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Effects of Pantoprazole 20 mg in Mild Gastroesophageal Reflux Disease: Once-Daily Treatment in the Acute Phase, and Comparison of On-Demand Versus Continuous Treatment in the Long Term

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ABSTRACT

Background: Gastroesophageal reflux disease (GERD) is a chronic disorder, and although effective short-term treatment strategies are known, the rate of relapse within 1 year is as high as 90% despite successful acute treatment. Consequently, most patients with GERD require an effective long-term management strategy to achieve adequate symptom control and maintain mucosal healing.

Objective: The present study was undertaken to compare the control of GERD symptoms during long-term (24-week) treatment with pantoprazole 20 mg used on-demand or continuously in patients with mild GERD after complete relief of acute GERD symptoms.

Methods: Patients with endoscopically confirmed Savary/Miller grade 0 (normal mucosa) or I (patchy red lesions without white coating or with central white coating) GERD were enrolled in this multinational, multicenter study comprising 2 phases. In the first phase, which was open label, patients were treated with pantoprazole 20 mg QD for 4 weeks. The presence and intensity of the symptoms of heartburn, acid regurgitation, and pain on swallowing were assessed. In the second phase, which was an open-label, 24-week, randomized design, only patients completely free of GERD symptoms after acute treatment were included. During this phase, on-demand treatment with pantoprazole 20 mg was directly compared with continuous treatment. The rate of failure to control GERD symptoms after 24 weeks of treatment was estimated using the Kaplan-Meier method. Subsequently, the difference between treatments (on-demand minus continuous) and its 95% CI were calculated, and the on-demand treatment was tested for noninferiority using a predefined noninferiority margin of 20%. The mean daily symptom loads were compared between the treatment groups using the 1-sided Wilcoxon rank sum test on a 5% α level. The point estimate of the difference was determined using the Hodges-Lehman estimator and

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the 1-sided 95% CI according to Moses. The number of patients unwilling to continue due to insufficient control of heartburn, acid regurgitation, and pain on swallowing was analyzed using the Kaplan-Meier (time-to-event) analysis. Analysis was performed in the same manner as for the rate of failure to control GERD symptoms, but the 95% CI was interpreted for statistical superiority.

Results: A total of 558 patients were enrolled in this study. At the end of the acute phase, 82.1% of patients in the per-protocol (PP) population and 79.1% in the intent-to-treat (ITT) population were relieved of all GERD symptoms, and subsequently entered the long-term phase. After 24 weeks of treatment, analysis of the failure rates revealed that on-demand treatment was noninferior to continuous treatment because the 95% CI was completely below 20% (ITT, 12.1% difference [95% CI, −∞ to 18.9%]; PP, 10.1% difference [95% CI, −∞ to 17.7%]). The higher perceived mean (SD) daily symptom load in the on-demand group (ITT, 1.26 [1.49] vs 0.82 [1.34]) was balanced by the reduced tablet intake in that group (PP, 0.51 [0.31] vs 0.97 [0.11] tablets/d; $P < 0.001$). With respect to the rate of patients unwilling to continue treatment, no statistically significant difference was observed between the on-demand and continuous groups (ITT/PP, 0.95/1.13 vs 0.95/1.26).

Conclusions: In this study of pantoprazole 20 mg tablets in patients with mild GERD, patients receiving on-demand treatment benefited despite their higher symptom load. The similar rates of unwillingness to continue treatment in both groups might suggest that patients were satisfied with the on-demand treatment strategy. On-demand treatment with pantoprazole 20 mg was found to be noninferior compared with continuous therapy with regard to symptom control. Both on-demand and continuous treatments were well tolerated. (*Curr Ther Res Clin Exp.* 2005;66:345–363)

Key words: drug administration schedule, follow-up study, gastroesophageal reflux/drug therapy, heartburn, long-term care, treatment outcome, pantoprazole, continuous, on-demand, as needed.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a chronic disorder, and although effective short-term treatment strategies are known, the rate of relapse within 1 year is as high as 90% despite successful acute treatment.[1] Consequently, most patients with GERD, irrespective of whether the underlying disease was initially mild or severe, require an effective long-term management strategy to achieve adequate symptom control and maintain mucosal healing.[1]

Traditionally, long-term management strategies have included daily maintenance treatment with proton pump inhibitors (PPIs) in low doses to maintain remission. However, recent studies[2–10] investigating PPIs used on-demand (1 dose on recurrence of symptoms, continued until symptom relief) showed that PPIs were more effective in preventing symptom relapse in nonerosive or mild GERD compared with placebo. These findings suggest that for the long-term manage-

ment of mild GERD (after acute symptom relief), on-demand PPI therapy might be more effective compared with step-down treatments, such as ranitidine or a motility agent. Galmiche et al[11] investigated the on-demand use of H_2-receptor antagonists. Although the improvement was statistically significant compared with placebo, a 40% success rate is not encouraging. In an uncontrolled trial, Wilhelmsen et al[12] reported better results with H_2-receptor antagonists used on-demand, with 84% of patients reporting satisfaction with the therapy. Encouraged by these findings, Bytzer and Blum[13] developed algorithms for clinical practice. The on-demand modality evolved from patient habits. Intake behavior and compliance studies have shown that patients with GERD symptoms generally do not use their medication as prescribed but only when their symptoms require treatment.[14] Symptom-triggered use might give patients a sense of self-empowerment over their disease state.[14] In addition to the expected improvement in patients' willingness to continue treatment, the on-demand approach would seem to have the potential to substantially lower drug acquisition costs.[15,16] The use of on-demand PPI therapy might avoid the costs of switching to a PPI due to failure with an H_2-blocker or a motility agent.

