ORIGINAL ARTICLE

A Placebo-Controlled Trial of Itopride in Functional Dyspepsia

Gerald Holtmann, M.D., Nicholas J. Talley, M.D., Ph.D., Tobias Liebregts, M.D., Birgit Adam, M.D., and Christopher Parow, M.D.

ABSTRACT

BACKGROUND

The treatment of patients with functional dyspepsia remains unsatisfactory. We assessed the efficacy of itopride, a dopamine D2 antagonist with acetylcholinesterase effects, in patients with functional dyspepsia.

METHODS

Patients with functional dyspepsia were randomly assigned to receive either itopride (50, 100, or 200 mg three times daily) or placebo. After eight weeks of treatment, three primary efficacy end points were analyzed: the change from baseline in the severity of symptoms of functional dyspepsia (as assessed by the Leeds Dyspepsia Questionnaire), patients' global assessment of efficacy (the proportion of patients without symptoms or with marked improvement), and the severity of pain or fullness as rated on a five-grade scale.

RESULTS

We randomly assigned 554 patients; 523 had outcome data and could be included in the analyses. After eight weeks, 41 percent of the patients receiving placebo were symptom-free or had marked improvement, as compared with 57 percent, 59 percent, and 64 percent receiving itopride at a dose of 50, 100, or 200 mg three times daily, respectively ($P<0.05$ for all comparisons between placebo and itopride). Although the symptom score improved significantly in all four groups, an overall analysis revealed that itopride was significantly superior to placebo, with the greatest symptom-score improvement in the 100- and 200-mg groups (−6.24 and −6.27, vs. −4.50 in the placebo group; $P=0.05$). Analysis of the combined end point of pain and fullness showed that itopride yielded a greater rate of response than placebo (73 percent vs. 63 percent, $P=0.04$).

CONCLUSIONS

Itopride significantly improves symptoms in patients with functional dyspepsia. (ClinicalTrials.gov number, NCT00272103.)

From the Department of Gastroenterology, Hepatology and General Medicine, Royal Adelaide Hospital and University of Adelaide, Adelaide (G.H., T.L., B.A.); and the Department of Medicine, University of Sydney, Nepean Hospital, Penrith (N.J.T.) — both in Australia; the Mayo Clinic College of Medicine, Rochester, Minn. (N.J.T.); and Global Scientific Support, Abbott, Ludwigshafen, Germany (C.P.). Address reprint requests to Dr. Holtmann at the Department of Gastroenterology, Hepatology and General Medicine, Royal Adelaide Hospital, North Terrace, Adelaide SA 5000, Australia, or at gholtman@mail.rah.sa.gov.au.

N Engl J Med 2006;354:832-40.

Dyspepsia remains a common and costly problem in primary care and gastroenterology practice; in most patients who are examined, no structural lesions causing these symptoms are found.[1] Dyspepsia in the absence of a clinically identifiable structural lesion is referred to as functional dyspepsia,[2,3] in part because disturbed gastrointestinal function is believed to play a role in the development of symptoms.[4]

Pharmacologic treatments for patients with functional dyspepsia remain unsatisfactory.[5] The results of controlled trials have generally been disappointing, and only small benefits relative to placebo have been found with histamine H_2-receptor antagonists,[6] proton-pump inhibitors,[7] and *Helicobacter pylori* eradication.[8] Although several randomized, controlled trials and meta-analyses have demonstrated the superiority of cisapride over placebo,[9-11] the use of cisapride is now restricted in most countries because of cardiac side effects.

In Japan, itopride, which is a dopamine D2 antagonist with acetylcholinesterase inhibitory actions, is often prescribed for patients with functional dyspepsia. Although this drug has been shown to stimulate gastric motility,[12] large, properly designed, randomized, controlled trials in patients with functional dyspepsia are lacking. In Japan, administration of 50 mg three times daily is standard practice. However, little is known regarding the dose response in other populations. For this reason, we aimed to study the efficacy of itopride in patients with functional dyspepsia in terms of symptom improvement and to compare various doses of itopride in terms of efficacy and safety in a white population.

