The subjective global assessment of relief was reported by the participants. The participants were asked to answer a question about the relief of their upper-abdominal complaints after treatment during the preceding 4 weeks with a 6-point Likert scale (symptom-free, markedly improved, moderately improved, slightly improved, unchanged and worse). (2) The integrative dyspeptic symptom score was defined as the sum of 8 symptom scores (for upper-abdominal pain, upper-abdominal discomfort, upper-abdominal soreness, early satiety, postprandial fullness, upper-abdominal pressure, upper-abdominal bloating and nausea) of the NDI questionnaire. An improvement in the integrative symptom score of more than 50% compared with the baseline score defined a "responder." (3) The NDI quality-of-life scores for 5 domains. The change in the quality of life was estimated by comparing the scores for each domain.

Statistical Methods

The data are presented as means ± standard deviations. An unpaired t test was used to examine the differences between the healthy volunteers and the patients with FD. The continuous variables were analyzed with a paired t test to examine the differences before and after itopride treatment. An unpaired t test and a χ^2 test or Fisher's exact test were used to examine differences between the responder and non-responder groups. Pearson's correlation was calculated to investigate the relationship between the total aggregate symptom score and the integrative dyspeptic symptom score. All statistical analyses were performed with the SPSS software package (SPSS Inc., Chicago, IL, USA). Differences were considered significant at a P-value of less than 0.05.

Results

Developmental Study

In total, 19 healthy control subjects (8 men, aged 31.3 ± 5.5

years) and 40 FD patients (10 men, aged 48.1 ± 14.0 years) participated in the study between January and September 2007. All the healthy volunteers ingested 500 mL of the nutrient as patients with FD ingested almost the same volume of nutrients (474.0 ± 62.3 mL). Nine of the patients with FD failed to ingest 500 mL of the nutrient because of intolerable symptoms: nausea in four, satiety in four, and both nausea and satiety in one.

The sum of satiety, postprandial discomfort and nausea score of healthy controls and the patients with FD were shown in Figure 1. The mean total aggregate symptom score measured during the NDT was significantly higher in patients with FD than in the healthy controls (368.1 ± 245.3 vs. 215.9 ± 171.2, respectively; $P = 0.018$) (Fig. 2).

Open Trial of Itopride

One hundred and two patients were screened in the clinical trial between May 2008 and July 2011. After exclusion, 88 patients were eligible for enrollment. Nine patients did not complete the study: 5 withdrew consents, 3 had adverse events and the symptoms of 1 worsened. Five patients with poor drug compliance (< 80%) were excluded from the final analysis. Among the remaining 74 patients, 35 were in the PDS group, 19 in the combined PDS + EPS group and 20 in the neither PDS nor EPS group. There were no significant differences in the baseline characteristics of the FD subtypes (Table 1).

At least a moderate improvement, rated on the subjective global assessment of relief, was reported by 74.3% of subjects, and this did not differ significantly among the FD subtypes (PDS, 77.1%; PDS + EPS, 73.7%; neither PDS nor EPS, 70.0%). The rate of responsiveness, measured with the integrative symptom questionnaire, was 66.2% and did not differ significantly among the subtypes (PDS, 62.9%; PDS + EPS,

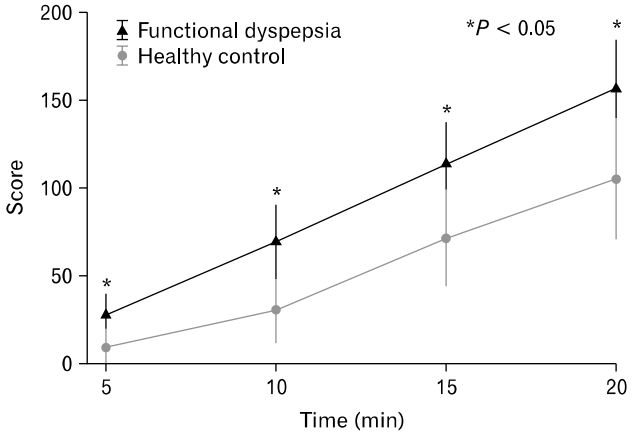

Figure 1. Nutrient drink test scores (mean ± 95% CI) in healthy controls and patients with functional dyspepsia.