Several long-term studies of up to 1-year duration with continuous pantoprazole 20 mg QD demonstrated maintenance of healing of erosive esophagitis, sustained symptom relief, and statistical superiority to placebo.[17–19] Furthermore, recent studies[20,21] of pantoprazole 20 mg on-demand in patients with nonerosive or mild GERD (grade 0 [normal mucosa] or I [patchy red lesions without white coating or with central white coating] according to Savary and Miller,[22] as modified by Siewert et al[23]) demonstrated that this treatment modality was more effective in maintaining control of the 3 major GERD symptoms—heartburn, acid regurgitation, and pain on swallowing—and other GERD symptoms compared with placebo, and was well tolerated. However, based on an unstructured MEDLINE search, fully published data from a direct comparison of on-demand versus maintenance treatment with pantoprazole are lacking.

Hence, the present study was undertaken to compare the control of GERD symptoms during long-term (24-week) treatment with pantoprazole 20 mg used on-demand or continuously in patients with mild GERD after complete relief of acute GERD symptoms.

PATIENTS AND METHODS

Design, Conduct, and Ethical Considerations

This multicenter study was conducted in 2 phases and involved 58 active centers: 29 in Germany, 12 in France, 11 in Switzerland, and 6 in Hungary. The first, acute phase was conducted as an open-label symptom-relief study. Patients aged 18 to 75 years who had endoscopically confirmed Savary/Miller[22,23] grade 0 or I GERD and who experienced frequent episodes of at least one of the characteristic GERD symptoms (heartburn, acid regurgitation, and/or pain on swallowing) during the previous 3 months were eligible for inclusion. At least one of the

symptoms had to be of at least moderate intensity on the last 3 days prior to inclusion.

In this acute phase, pantoprazole 20 mg QD was administered for 4 weeks. For the evaluation of symptoms, patients recorded the presence and intensity of the symptoms of heartburn, acid regurgitation, and pain on swallowing in a patient diary on a daily basis. During the baseline visit and each follow-up visit, patients were asked about the intensity of heartburn, acid regurgitation, pain on swallowing, and 3 other symptoms (epigastric pain, abdominal pain, and retrosternal feeling of tightness) by the investigator. At the baseline visit, a complete medical history was documented, including demographic data, previous treatments for GERD symptoms, completed treatments for any other diseases, recent concomitant medication, and clinical symptoms. For tolerability assessment, a physical examination was performed at the final visit, and blood, serum, and urine samples were analyzed at the first and final follow-up visits.

Patients who were completely free of heartburn, acid regurgitation, and pain on swallowing and whose other symptoms (epigastric pain, abdominal pain, retrosternal feeling of tightness) were at most mild in severity for at least 3 consecutive days prior to the first follow-up visit (after 4 weeks) entered the long-term phase of the study. This phase was performed as an open-label, randomized, parallel-group comparison of on-demand and continuous treatment for 6 months (24 weeks), with patients receiving either on-demand pantoprazole 20 mg QD or continuous pantoprazole 20 mg QD. Randomization was performed using a computer-generated list. The study medication was packed in a sealed box and allocated according to the numbering in ascending order. The patient and the investigator first learned to which treatment group the patient was assigned when the patient opened the box. Patients in the on-demand group were asked to use the medication only if at least one of the characterisic GERD symptoms required treatment, with a maximum of 1 tablet/d; those in the continuous group were instructed to receive 1 tablet of pantoprazole 20 mg QD.

Each patient was scheduled for a total of 4 visits—the visit at the beginning of the study and 3 follow-up visits at 4, 16, and 28 weeks after the start of the study. To help calculate the mean symptom load (described later), all unused medication was counted and documented by the investigator on the case-report form at each follow-up visit.

For both phases, patients were excluded if they met any of the following criteria: the presence of any other gastrointestinal diseases (eg, endoscopically confirmed Savary/Miller grades II to IV GERD); florid peptic ulcer; known history of Zollinger-Ellison syndrome, pyloric stenosis, ulcer complications, or gastric surgery (except appendectomy, cholecystectomy, and polypectomy); or severe disease of any other body system. The use of *Helicobacter pylori* eradication therapy, systemic glucocorticosteroids, NSAIDs (except aspirin up to 150 mg/d), and supportive medication for the treatment of gastrointestinal complaints (eg, PPIs, H_2-receptor antagonists, prokinetics, sucralfate) was prohibited throughout the study.

The study was conducted according to the Good Clinical Practice guideline[24] and the Declaration of Helsinki and its amendments.[25] Independent local ethics committees in the respective countries approved the protocol. Before enrollment, all patients provided written informed consent to participate.