METHODS

STUDY DESIGN AND PATIENT POPULATION

Patients

Outpatients who were considered to have functional dyspepsia on the basis of the Rome II criteria[3] were eligible for the trial. Functional dyspepsia was diagnosed if persistent or recurrent upper abdominal pain or discomfort was present. Discomfort was characterized by the presence of one or more symptoms that included early satiety, postprandial fullness, bloating, and nausea. Symptoms had to be present for at least 12 weeks within the preceding 12 months, without an identifiable structural or biochemical abnormality to which they could be attributed. Symptoms predominantly related to reflux (e.g., retrosternal pain, burning, and regurgitation) were considered features of gastroesophageal reflux disease, rather than of functional dyspepsia. Therefore, patients who had only reflux-related symptoms or who had predominantly reflux-related symptoms were not eligible for participation.

Patients were recruited by 78 physicians in private practice in Germany and one tertiary university hospital, the University Hospital Essen, in Germany. Before patients could be included in the trial, they underwent physical examination, laboratory tests (including white-cell and red-cell counts, measurement of blood sugar during fasting, and liver-function tests), abdominal ultrasonography, and upper gastrointestinal endoscopy so that a structural cause for the symptoms could be ruled out. Patients were excluded if they were taking other medications that may alter gastric function, including macrolide antibiotics.

Between three and seven days (median, four) after a diagnosis of functional dyspepsia was established, gastrointestinal symptoms and the disease-specific quality of life were reevaluated to determine patients' baseline status, and patients were randomly assigned to receive either placebo (three times daily) or one of three doses of itopride (50, 100, or 200 mg three times daily). The study medication was given in a double-blind fashion for eight weeks.

The study was approved by the ethics committee of the University Hospital Essen and by the ethics committees of all local study centers. All the patients gave written informed consent.

Randomization and Blinding

The randomization code was generated with use of Proc Random (SAS, version 6.12). Since only two sizes of active tablet (50 mg and 100 mg) were used, patients received two tablets three times daily by means of a double-dummy technique. The study medication was packaged identically for the four dosage groups and was identifiable only by a randomization number. Medications were delivered to the centers in blocks of eight. Patients' screening numbers were assigned at the initial visit and were used as individual identification numbers at each center during the screening phase. Patients who met all the inclusion and exclusion criteria were assigned a randomization number in ascending order and treated with the correspondingly identified study medication.

ASSESSMENTS

Symptoms and Global Relief

We used the validated Leeds Dyspepsia Questionnaire (LDQ)[13] to assess dyspeptic symptoms at baseline and after four and eight weeks of treatment. The LDQ, which is administered by an investigator in a face-to-face interview, measures eight dyspepsia symptoms on scales with six grades each (where a grade of 0 indicates not present, 1 very mild, 2 mild, 3 moderate, 4 severe, and 5 very severe); a summary score with a range of 0 to 40 represents the severity of dyspepsia. Patients' global assessments of efficacy were evaluated at eight weeks with the use of a global scale with the following five grades: symptom-free, markedly improved, moderately improved, not changed, and deteriorated.

Pain and fullness are considered to be the two most important symptoms of functional dyspepsia. We evaluated the severity of pain in the upper abdomen and the severity of fullness after eating as a combined end point. A positive response to treatment was prespecified as improvement by at least one grade on a five-grade scale (absent, very mild or mild, moderate, severe, or very severe) with respect to at least one of the two symptoms (pain or fullness) and no deterioration in the other symptom.

Primary Outcome Variables

Three primary efficacy criteria were used in this study and were tested in a prespecified order. The change in the summary LDQ score relative to baseline[13] after eight weeks of treatment was the first primary outcome variable. Patients' global assessment of efficacy every two weeks was the second primary outcome variable. Finally, the composite response criterion with respect to the severity of pain in the upper abdomen and the severity of a feeling of excessive fullness after eating was evaluated as the third primary outcome variable.

Disease-Specific Quality of Life

To assess the effects of treatment on disease-specific quality of life, we used the validated long version of the Nepean Dyspepsia Index (NDI)[14] and calculated a total quality-of-life score. The NDI quality-of-life score ranges from 0 to 99, with higher scores indicating worse quality of life.

Compliance and Safety

At each visit, patients returned their medication containers, and pills were counted. A patient who took between 80 percent and 120 percent (some patients were treating themselves off protocol under the erroneous assumption that "more is better") of the prescribed pills was considered to be compliant. At baseline and after four and eight weeks, a wide array of laboratory tests was performed, including liver-function and renal-function tests, hematologic tests, measurement of blood glucose, and measurement of serum prolactin. Twelve-lead resting electrocardiograms were obtained at the screening visit and after four and eight weeks of treatment.