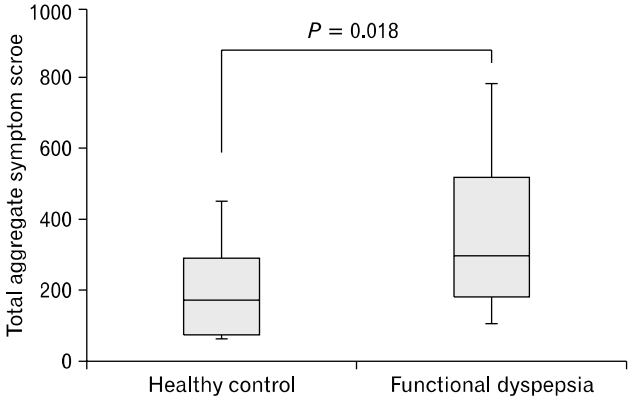

Figure 2. The mean total aggregate symptom score measured during the nutrient drink test in patients with functional dyspepsia and the healthy controls.

Table 1. Baseline Characteristics of the Study Populations

Parameter	PDS (n = 35)	PDS + EPS (n = 19)	Neither PDS nor EPS (n = 20)	Total (n = 74)
Age (mean ± SD, yr)	39.8 ± 14.2	41.9 ± 16.1	43.4 ± 14.6	41.3 ± 14.6
Female (n [%])	26 (74.3)	15 (78.9)	15 (75.0)	56 (75.7)
BMI (mean ± SD, kg/m^2)	22.1 ± 3.3	20.3 ± 1.8	21.8 ± 2.7	21.6 ± 2.9
Education (College, n [%])	26 (74.3)	16 (84.2)	14 (70.0)	56 (75.7)
Married (n [%])	14 (40.0)	8 (42.1)	8 (40.0)	30 (40.5)
Smoking (n [%])	3 (8.6)	2 (10.5)	2 (10.0)	7 (9.5)
Alcohol (n [%])	12 (34.3)	5 (26.3)	6 (30.0)	23 (31.1)
Coffee (n [%])	20 (57.1)	6 (31.6)	13 (65.0)	39 (52.7)
H. pylori (+) (n [%])	7/22 (31.8)	3/11 (27.3)	4/10 (40.0)	14/43 (32.6)

PDS, postprandial distress syndrome; EPS, epigastric pain syndrome; BMI, body mass index; *H. pylori*, *Helicobacter pylori*.

68.4%; neither PDS nor EPS: 70.0%). The integrative dyspeptic symptom scores, quality-of-life scores and total aggregate symptom scores on the drink test improved significantly after itopride treatment (Table 2). Twelve of the patients (16.2%) failed to ingest 500 mL of the nutrient because of dyspeptic symptoms (nausea in 4, satiety in 3, bloating in 2 and both nausea and bloating in 3) during the baseline NDT. Eight patients (10.8%) failed to ingest 500 mL of the nutrient because of dyspeptic symptoms (nausea in 1, satiety in 2, bloating in 2 and both satiety and bloating in 3) during the second NDT.

There were no significant differences in the baseline characteristics of the responder and non-responder groups, except in age (Table 3). The NDI quality-of-life scores in all domains, except eating/drinking, were more improved in the responder group than in the non-responder group (Table 4), as were the total aggregate symptom scores on the NDT.

Table 2. Comparisons of Outcome Parameters Between Baseline and After Itopride Treatment

Outcome parameters	Baseline	After treatment	*P*-value
Integrative dyspeptic symptom score	45.6 ± 15.4	21.0 ± 16.8	< 0.001
NDI quality of life questionnaire			
Tension/sleep	65.5 ± 17.9	80.4 ± 9.6	< 0.001
Interference with daily activities	69.9 ± 18.1	82.6 ± 10.5	< 0.001
Eating/drinking	61.7 ± 21.7	76.3 ± 12.9	< 0.001
Knowledge/control	59.2 ± 22.6	78.7 ± 12.8	< 0.001
Work/study	64.5 ± 21.4	79.4 ± 10.7	< 0.001
Nutrient drink test			
Total aggregate symptom score	737.7 ± 438.9	472.1 ± 357.5	< 0.001
Symptom score during taking nutrient	571.0 ± 371.4	358.4 ± 269.8	< 0.001
Symptom score at 30 min after taking nutrient	166.8 ± 105.3	113.6 ± 106.9	< 0.001

NDI, Nepean Dyspepsia Index.
Data are presented as mean ± SD.