Symptom Assessment

Assessment by Patient Diary

Patients were instructed to document the symptom intensity of the 3 GERD symptoms (heartburn, acid regurgitation, and pain on swallowing) each day, using a 4-point scale (0 = none; 1 = mild; 2 = moderate; and 3 = severe).

Investigator's Assessment

At each visit, the investigator questioned the patient about the intensity of the symptoms of heartburn, acid regurgitation, and pain on swallowing, and 3 additional symptoms (epigastric pain, abdominal pain, retrosternal feeling of tightness) during the prior 3 consecutive days. Analogous to the patient's diary, the intensity was assessed on a 4-point scale (0 = none; 1 = mild; 2 = moderate; and 3 = severe).

Primary End Point

In this study, 2 treatment modalities were directly compared—on-demand treatment (with a mean of <1 tablet/d) versus continuous treatment (with exactly 1 tablet/d). Hence, the primary end point of the study was assessed only in the long-term phase. Our intention was to demonstrate that on-demand therapy could be used to sufficiently (ie, acceptable to the patient) control heartburn, acid regurgitation, and pain on swallowing. Thus, the primary variable in this study was the difference in the estimated rates of patients with uncontrolled heartburn, acid regurgitation, and pain on swallowing between the 2 treatment groups. The symptoms (as assessed in the patient's diary) were considered controlled until the *time of failure,* which was defined as the first point at which one of the following events occurred: (1) GERD symptoms of at least moderate severity were present for 3 or more consecutive days despite medication (event time = the first of these 3 days); (2) use of >1 tablet of study medication on >3 consecutive days (event time = the first of these 3 days); or (3) premature withdrawal from the study due to lack of efficacy (event time = the date of withdrawal).

Secondary End Points

At the end of the acute phase (after 4 weeks of treatment), the overall symptom relief rate (based on the investigator's assessment) and the relief rates for each symptom were calculated by dividing the number of patients free of symptoms by the number of patients with symptoms at baseline.

A secondary variable assessed for the long-term phase was the *perceived mean daily symptom load,* which combined information about symptoms (as assessed in the patient's diary) and medication intake. Using the symptom intensity of the 3 GERD symptoms (heartburn, acid regurgitation, and pain on

swallowing), a *sum score* was calculated (range, 0–9) for each day of treatment. Because this sum score reflected only a selective status of the patient's GERD symptoms (ie, for a single point in time), an overall measure of the patient's symptoms was more appropriate and was done by adding the sum scores of all days and dividing that sum by the number of days that the patient participated in the study. In practice, we used the area under the overall sum score of symptoms curve over the individual study time (AUC). The calculation of the AUC for a defined time period is commonly used to transfer a time-dependent function to a single value. Because the intake of study medication could vary greatly in the on-demand treatment group, medication intake was included in the calculation of the perceived mean daily symptom load. Thus, the number of tablets of study medication used was divided by the individual study time, and this ratio was multiplied by the AUC. Because patients in the on-demand group, in the most extreme cases, might not have used any study medication (0), a weighting factor of 1 was added to ensure meaningful results. The perceived mean daily symptom load could range from 0 to 18 (maximum symptom load).

Tolerability

Adverse events (AEs) were documented at each follow-up visit. The investigator assessed AEs using laboratory analysis, spontaneous reporting, and open questioning, and classified the causal relationship to the study medication as unrelated, unlikely to be related, likely to be related, or definitely related. The severity of AEs was graded as mild, moderate, or severe.

Statistical Analysis

The sample size was determined using nQuery Advisor version 4.0 (Statistical Solutions, Saugus, Massachusetts). We assumed a failure rate to control GERD symptoms after 24 weeks of treatment of 20% for continuous treatment and at most 27.5% for on-demand treatment. Although it is common to select as delta the proportion of the difference between an active treatment and placebo, when comparing 2 regimens of the same treatment, as was done in the present study, delta can be larger, especially if it is unclear how often patients in the on-demand group would use their medication; thus, we defined a noninferiority margin of 20%. With these values, we calculated that 300 patients (150 per group) were required to achieve a power of 80% (1-sided 95% CI). Assuming a symptom relief rate of 80% for the acute phase, a rate of 90% of patients continuing the long-term phase, and 80% of these belonging to the per-protocol (PP) population, 520 patients had to be included initially.

The primary end point in this study was the difference in the estimated rates of patients with uncontrolled heartburn, acid regurgitation, and pain on swallowing between the 2 treatment groups (long-term phase). In each treatment group, a survival analysis was performed according to Kaplan-Meier, leading to estimates of the "survival rate" and its standard error (SE). In these analyses, "survival" was associated with "no failure to control all 3 characteristic GERD symp-

toms." The difference, "survival rate in the on-demand group minus that in the continuous group," and its SE were determined using the Kaplan-Meier results. Using these results, the 1-sided 95% CI was calculated. Noninferiority of the on-demand treatment with respect to the continuous therapy was concluded if the noninferiority margin of 20% was outside of the 1-sided 95% CI. Thus, the null hypothesis (that the on-demand therapy is statistically inferior to the continuous therapy) was tested against the alternative hypothesis (that on-demand is noninferior).