STATISTICAL ANALYSIS

Sample sizes were determined prospectively with reference to other studies that used similar end points. A sample size of 100 patients per group was suitable to identify, with a power of 0.8, a standardized difference (the difference divided by the standard deviation) of 0.4 with an alpha significance level of 0.05 (two-sided). When the same alpha value was used in the testing of hypotheses according to a sequence determined a priori, a sample size of 100 patients per study group was also found suitable to identify a difference of 20 percentage points (40 percent vs. 60 percent) in response rates. All analyses was performed on an intention-to-treat basis, with the last observation carried forward in cases of premature study termination. The last-observation-carried-forward method was appropriate because no more than 10 percent of the observations were missing in each analysis. Missing items on the LDQ were completed before unblinding by means of a prospectively defined imputation technique. Treatment comparisons were made with the use of a hierarchical test system with an overall two-sided alpha error rate of 0.05.

As the first of five hypotheses ordered a priori, the global hypothesis that there would be a treatment difference between the pooled active-treatment groups and the placebo group was evaluated by one-factorial analysis of variance (linear contrast of 3D0+D1+D2+D3), where D0 denotes placebo, D1 50 mg of itopride three times daily, D2 100 mg of itopride three times daily, and D3 200 mg of itopride three times daily, testing the

null hypothesis that three times the difference observed in the placebo group subtracted from the sum of the differences in the three itopride groups equaled 0). Thus, the linear contrast compared the average changes in the LDQ score in the active-treatment groups with the changes in the LDQ score in the placebo group. Second, monotonic dose responses were tested in a parametric model (linear contrast of 3D0−1D1+1D2+3D3). Testing of the three additional hypotheses involved pairwise comparisons of placebo with itopride, starting with the highest dose (linear contrasts of D3−D0, D2−D0, and D1−D0). This test procedure (which was stopped when the first test result provided a P value ≥0.05) is more conservative than the procedure described by Holm.[15]

To investigate the clinical meaningfulness of the LDQ results, the same test procedure was repeated with Fisher's exact test and the Cochran–Armitage test for the two binary outcomes: the response based on patients' global assessment of efficacy and the response based on the LDQ pain and fullness items at week 8. In accordance with the main objective of the study — namely, to analyze the overall effect of itopride on symptoms and to identify one (or two) doses for further study — our analyses focused on the population of all patients with available LDQ data, and when data were missing, we used the last observation carried forward. Twenty-five patients with no efficacy data after treatment were excluded from the analyses. The statistical analyses were performed with SAS software (version 6.12).[16,17]

This study was designed by the two senior authors (Drs. Holtmann and Talley) in cooperation with employees of the sponsor (Knoll, Germany), with advice from the statistician and a contract research organization that acted on behalf of the sponsor. The data were collected and analyzed by the contract research organization. The manuscript was written by the academic authors, with input and critical review from all persons involved in the design and data analysis. The academic authors vouch for the veracity and completeness of the data and data analyses.

RESULTS

STUDY POPULATION

Six hundred six outpatients with a suspected diagnosis of functional dyspepsia were screened (Fig. 1). Fifty-two patients were excluded, leaving 554 patients who were randomly assigned. Six did not receive study medication, resulting in a study population of 548 patients. The patients' ages ranged from 18 to 94 years (mean [±SD] age, 47.9±15.8 years). Overall, 63.5 percent of the patients were female. The baseline characteristics of the study population were similar among the groups (Table 1).

Eighteen patients in the placebo group did not complete the eight-week treatment, whereas 37 patients in the itopride groups (12 assigned to 50 mg three times daily, 11 assigned to 100 mg three times daily, and 14 assigned to 200 mg three times daily) did not complete treatment. In the itopride groups, 19 patients (4.7 percent) discontinued treatment prematurely because of adverse events, as compared with 10 patients (7.0 percent) in the placebo group.

RESPONSE TO TREATMENT

Symptom-severity scores on the LDQ improved from baseline during treatment in all four study groups. Testing of the global hypothesis (that there would be a difference between the results in the placebo group and the pooled results in the three itopride groups) revealed that itopride was significantly superior to placebo (Table 2 and Fig. 2). The test for a dose response did not reach statistical significance (P=0.06). The difference between placebo and itopride given at a dose of 50 mg three times daily was not significant (P=0.07), but the differences between placebo and itopride at a dose of 100 mg three times daily and between placebo and itopride at a dose of 200 mg three times daily were both significant, at P=0.05.