Table 3. Comparisons of Baseline Characteristics Between Responders and Non-responders

Parameter		Responders (n = 49)	Non-responders (n = 25)	*P*-values
Subgroup (n [%])	PDS	22 (62.9)	13 (37.1)	0.841
	EPS + PDS	13 (68.4)	6 (31.6)	
	Neither PDS nor EPS	14 (70.0)	6 (30.0)	
Age (mean ± SD, yr)		38.8 ± 13.6	46.0 ± 15.8	0.046
Female (n [%])		35 (71.4)	21 (84.0)	0.268
BMI (mean ± SD, kg/m^2)		21.5 ± 3.0	21.7 ± 2.6	0.849
Education (College, n [%])		37 (75.5)	15 (60.0)	0.188
Marriage (n [%])		30 (61.2)	17 (68.0)	0.618
Smoking (n [%])		7 (14.3)	0 (0.0)	0.088
Alcohol (n [%])		18 (36.7)	5 (20.0)	0.188
Coffee (n [%])		26 (53.1)	13 (52.0)	1.000
H. pylori (+) (n [%])		12/29 (41.4)	2/14 (14.3)	0.095
Integrative dyspeptic symptom score (mean ± SD)		46.9 ± 14.4	43.0 ± 17.2	0.308
NDI quality of life questionnaire (mean ± SD)				
Tension/sleep		64.9 ± 17.5	67.2 ± 19.3	0.627
Interference with daily activity		70.1 ± 17.4	69.3 ± 20.3	0.877
Eating/drinking		62.3 ± 20.0	60.0 ± 26.7	0.693
Knowledge/control		59.1 ± 21.3	59.5 ± 26.6	0.955
Work/study		64.6 ± 20.7	64.5 ± 23.8	0.990

PDS, postprandial distress syndrome; EPS, epigastric pain syndrome; *H. pylori*, *Helicobacter pylori*; NDI, Nepean Dyspepsia Index.

Table 4. Comparison of Changes in Outcome Parameters Between Responders and Non-responders

Parameter	Responders (n = 49)	Non-responders (n = 25)	*P*-value
NDI quality of life questionnaire			
Δ Tension/sleep	19.2 ± 14.1	6.7 ± 12.5	< 0.001
Δ Interference with daily activities	15.8 ± 14.7	6.6 ± 11.8	0.008
Δ Eating/drinking	16.1 ± 17.4	11.4 ± 18.6	0.291
Δ Knowledge/control	24.0 ± 17.4	10.6 ± 19.4	0.003
Δ Work/study	19.0 ± 16.4	6.6 ± 14.4	0.002
Nutrient drink test			
Δ Total aggregate symptom score	-331.3 ± 375.2	-125.6 ± 334.0	0.028
Δ Symptom score during taking nutrient	-261.5 ± 315.2	-108.0 ± 258.7	0.046
Δ Symptom score at 30 min after taking nutrient	-69.8 ± 88.6	-17.6 ± 112.3	0.028

NDI, Nepean Dyspepsia Index.
Δ = [score after treatment] − [baseline score]. Data are presented as mean ± SD.