The secondary end point for the acute phase was the symptom relief rate, together with its 95% binomial confidence limits after 4 weeks of treatment with pantoprazole 20 mg. *Relief* was defined as being free of heartburn, acid regurgitation, and pain on swallowing on the 3 consecutive days before assessment and having one or more additional symptoms of at most mild intensity.

The secondary end point for the long-term phase was the perceived mean daily symptom load (time- and medication-weighted symptom load). The mean values of both treatment groups were compared using the Wilcoxon rank sum test (1-sided) at a 5% α level. Thus, the null hypothesis (no difference between treatments) was tested versus the alternative hypothesis (that on-demand treatment was statistically superior to continuous therapy). In addition, the point estimate of the difference between the 2 treatments was determined using the Hodges-Lehman estimator and the 1-sided 95% CI according to Moses.[26] A 95% CI not including the value 0 indicated statistical significance. The amount of study medication used was analyzed descriptively and compared using the Wilcoxon rank sum test (2-sided). The numbers of patients unwilling to continue due to insufficient control of heartburn, acid regurgitation, and/or pain on swallowing were analyzed using the Kaplan-Meier (time-to-event) analysis. Analysis was done in the same manner as for the primary end point, but the 95% CI was interpreted for statistical superiority. In general, dichotomous parameters were compared using the Fisher exact test (2-tailed), and ordinal variables were compared using the Wilcoxon rank sum test.

Tablets Used

The number of pantoprazole tablets used was analyzed by means of descriptive statistics for the absolute numbers taken over the entire observation period and for the mean number of tablets taken per day by each individual during the long-term phase.

Data Sets Analyzed

Statistical analysis was performed in both the intent-to-treat (ITT) and PP populations. Both populations were defined separately in the acute and long-term phases, as shown in **Figure 1**. The ITT population (acute phase) comprised all patients for whom it could not be ruled out that study medication was received. In the long-term phase, the ITT population was defined as eligible patients for whom it could not be ruled out that study medication was received and who attended at least one follow-up visit after starting the long-term phase.

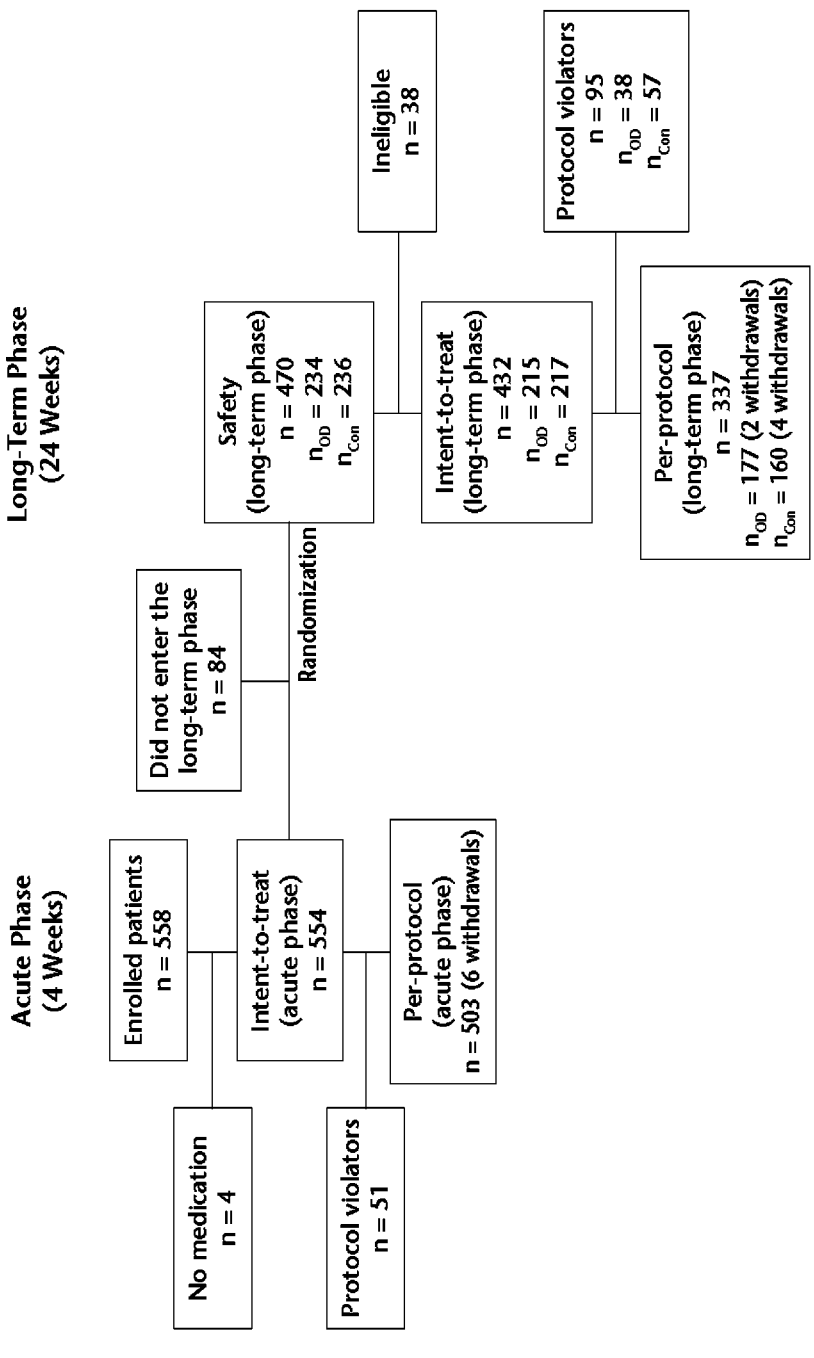

Figure 1. Disposition of patients receiving pantoprazole 20 mg tablets for the treatment of gastroesophageal reflux disease.
OD = on-demand; Con = continuous.