Testing of all the a priori planned hypotheses for response rates with regard to patients' global assessment of efficacy showed significance (Table 2 and Fig. 3). The overall response rate was 59.9 percent with active treatment (232 of 387 patients had a response), as compared with 41.2 percent with placebo (56 of 136 patients had a response) (P<0.001). There was a significant association between the dose of itopride and the response rate (P<0.001). The global hypothesis with regard to response rates according to the severity of pain and fullness on the LDQ yielded a significant discrimination between itopride and placebo, but results on subsequent

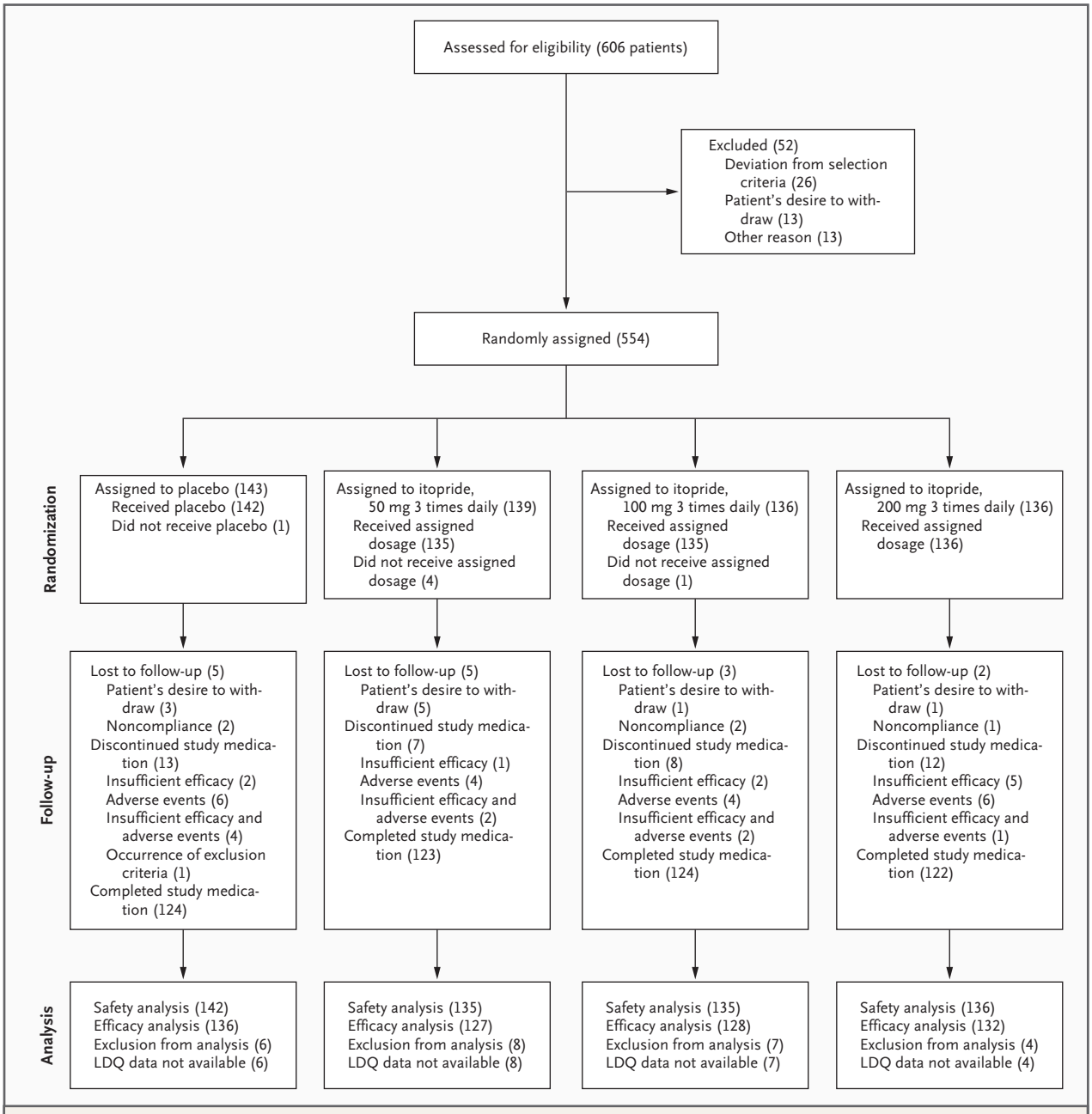

Figure 1. Enrollment, Randomization, Follow-up, and Analysis.
LDQ denotes the Leeds Dyspepsia Questionnaire.

tests that assessed the dose response and that compared each dose group with placebo were not statistically significant (Table 2).