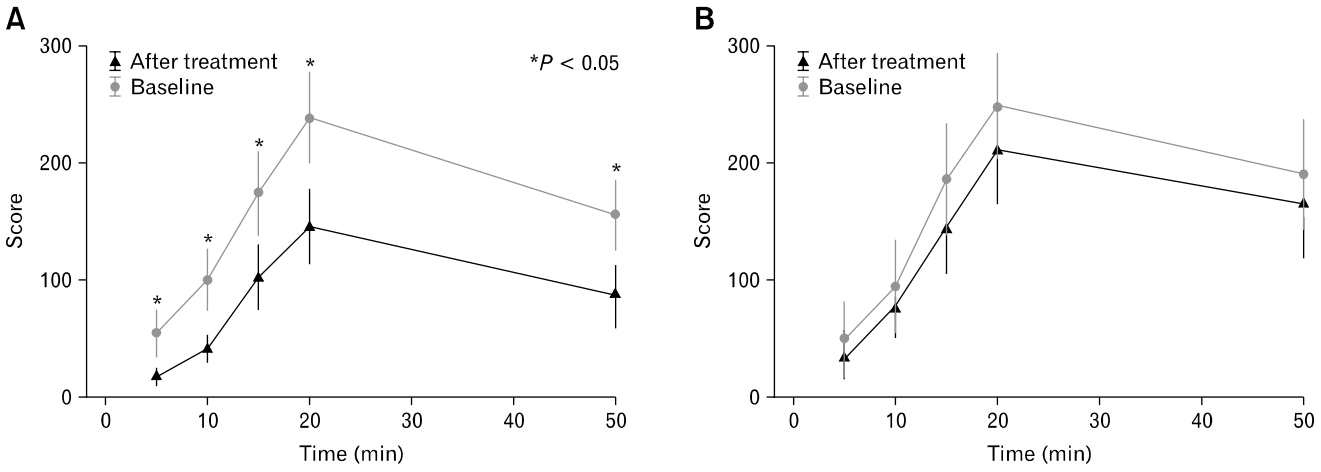

Figure 3. Comparison of nutrient drink test scores (mean ± 95% CI) between baseline and after itopride treatment in responders (A) and non-responders (B).

The symptom scores decreased significantly at all time points after the itopride treatment in the responder group, whereas there was no significant difference in these scores after treatment in the non-responder group (Fig. 3). The total aggregate symptom score for the NDT correlated significantly with the integrative dyspeptic symptom score, both at baseline ($r = 0.374$, $P = 0.001$) and after the itopride treatment ($r = 0.480$, $P < 0.001$, respectively; Fig. 4).

Discussion

We developed a novel NDT protocol to measure dyspeptic symptoms during and after ingestion of 500 mL of a nutrient drink. This test showed significant difference between healthy controls and patients with FD. The total aggregate symptom scores for the NDT showed the effect of itopride fairly well and differentiated drug responders from non-responders. They also correlated moderately well with the integrative dyspeptic symptom scores from the symptom checklist. Taken together, this study suggests that the NDT can be applied to clinical trials or drug development programs.

Drink tests have been developed as a noninvasive means to assess upper digestive symptoms and gastric accommodation. They measure the maximum tolerated volume, which indicates maximal satiety. Patients with FD or gastroparesis are satiated or develop dyspeptic symptoms at ingested volumes below those

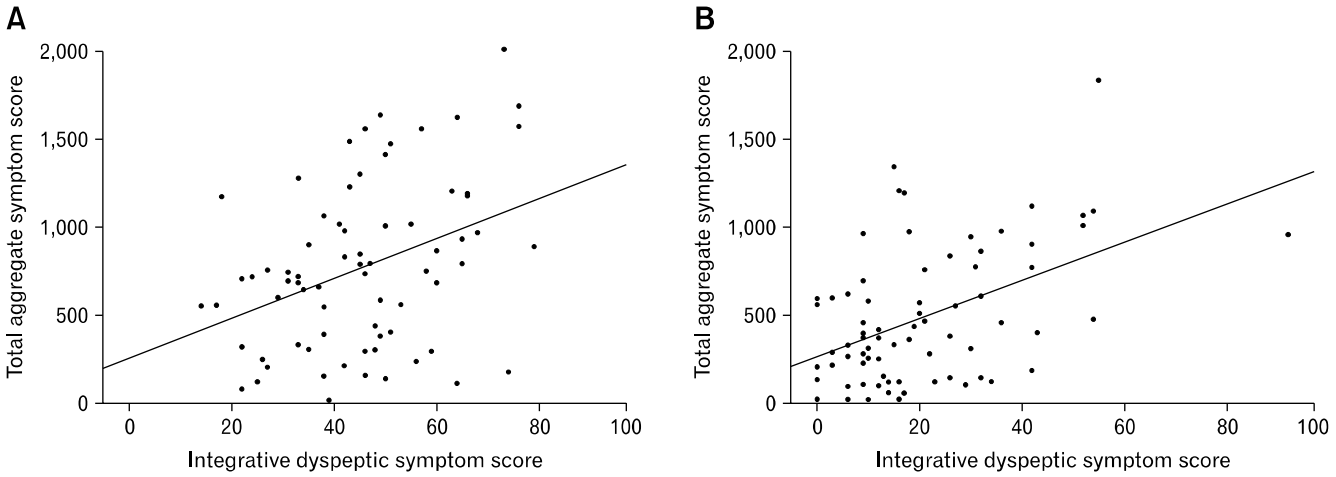

Figure 4. The relationship between total aggregate symptom score and total Nepean Dyspepsia Index symptom score in baseline (A) and after itopride treatment (B).