The PP analysis excluded protocol violators. The safety population (long-term phase) comprised all patients for whom it could not be ruled out that study medication was received.

RESULTS

Study Population

A total of 558 patients were enrolled in the study (**Figure 1**). Four patients did not receive study medication, leaving 554 patients in the acute phase ITT population. Fifty-one patients were excluded from the acute phase PP analysis due to protocol violations, leaving 503 patients (including 6 withdrawals) in the acute phase PP population. The most common protocol violations were loss to follow-up (except withdrawals; 23 patients), use of a prohibited concomitant medication (19 patients), and deviations from specified follow-up visit dates (8 patients). Patients classified as withdrawals in the acute phase withdrew prematurely because of an AE (definitely related, 1 patient; likely related, 3; and lack of efficacy, 2).

After 4 weeks of treatment with pantoprazole 20 mg, 84 patients did not enter the long-term phase (55 patients did not have relief of heartburn, acid regurgitation, and/or pain on swallowing; 23 withdrew during the acute phase [6 due to AEs; 6, subsequent violations of inclusion/exclusion criteria; 2, protocol violation (poor compliance); 2, lack of efficacy; 7, other reasons]; and 6 discontinued due to other reasons), leaving 470 patients in the safety population of the long-term phase. Thirty-eight of these patients entered the long-term phase even though heartburn, acid regurgitation, and/or pain on swallowing were still present. Consequently, these patients were classified as ineligible and were excluded from the ITT population. The remaining 432 patients were randomized to treatment (on-demand, 215 patients; continuous, 217 patients). Ninety-five patients were excluded from the PP population because they were classified as protocol violators. The most common violations were use of a prohibited concomitant medication (30 patients), loss to follow-up (29 patients), and having >10% of diary cards unavailable for evaluation (18 patients). Thus, the PP population comprised 337 patients, 177 (including 2 withdrawals) who received on-demand therapy and 160 (including 4 withdrawals) who received continuous therapy. The 6 patients withdrew prematurely due to lack of efficacy (4 patients) and an AEs (2 patients, likely related).

The demographic characteristics and medical history of the patients included in the ITT population are shown in **Table I**. No statistically significant between-group differences were found.

Efficacy

Acute Phase

After 4 weeks of treatment with pantoprazole 20 mg QD, overall symptom relief rates were 79.1% (438/554) and 82.1% (413/503) in the ITT and PP populations, respectively. Relief rates of the individual symptoms were 83.3% (449/539)

Table I. Baseline demographic and clinical characteristics of the intent-to-treat population of patients receiving pantoprazole 20 mg tablets on-demand or continuously for the treatment of mild gastroesophageal reflux disease (GERD) (long-term [24-week] phase) (n = 432).

Characteristic	On-Demand (n = 215)	Continuous (n = 217)	*P*
Age, mean (SD), y	50.4 (13.6)	51.8 (13.5)	0.404
Sex, no. (%)			0.848
Female	115 (53.5)	114 (52.5)	
Male	100 (46.5)	103 (47.5)	
Body mass index, mean (SD), kg/m^2	26.9 (4.6)	26.6 (4.1)	0.566
Initial GERD grade,* no. (%)			0.10
0	48 (22.3)	64 (29.5)	ND
I	167 (77.7)	153 (70.5)	ND

ND = not determined.
*GERD grade according to Savary and Miller,[22] modified by Siewert et al[23]: grade 0 = normal mucosa; grade I = patchy red lesions without white coating or with central white coating.

for heartburn, 80.0% (403/504) for acid regurgitation, and 91.0% (294/323) for pain on swallowing in the ITT population; in the PP population, relief rates were 86.1% (422/490) for heartburn, 83.3% (378/454) for acid regurgitation, and 94.2% (278/295) for pain on swallowing. For the calculation of symptom relief rates, only patients who experienced the respective symptom at baseline were included. The numbers of patients with symptoms at baseline varied between symptoms and were less than the total number of patients included in the acute phase because not all enrolled patients suffered all symptoms (to be eligible for the study, patients had to experience only 1 of the 3 characteristic GERD symptoms).

Long-Term Phase

Estimated Rate of Patients with Uncontrolled Symptoms

The effect of both treatment modalities on symptom control, measured as the estimated failure rates of patients with uncontrolled heartburn, acid regurgitation, and pain on swallowing in each treatment group at the end of the long-term therapy, was assessed as the primary end point. In the PP population, treatment failed to control symptoms in an estimated 29.5% of patients in the on-demand group and an estimated 19.4% of patients in the continuous group; thus the between-group difference was 10.1%. As the upper limit of the 95% CI was 17.7% and, thus, less than the noninferiority margin of 20%, noninferiority was concluded. This result was similar in the ITT population: in the on-demand group the estimated failure rate was 30.7% compared with a rate of 18.6% in the continuous group. Thus, the difference was 12.1%, and the upper limit of the 95% CI was 18.9% (**Table II**). The calculated rates of

patients with controlled heartburn, acid regurgitation, and pain on swallowing (symptom relief rates using survival time methods [ie, 100% minus failure rate]) are shown in **Figure 2**.