At the end of treatment, the NDI quality-of-life scores were better among patients who were treated with active medication than among those who received placebo. The NDI quality-of-life score improved by a mean of 13.2±19.4 with placebo and by 18.0±21.9 with itopride (P=0.02). However, differences between the various doses of itopride tested were not statistically significant.

Only 112 of the 548 patients (20 percent) tested positive for *H. pylori*. Overall, 147 of the 436 patients who tested negative for *H. pylori*

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Placebo	Itopride			P Value†
		50 mg Three Times Daily	100 mg Three Times Daily	200 mg Three Times Daily	
No. of patients	142	135	135	136	
Age — yr					
Mean	49.3±15.5	47.8±16.1	45.8±16.3	48.7±15.4	0.28
Range	18–80	18–88	18–82	18–94	
Sex — no. (%)					
Female	89 (62.7)	87 (64.4)	78 (57.8)	94 (69.1)	0.28
Male	53 (37.3)	48 (35.6)	57 (42.2)	42 (30.9)	
Negative for *Helicobacter pylori* — no. (%)	118 (83.1)	113 (83.7)	106 (78.5)	99 (72.8)	0.09
Dysmotility-type dyspepsia — no. (%)	40 (28.2)	28 (20.7)	37 (27.4)	34 (25.0)	0.49
Ulcer-type dyspepsia — no. (%)	46 (32.4)	54 (40.0)	38 (28.1)	49 (36.0)	0.20
Concomitant heartburn — no. (%)	33 (23.2)	28 (20.7)	25 (18.5)	31 (22.8)	0.78
Concomitant irritable bowel syndrome — no. (%)	18 (12.7)	22 (16.3)	21 (15.6)	18 (13.2)	0.79
Summary LDQ score‡	11.9±6.2	11.8±6.3	12.5±6.5	12.3±6.5	0.76
Nepean Dyspepsia Index§	30.2±18.5	31.7±21.4	30.0±20.4	33.0±21.2	0.59

* Plus–minus values are means ±SD.
† P values are for the comparison among all four study groups.
‡ The Leeds Dyspepsia Questionnaire (LDQ) measures eight dyspepsia symptoms on scales with six grades each (where a grade of 0 indicates not present, 1 very mild, 2 mild, 3 moderate, 4 severe, and 5 very severe); a summary score with a range of 0 to 40 represents the severity of dyspepsia.
§ The Nepean Dyspepsia Index quality-of-life score ranges from 0 to 99, with higher scores indicating worse quality of life.

(33.6 percent) reported severe or very severe epigastric pain, as compared with 25 of the 110 patients (22.7 percent) who had *H. pylori* infection (P=0.02). *H. pylori* status had no significant influence on the outcome variables (data not shown).

Overall, 89 of the 548 patients in the study population reported concomitant symptoms of gastroesophageal reflux disease during the initial clinical assessment. These symptoms did not dominate the clinical picture. Because of their significantly higher scores for epigastric pain and excessive fullness, patients with concomitant symptoms of gastroesophageal reflux disease had significantly higher severity scores on the LDQ than did patients without gastroesophageal reflux disease (18.9±5.7 vs. 10.8±5.6, P<0.001). Concomitant symptoms of gastroesophageal reflux disease were not associated with the response to therapy (data not shown).

ADVERSE EVENTS

Adverse events during the treatment period were reported in 37.3 percent, 35.6 percent, 40.0 percent, and 39.0 percent of the patients treated with placebo and those treated with itopride at doses of 50, 100, and 200 mg three times daily, respectively. No relevant difference in the overall incidence of adverse events was seen with the use of itopride (38.2 percent), as compared with placebo (37.3 percent) (P=0.9). The most frequently affected body system was the gastrointestinal tract, which accounted for adverse events in 14.1 percent of the patients in the placebo group and 12.6 percent, 11.1 percent, and 7.4 percent of the patients in the groups assigned to 50 mg, 100 mg, and 200 mg of itopride three times daily, respectively. Abdominal pain, diarrhea, nausea, and constipation were the most frequently reported events. Most adverse events were of mild or moderate