typically required by controls to achieve these endpoints. Various drink test protocols have been developed, using either water or nutrient-containing beverages with various ingestion rates. Two water drink test protocols have been reported, which involve either drinking water ad libitum over a 5-minute period or drinking 100 mL of water every minute, until the point of fullness is reached. There was a significant correlation between the results of the 2 tests.[9] NDTs have been performed in several ways, including slow drinking at a rate of 15-30 mL/min and rapid drinking at a rate of 100 mL/min. One study reported a significant correlation between the water drink test and the rapid NDT, whereas another study showed no significant correlation.[9,11] Unlike previous protocols, our drink test protocol used a 500 mL volume of nutrient drink as the fixed standard test volume and quantified the meal-induced dyspeptic symptoms by summing 5 symptom scores. The total aggregate symptom score reflected the dyspeptic symptoms because it correlated significantly with the integrative dyspeptic symptom score. We selected a 500 mL volume of nutrient drink for the test for the following reasons. First, the volume of nutrient drink causing maximum satiety in previously reported studies ranged from 361 to 562 mL in patients with FD.[7,13,20,21] Second, we considered that people usually tend to stop eating food before they reach maximal satiety. Maximal satiety is the worst possible level of unpleasant sensation, and so does not allow the quantification of dyspeptic symptoms. In this study, 22.5% of patients with FD in the developmental study and 16.2% of patients with FD in the open trial of itopride failed to drink 500 mL of nutrient. These findings support the use of 500 mL as the optimal volume for a slow NDT.

Dyspeptic symptoms may originate from many factors, including abnormal gastroduodenal motor and sensory function, *Helicobacter pylori* gastritis, and central nervous system dysfunction. It is unclear exactly what physiologic processes are assessed by NDTs. It is also not determined whether the results of drink tests can guide therapy or not. The total aggregate symptom score, measured during meal intake, can quantify meal-induced satiation, which could reflect gastric accommodation, and the scores at 30 minutes after a meal may reflect gastric emptying. This hypothesis was supported by our previous study, which showed significant negative linear correlation between the postprandial gastric volume change measured by SPECT and the total aggregate symptom score of NDT in healthy volunteers.[22] This correlation was also observed even after exenatide. Tack et al. also demonstrated that maximal tolerated volume measured by slow nutrient drink correlated with meal induced accommodation determined by gastric barostat.[7] However, discrepant results have been reported. Maximal tolerated volume measured by both rapid nutrient and water drink tests did not accurately predict impaired accommodation determined by barostat[11] or SPECT.[23] On the other hand, a few studies have demonstrated the association between gastric emptying and maximal tolerated volume by slow NDT.[7,12] It is not surprising to see the discrepancy between dyspeptic symptoms and physiological tests with regard to multiple etiologies of FD. The symptom score of NDT could reflect comprehensive gastroduodenal responses to nutrient. Therefore, this test may have the advantage for meal related dyspepsia over other objective scales which reflect only one pathophysiologic mechanism such as gastric emptying sintigraphy or SPECT.

In the open trial of itopride, the NDT showed its potential utility as a scale for responsiveness measurement in clinical trials of FD treatments. The total aggregate symptom scores during and after the NDT were significantly improved by the treatment, as were the dyspeptic symptoms. They also correlated well with the integrated dyspeptic symptom scores. The nutrient drink test results also reflected the therapeutic responsiveness to itopride. Only the responder group showed significant improvement in their total aggregate symptom scores on the nutrient drink test after itopride treatment, whereas the non-responders did not. Our previous study showed that this nutrient drink test protocol demonstrated the effects of erythromycin and exenatide, which modify gastric motility, fairly well.[22] A recent trial of amitriptyline for FD used maximal satiety as an outcome parameter when drinking 100 mL of a nutrient drink at every minute.[16] However, amitriptyline did not affect the subjects' drinking capacity or the postprandial symptoms evoked by the drink test, although the total clinical symptom score and nausea were reduced after treatment.

The NDT has several advantages in clinical trials of FD treatments, including its noninvasiveness, easy performance, and low cost.[24,25] Our novel NDT showed significant difference between healthy controls and patients with FD. It also showed an excellent capacity to measure drug responsiveness in a clinical trial. Therefore, this test is a suitable and practical scale for responsiveness measurement for research studies and multicenter clinical trials.

In conclusion, our novel NDT was able to quantify dyspeptic symptoms and reflected the therapeutic effects of itopride treatment in a clinical trial of patients with FD. This NDT can be used as an effective parameter in clinical trials or drug development programs for assessing the effects of novel therapies on postprandial symptoms.

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