Perceived Mean Daily Symptom Load

The perceived mean daily symptom loads (ie, the time- and medication-weighted symptom loads) are shown in **Table III**. Patients treated with pantoprazole on-demand had a significantly higher GERD symptom load compared with patients treated with pantoprazole continuously over 24 weeks (ITT and PP, $P < 0.001$). Consistent with the Wilcoxon test, the point estimate of the difference between treatments (on-demand minus continuous using the Hodges-Lehman estimator) was 0.38, with a lower confidence limit of 0.26, in the ITT population; it was 0.34, with a lower confidence limit of 0.21, in the PP population. Because the value 0 was outside of the 95% CI, the difference was considered statistically significant.

Unwillingness to Continue

A total of 30 patients in the ITT population (13/215 [6.0%] in the on-demand group and 17/217 [7.8%] in the continuous group) discontinued the long-term phase prematurely. The rate of premature discontinuation due to insufficient symptom control was not statistically significantly different in the on-demand group compared with that in the continuous group (the value 0 was within the 95% CI of the estimated difference between treatment groups). In the ITT population, the estimated difference was 0.0% (95% CI, –∞% to 1.13%); in the PP population, the estimated difference was –0.13% (95% CI, –∞% to 1.29%) (**Figure 3**).

Table II. Estimated rates of treatment failure* in patients receiving pantoprazole 20 mg tablets on-demand or continuously for the treatment of gastroesophageal reflux disease (GERD) (long-term [24-week] phase).

Population/Parameter	On-Demand	Continuous	Difference, % (95% CI)
ITT			
No. of patients	215	217	–
Estimated treatment failure rate, %	30.7	18.6	12.1
95% CI, %	24.5 to 37.0	13.4 to 23.8	–∞ to 18.9
PP			
No. of patients	177	160	–
Estimated treatment failure rate, %	29.5	19.4	10.1
95% CI, %	22.8 to 36.2	13.3 to 25.6	–∞ to 17.7

ITT = intent-to-treat; PP = per-protocol.
*Patients in whom treatment failed to control the 3 characteristic symptoms of GERD—heartburn, acid regurgitation, and pain on swallowing.

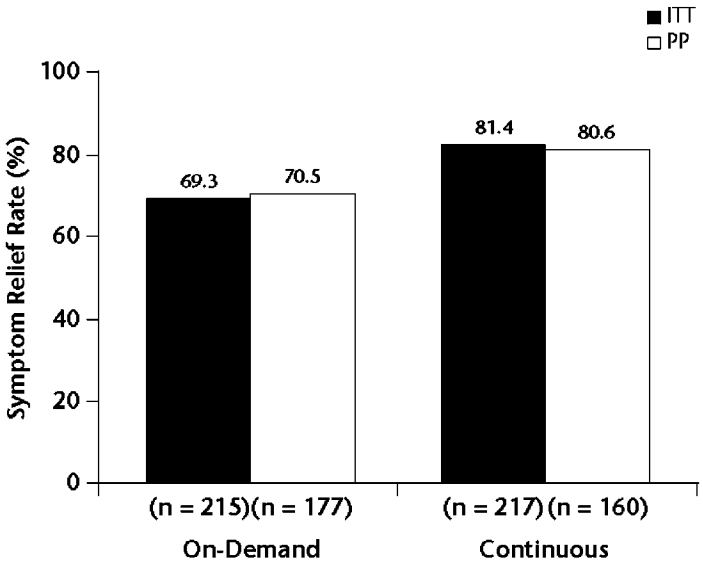

Figure 2. Rates of symptom relief (controlled heartburn, acid regurgitation, and pain on swallowing) in patients receiving pantoprazole 20 mg tablets for the treatment of gastroesophageal reflux disease (long-term [24-week] phase). ITT = intent-to-treat population; PP = per-protocol population. No significant between-group differences were found.

Table III. Perceived mean daily symptom load (MDSL)* in patients receiving pantoprazole 20 mg tablets on-demand or continuously for the treatment of gastroesophageal reflux disease (long-term [24-week] phase).

Population/Parameter	On-Demand	Continuous	Difference, %† (95% CI)	*P*
ITT				
No. of patients	212‡	217	–	–
MDSL, mean (SD)	1.26 (1.49)	0.82 (1.34)	0.38 (0.26–∞)	<0.001
PP				
No. of patients	177	160	–	–
MDSL, mean (SD)	1.15 (1.33)	0.90 (1.47)	0.34 (0.21–∞)	<0.001

ITT = intent-to-treat; PP = per-protocol.
*See text for method of calculation.
†Point estimate of the difference between treatments (on-demand minus continuous using the Hodges-Lehman estimator).
‡Data were unavailable in 3 patients.