Table 2. Primary Outcome Variables among 523 Patients.*

Variable	Change from Baseline in LDQ Score		Response Rates			
			Patients' Global Assessment of Efficacy		Severity of Pain and Fullness	
	score	*P value*	*no./total no. (%)*	*P value†*	*no./total no. (%)*	*P value†*
Placebo	−4.50±0.63		56/136 (41.2)		86/136 (63.2)	
Itopride						
All doses, pooled	−6.22±0.37	0.02	232/387 (59.9)	<0.001	282/387 (72.9)	0.04
50 mg three times daily	−6.16±0.65	0.07	72/127 (56.7)	0.01	95/132 (72.0)	0.12
100 mg three times daily	−6.24±0.64	0.05	75/128 (58.6)	0.007	95/128 (74.2)	0.06
200 mg three times daily	−6.27±0.63	0.05	85/132 (64.4)	<0.001	95/132 (72.0)	0.15

* Plus–minus values are means ±SD. The Cochran–Armitage test for a dose response in patients' global assessment of efficacy revealed a significant dose-related effect (P<0.001), whereas the response rates based on the severity of pain or fullness (P=0.11) and linear contrasts for monotonic dose responses according to the change in the Leeds Dyspepsia Questionnaire (LDQ) score (P=0.06) were not significant.
† P values are for the comparison with placebo.

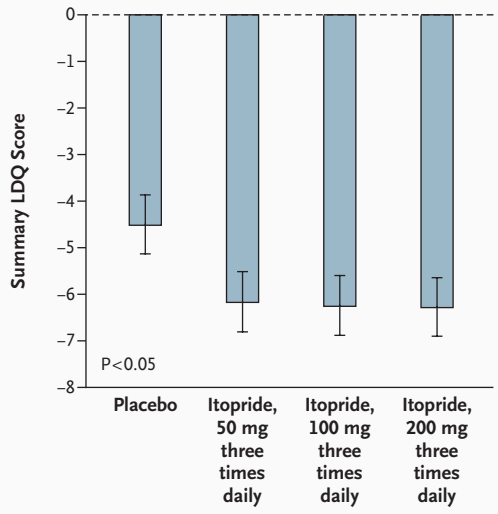

Figure 2. Mean Changes from Baseline in the Summary Score for Symptom Severity on the Leeds Dyspepsia Questionnaire (LDQ).
P<0.05 for the comparison between active treatment and placebo among all patients analyzed (n=523).
I bars represent the standard error.

intensity and had resolved by the end of the study. Serious adverse events during the treatment period were seen in 2.8 percent of the patients in the placebo group and 1.2 percent of patients in the overall active-treatment group. They were not considered by the investigators to be related to the study medication.

Prolactin levels significantly increased during treatment with 100 mg and 200 mg of itopride given three times daily, as compared with placebo (increase in the placebo group, 5.1 percent, vs. increases of 5.8 percent, 16.4 percent, and 20.7 percent in the groups assigned to 50 mg, 100 mg, and 200 mg of itopride three times daily, respectively). No clinical symptoms or signs were related to changes in the prolactin level. Treatment with itopride was not associated with any electrocardiographic changes; in particular, there was no prolongation of the corrected QT interval.

DISCUSSION

Disturbances in gastrointestinal motility and sensory function are now believed to play a key role in the development of symptoms in patients with functional dyspepsia.[18-20] We assessed and compared the effects of three doses of a benzamide, itopride, with placebo. In this eight-week study, itopride significantly improved symptoms in patients with functional dyspepsia.

It is noteworthy that the improvement in the symptom score during treatment with any of the three doses of itopride was approximately 50 percent greater than the improvement with placebo. Although the importance of the improvement in a symptom score might be questioned, the proportion of patients who had a global benefit was also significantly higher in the itopride groups than in the placebo group. Furthermore, itopride

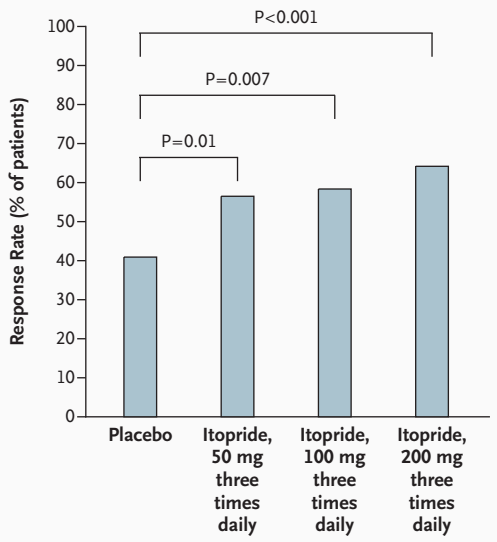

Figure 3. Response Rates Based on Patients' Global Assessment of Efficacy.