Tolerability

Tolerability data were analyzed in the ITT population in the acute phase (n = 554) and in the safety population in the long-term phase (n = 470) (**Table IV**). One of 87 (1%) AEs (gastrointestinal disorder) in the acute phase was considered definitely related to pantoprazole use; none of the AEs in the long-term phase were considered definitely related to treatment. The most common AE symptoms in the long-term phase were bronchitis (on-demand: 6 AE symptoms, 2% of patients; continuous: 9 AE symptoms, 3% of patients), lumbar pain (on-demand: 5 AE symptoms, 2% of patients; continuous: 6 AE symptoms, 2% of patients), and cervicobrachialgia (on-demand: 4 AE symptoms, 2% of patients; continuous: 5 AE symptoms, 2% of patients). In the long-term phase, none of the serious AEs were considered to be related to the study medication. No statistically significant differences in the safety profile between the on-demand and continuous groups were found.

Tablets Used

Both the absolute and mean number of tablets taken per day were significantly lower in the on-demand group compared with the continuous group (ITT and PP, $P < 0.001$) (**Table V**).

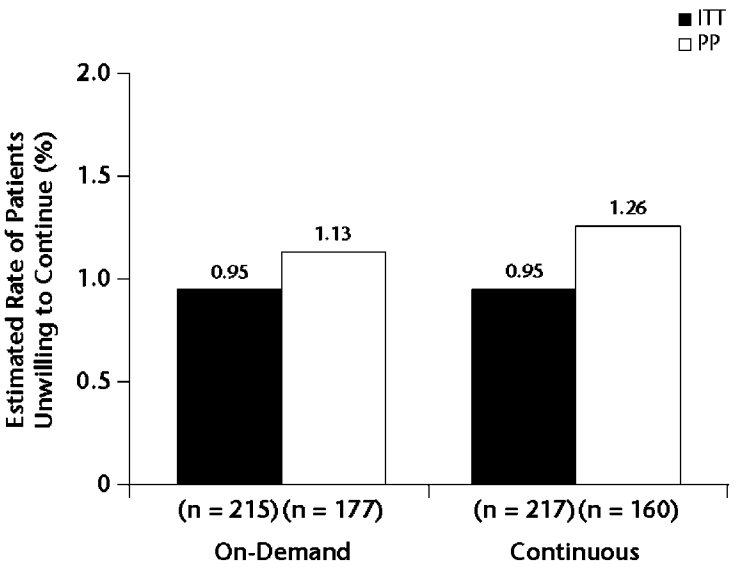

Figure 3. Estimated rates of patients unwilling to continue treatment due to inadequate symptom control (long-term phase) (analyzed using the Kaplan-Meier method in the intent-to-treat [ITT] and the per-protocol [PP] populations). No significant between-group differences were found.

Table IV. Adverse events (AEs) in patients receiving pantoprazole 20 mg tablets for the treatment of gastroesophageal reflux disease.*

Parameter	Acute (4-wk) Phase (ITT) (n = 554)	Long-Term (24-wk) Phase (Safety)	
		On-Demand (n = 234)	Continuous (n = 236)
No. (%) of patients with AEs†	64 (12)	70 (30)	88 (37)
No. of AE symptoms	87	149	178
Most common AE symptoms, no. of symptoms (% of patients)			
Bronchitis	0	6 (2)	9 (3)
Lumbar pain	4 (<1)	5 (2)	6 (2)
Cervicobrachialgia	0	4 (2)	5 (2)
Influenza-like symptoms	4 (<1)	0	0
Exanthema	3 (<1)	0	0
Relation to treatment, no. (%) of AEs			
Unrelated	62 (71)	115 (77)	151 (85)
Not likely related	16 (18)	25 (17)	20 (11)
Likely related	8 (9)	9 (6)	7 (4)
Definitely related	1 (1)	0	0
Intensity, no. (%) of AEs			
Mild	35 (40)	62 (42)	77 (43)
Moderate	41 (47)	71 (48)	81 (46)
Severe	11 (13)	16 (11)	20 (11)
Serious AEs,‡ no. of symptoms (% of patients)	4 (<1)	6 (3)	14 (6)
AEs leading to withdrawal, no. of symptoms (% of patients)	6 (1)	5 (2)	11 (5)

ITT = intent-to-treat.
*No significant between-group differences were found.
†Some patients experienced >1 AE.
‡None of the serious AEs were treatment related.

DISCUSSION

This study was designed to compare the control of GERD symptoms during long-term treatment with pantoprazole 20 mg used on-demand versus continuously in patients with mild GERD after acute relief of heartburn, acid regurgitation, and pain on swallowing. A recent study of pantoprazole 20 mg in 1552 patients with mild GERD showed that only 40.3% of patients used their medication as prescribed (once daily); noncompliers used it 2 to 6 d/wk (intermittent).[27] This find-

Table V. Pantoprazole 20 mg tablets used* per patient on-demand or continuously for the treatment of gastroesophageal reflux disease (long-term [24-week] phase). Values are presented as mean (SD).