Data are shown for all patients analyzed. The graph depicts the proportion of patients who reported that they were symptom-free or that their symptoms had markedly improved after eight weeks.

was specifically associated with improvements in pain and fullness, which are believed to be key symptoms of functional dyspepsia.[2,3] We calculated that to achieve marked or complete improvement in symptoms in one patient, six patients would need to be treated. In comparison, when proton-pump inhibitors are used in patients with functional dyspepsia, the number needed to treat is nine.[7] Thus, itopride appears to be efficacious in the treatment of a common condition for which few effective alternative therapies are currently available.

Itopride is thought to exert prokinetic effects by way of antidopaminergic and antiacetylcholinesterase actions[12] and probably to have effects on gastric accommodation and gastric hypersensitivity. In our study, we did not measure gastric emptying. Thus, we cannot determine whether gastric emptying was associated with the response to therapy. Stimulation of central dopamine receptors enhances prolactin release, and we observed increased prolactin levels during treatment with itopride. This effect was not associated with any clinical symptoms or signs during the eight-week period of therapy. In previous studies, an augmented increase in prolactin levels in patients with functional dyspepsia after stimulation of central serotoninergic receptors has been observed following treatment with buspirone that stimulates central serotoninergic 1A receptors.[12] Of note, the prolactin level was closely correlated with the degree of delayed solid-phase gastric emptying assessed scintigraphically.[21]

Previous trials of treatments for functional dyspepsia have been criticized for various methodologic limitations.[22] The current trial was designed with a sufficient sample size, strict entry criteria, and application of valid outcome measures. The Rome II criteria were used to enroll patients; patients whose symptoms were predominantly those of gastroesophageal reflux disease were not eligible to participate. Nevertheless, there is remarkable overlap between functional dyspepsia and concomitant reflux symptoms.[23] Indeed, in our trial, 89 of the 548 patients who were randomly assigned to a study group also had some reflux symptoms. Although dyspepsia symptoms were significantly more severe, and scores for epigastric pain and excessive fullness were higher, among patients with reflux symptoms, their overall response to treatment was not different from that of patients who had no reflux symptoms. Therefore, it is reasonable to assume that the outcome of this study was not due to a favorable response to treatment with a prokinetic agent among patients with reflux.

It is important to note that the trial was not powered a priori to achieve statistically significant results, in terms of pairwise comparisons between individual itopride doses and placebo. Instead, the sample size was calculated to identify a difference that was believed to be clinically significant.[7,8] In reality, the response to therapy was considerably better than expected. Trials longer than eight weeks are needed to confirm the current findings and to determine whether the benefits persist after treatment is stopped.

In summary, the results of this multicenter, placebo-controlled trial suggest that itopride, a dopamine D2 antagonist with acetylcholinesterase effects, is superior to placebo in the treatment of functional dyspepsia. The exact mechanisms by which itopride improves symptoms remain to be established, and further clinical trials are needed to assess the efficacy and optimal duration of treatment in various populations.

Supported by Knoll, which is now owned by Abbott Laboratories, and by a grant (Ho 1193/4-1) from Deutsche Forschungsgemeinschaft.

Dr. Holtmann reports having received consulting fees from Knoll. Dr. Talley reports having received research grant support from Axcan Pharmaceuticals, research support from Abbott Laboratories, and having been a consultant for Knoll. Dr. Parow is an employee of Abbott Laboratories. No other potential conflict of interest relevant to this article was reported.

We are indebted to Dr. J. Schnitker (Institute for Applied Statistics [IAS], Bielefeld, Germany) and the IAS staff for the statistical analyses and monitoring of the study, to Drs. G. Boos and B. Matiba (Abbott, Ludwigshafen, Germany) for their contributions to the study design and the conduct of the trial, and to our colleagues who helped to recruit the patients.

REFERENCES

1. Richter JE. Dyspepsia: organic causes and differential characteristics from functional dyspepsia. Scand J Gastroenterol Suppl 1991;182:11-6.