Population/Parameter	On-Demand	Continuous	*P*
ITT			
No. of patients	215	217	–
Daily	0.51 (0.31)	0.93 (0.17)	<0.001
Total	83.2 (52.4)	152.4 (38.2)	<0.001
PP			
No. of patients	177	160	–
Daily	0.51 (0.31)	0.97 (0.11)	<0.001
Total	84.3 (51.4)	161.8 (27.3)	<0.001

ITT = intent-to-treat; PP = per-protocol.
*Analyzed using descriptive statistics for the absolute number of tablets used over the entire observation period and for the mean number of tablets used per day by each individual.

ing suggests that on-demand use of medication in the long term matches patients' self-medication behavior. Preliminary data from a 1-year study of on-demand versus continuous use of pantoprazole in 100 patients with mild GERD showed that both treatment modalities were similarly tolerable, although the frequency of symptomatic reflux episodes was significantly increased from baseline in the on-demand group after 3 months.[28] Based on our literature search, data from a direct comparison of on-demand and continuous use of pantoprazole in a large clinical setting have not been fully published to date.

The primary end point of the present study was the estimated rate of patients with uncontrolled heartburn, acid regurgitation, and pain on swallowing in the long-term phase. During this phase, on-demand treatment with pantoprazole 20 mg was compared directly with continuous treatment with pantoprazole. The comparison of the 2 treatment groups by means of a noninferiority test was chosen as the primary end point because although it was anticipated that on-demand therapy would be statistically inferior to continuous therapy in controlling GERD symptoms, we attempted to show that patients would tolerate a certain level of symptoms but would medicate themselves when the symptoms became sufficiently severe. *On-demand therapy* implies that the patients experience at least mild GERD symptoms for a short period before they begin using tablets. This period could vary greatly due to different on-demand habits of the study patients. Indeed, 12.1% more patients in the on-demand group than the continuous group failed to control their symptoms. However, on-demand treatment was shown to be noninferior to continuous treatment.

To obtain data comparable to that in 2 studies of pantoprazole,[20,21] the perceived mean daily symptom load was assessed in both groups. We used this as

an additional efficacy end point because symptom load was considered the most appropriate model of the clinically relevant question of symptom control in long-term treatment of GERD. In the literature, some authors recommend unwillingness to continue as a measurement of the efficacy of on-demand treatment.[2–4] However, this parameter is only an indirect measure of the control of GERD symptoms and reflects one point in time in patients who discontinued treatment, thereby assessing only a subset of patients. Patients treated with pantoprazole on-demand had a significantly higher perceived mean daily symptom load compared with patients treated with pantoprazole continuously over 24 weeks. This finding is not surprising and was anticipated because in contrast to patients assigned to receive continuous therapy, patients in the on-demand group were instructed to use the study medication only when their symptoms required treatment. Again, it could be assumed that patients did not use tablets until they experienced a short period of at least mild symptoms, and self-medication habits can vary greatly from patient to patient.

The main outcome of this study was further supported by the rate of patients unwilling to continue the study, a variable often used in studies of other PPIs. The rate of premature discontinuation due to insufficient control of heartburn, acid regurgitation, and pain on swallowing was not significantly different in the on-demand group compared with that in the continuous group. This result suggests that patients felt sufficiently treated regardless of their treatment regimen, although the symptom load was significantly higher in the on-demand group. However, the symptom load in the on-demand group might have been higher compared with the continuous group because symptoms must develop for a patient to use the study medication. It is possible that many patients in the on-demand group continued treatment despite a higher symptom load because on-demand treatment might confer an increased sense of control. Results from a study comparing continuous esomeprazole 20 mg with on-demand esomeprazole 40 mg showed that both regimens provided similar rates of patient satisfaction (89.6% and 88.4%, respectively).[29] In the present study, the similarity of the rates of patients willing to continue treatment between the 2 groups might suggest that on-demand treatment is noninferior to continuous treatment with regard to patients' perceptions of treatment. In previous work, discontinuation rates were 14% with omeprazole 20 mg,[2] and 5% to 14% with esomeprazole 20 mg[3,4,7]; the rates of patients unwilling to continue on-demand therapy of 6-month duration were 11% with esomeprazole 40 mg,[4] 15% with lansoprazole 15 mg,[8] and 6% with rabeprazole 10 mg.[10]

The amount of medication used in the on-demand group was nearly half that in the continuous group; the difference was statistically significant. These findings verify that patients' dosing habits were based on as-needed decisions and that on-demand therapy can be clearly distinguished from continuous therapy. Our findings were also comparable to those from previous studies of on-demand treatment. In one study of 6 months of on-demand therapy, the mean numbers of tablets used per day were 0.43 with omeprazole 20 mg,[2] 0.33 with esomeprazole

20 mg,[4] and 0.40 with lansoprazole 15 mg.[8] Due to the reduced number of tablets received (less than half the amount with daily use), on-demand treatment has the potential to be more cost-effective compared with continuous treatment.[16]

CONCLUSIONS

In this study of pantoprazole 20 mg tablets in patients with mild GERD, patients receiving on-demand treatment benefited despite their higher symptom load. The similar rates of unwillingness to continue treatment between the 2 groups might suggest that patients were satisfied with the on-demand treatment strategy. On-demand treatment with pantoprazole 20 mg was found to be noninferior compared with continuous therapy with regard to symptom control. Both on-demand and continuous treatments were well tolerated.

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