2. Talley NJ, Colin-Jones D, Koch KL, Koch M, Nyrén O, Stanghellini V. Functional dyspepsia: a classification with guidelines for diagnosis and management. Gastroenterol Int 1991;4:145-60.

3. Talley NJ, Stanghellini V, Heading RC, Koch KL, Malagelada JR, Tytgat GN. Functional gastroduodenal disorders. Gut 1999;45:Suppl 2:II-37–II-42.

4. Talley NJ. Functional dyspepsia — should treatment be targeted on disturbed physiology? Aliment Pharmacol Ther 1995; 9:107-15.

5. Holtmann G, Talley NJ. Functional dyspepsia: current treatment recommendations. Drugs 1993;45:918-30.

6. Talley NJ, McNeil D, Hayden A, Piper DW. Randomized, double-blind, placebo-controlled crossover trial of cimetidine and pirenzepine in nonulcer dyspepsia. Gastroenterology 1986;91:149-56.

7. Moayyedi P, Delaney BC, Vakil N, Forman D, Talley NJ. The efficacy of proton pump inhibitors in nonulcer dyspepsia: a systematic review and economic analysis. Gastroenterology 2004;127:1329-37.

8. Laine L, Schoenfeld P, Fennerty MB. Therapy for *Helicobacter pylori* in patients with nonulcer dyspepsia: a meta-analysis of randomized, controlled trials. Ann Intern Med 2001;134:361-9.

9. Talley NJ, Vakil NB, Moayyedi P. American Gastroenterological Association technical review on the evaluation of dyspepsia. Gastroenterology 2005;129:1756-80.

10. Dobrilla G, Comberlato M, Steele A, Vallaperta P. Drug treatment of functional dyspepsia: a meta-analysis of randomized controlled clinical trials. J Clin Gastroenterol 1989;11:169-77.

11. Veldhuyzen van Zanten SJ, Jones MJ, Verlinden M, Talley NJ. Efficacy of cisapride and domperidone in functional (nonulcer) dyspepsia: a meta-analysis. Am J Gastroenterol 2001;96:689-96.

12. Iwanaga Y, Miyashita N, Saito T, Morikawa K, Itoh Z. Gastroprokinetic effect of a new benzamide derivative itopride and its action mechanisms in conscious dogs. Jpn J Pharmacol 1996;71:129-37.

13. Moayyedi P, Duffett S, Braunholtz D, et al. The Leeds Dyspepsia Questionnaire: a valid tool for measuring the presence and severity of dyspepsia. Aliment Pharmacol Ther 1998;12:1257-62.

14. Talley NJ, Haque M, Wyeth JW, et al. Development of a new dyspepsia impact scale: the Nepean Dyspepsia Index. Aliment Pharmacol Ther 1999;13:225-35.

15. Holm S. A simple sequentially rejective multiple test procedure. Scand J Stat 1979;6:65-70.

16. SAS/STAT software: changes and enhancements through Release 6.12. Cary, N.C.: SAS Institute, 1997.

17. SAS/STAT user's guide, vol. 1 and 2. Cary, N.C.: SAS Institute, 1990.

18. Holtmann G, Gschossmann J, Neufang-Huber J, Gerken G, Talley NJ. Differences in gastric mechanosensory function after repeated ramp distensions in nonconsulters with dyspepsia and healthy controls. Gut 2000;47:332-6.

19. Holtmann G, Talley NJ, Mitchell H, Hazell S. Antibody response to specific *H. pylori* antigens in functional dyspepsia, duodenal ulcer disease, and health. Am J Gastroenterol 1998;93:1222-7.

20. Zighelboim J, Talley NJ. What are functional bowel disorders? Gastroenterology 1993;104:1196-201. [Erratum, Gastroenterology 1993;105:649.]

21. Dinan TG, Chua AS, Keeling PW. Serotonin and physical illness: focus on non-ulcer dyspepsia. Invicta Satellite Meeting: depression and the physically ill. J Psychopharmacol 1993;7(Suppl):126-30.

22. Veldhuyzen van Zanten SJ, Cleary C, Talley NJ, et al. Drug treatment of functional dyspepsia: a systematic analysis of trial methodology with recommendations for design of future trials. Am J Gastroenterol 1996;91:660-73.

23. Agreus L, Svardsudd K, Nyren O, Tibblin G. Irritable bowel syndrome and dyspepsia in the general population: overlap and lack of stability over time. Gastroenterology 1995;109:671-80.