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Which Dyspepsia Patients Will Benefit From Omeprazole Treatment?

Analysis of a Danish Multicenter Trial

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OBJECTIVE: The effect of omeprazole therapy in dyspepsia is unpredictable. The aim of this study was to identify patient characteristics and symptoms associated with the omeprazole response to improve selection of patients for empirical treatment with omeprazole.

METHODS: Data from a randomized controlled trial of 471 patients with ulcer-like or reflux-like dyspepsia treated with omeprazole 20 mg daily (243 patients) or placebo (228 patients) for 2 wk were studied using logistic regression analysis. The patients were randomly divided into a model sample (N = 236) for modeling the association between the omeprazole response and descriptive variables, and a test sample (N = 235) for testing the obtained model.

RESULTS: In the model sample a high body mass index, the use of antacids or H2-blockers within the last month, or pain at night time were independently associated with a good omeprazole response, whereas the presence of nausea was associated with a poor omeprazole response. Using these variables combined into a therapeutic index, the independent test sample patients could be classified into predicted good (N = 56), medium (N = 88), and poor omeprazole responders (N = 91). In these groups the observed therapeutic gain of omeprazole (omeprazole response minus placebo response) was 39.4%, 19.3%, and 4.6%, respectively ($p = 0.013$). For clinical use, an easy-to-use pocket chart to obtain the therapeutic index in a given patient has been devised.

CONCLUSIONS: In dyspepsia the identification of potential responders to omeprazole can be improved by considering certain patient characteristics and symptoms associated with the omeprazole response. Applying these data using a simple pocket chart may assist decision about empirical omeprazole therapy in patients with dyspepsia in general practice. (Am J Gastroenterol 2000;95:2777–2783. © 2000 by Am. Coll. of Gastroenterology)

INTRODUCTION

The annual incidence of dyspepsia in general practice in Denmark is 3.4% (1), and 5% of all consultations are because of dyspepsia (2). Because of this high prevalence of dyspepsia, endoscopy is not feasible as a diagnostic tool in the initial phase. A recent working party has suggested testing for *Helicobacter pylori* (Hp) infection followed by eradication therapy in Hp-positive patients (3). In Hp-negative and in patients still having dyspeptic symptoms after Hp eradication therapy, empirical therapy based on the presenting symptoms has been suggested (3).

In patients presenting with symptoms suggestive of acid-related dyspepsia, a proton pump inhibitor will often be given as the initial treatment. However, in such patients the effect of proton pump inhibitors may be disappointingly low—only up to 25% better than that of antacids (4, 5).

In patients consulting the general practitioner (GP) because of symptoms of predominantly reflux-like or ulcer-like dyspepsia, omeprazole for 2 wk led to relief of symptoms in only half of the patients, compared to a relief rate of one third in placebo-treated patients (6). Thus, the therapeutic gain of omeprazole in such patients is modest. The reason for this small effect of omeprazole is probably that patients diagnosed by their symptoms as reflux-like or ulcer-like dyspepsia represent a heterogeneous group, also comprising patients with other types of dyspepsia not responsive to treatment with proton pump inhibitors.

The aim of this study was 1) to identify symptoms and patient characteristics associated with a favorable response to omeprazole treatment, 2) to combine such variables for a therapeutic index of omeprazole responsiveness, and 3) to express the therapeutic information in a pocket chart to be used for easy identification of those patients with dyspepsia who may be expected to benefit from empirical treatment with proton pump inhibitors.

MATERIALS AND METHODS

Data from patients included in a randomized clinical trial (6) of omeprazole 20 mg daily for 2 wk *versus* placebo in patients with dyspepsia were used in the present study. The patients were interviewed by the general practitioner about the presence or absence of 18 different dyspeptic symptoms, which were used to classify the dyspepsia as dysmotility-like, ulcer-like, reflux-like, or uncharacteristic (7). The par-

ticular type of dyspepsia was defined as that for which the patient presented the largest number of positive symptoms.

Patients were included in the trial if they presented with reflux-like or ulcer-like dyspepsia, had no history of peptic ulcer disease or reflux esophagitis, were aged between 18 and 65 yr, and had had symptoms for >1 wk. Patients were not included if they presented with one or more alarm symptoms (weight loss, dysphagia, blood in stools, black stools, anemia, jaundice) or were users of nonsteroidal anti-inflammatory drugs (NSAID). No patient had endoscopy or laboratory investigations performed. The patients analyzed in this study comprise 471 (omeprazole 243, placebo 228) *per protocol*–treated patients with complete 2-wk follow-up. (Six patients from the clinical trial were not included in this study: two omeprazole-treated and four placebo-treated patients, in whom overall but not specific symptoms were recorded at the end of the treatment.) The variables analyzed are presented in Table 1.

To develop and validate a model for prediction of the response after 2 wk, the 471 patients were divided randomly into two samples: a model sample (236 patients) and a test sample (235 patients). The distribution of the variables did not show any imbalance between the placebo and the omeprazole groups, either in the model sample or in the test sample.

In the model sample, the association between the response and the descriptive variables including their possible dependence on (or "interaction" with) the therapy given (omeprazole or placebo) was studied using logistic regression analysis (8). The analysis resulted in a logistic regression model for prediction of the response after 2 wk. The model included both "prognostic" variables associated with the response independently of the therapy (similar associations in omeprazole and placebo groups), and "therapeutic" variables for which the association with the response differed significantly between the omeprazole and placebo groups. The details of the logistic regression model used in this study are presented in the Appendix.

Because the "therapeutic" variables hold information that characterizes omeprazole responders and non-responders, the "therapeutic" terms of the obtained model were combined to provide a therapeutic index that, when calculated for a given patient, directly indicates the predicted magnitude of the therapeutic gain of omeprazole treatment for that patient. The predictive value of the therapeutic index was tested in the 235 independent patients in the test sample. For each of these patients the therapeutic index was calculated, and the patients were then classified into three groups according to the value of their therapeutic index. Round cut-off values were defined allowing a reasonable number of patients in each group. In each of the three groups, the observed response in percentages was recorded. The therapeutic gain (the percentage of response in omeprazole-treated patients minus the percentage of response in placebo-treated patients) was calculated in the three groups. Significance testing was performed using Armitage's test for trend in proportions (8) and Fisher's exact probability test (8). To simplify use in new patients, a pocket chart for easy calculation of the therapeutic index in a given patient was developed, as described in the Appendix.

Table 1. Distribution of Analyzed Variables in the 471 Patients With Dyspepsia

Quantitative Variable	Mean	(Range)
Age (yr)	42	(18–65)
Body mass index (kg/m^2)	24.6	(17.1–45.0)
Patient's general well-being (mm on VAS)	51	(3–100)
Qualitative Variable	**Percent**	
Female	51.2	
Treatment		
Placebo	48.4	
Omeprazole	51.6	
Type of dyspepsia		
Ulcer-like	42.0	
Reflux-like	67.3	
Duration of present episode		
<1 wk	6.6	
1–4 wk	38.0	
>4 wk	55.4	
Epigastric pain	89.6	
Acid regurgitation	68.6	
Pain relieved by antacids	63.5	
Pain at night time	57.7	
Pain relieved by food	50.7	
Heartburn	46.3	
Pain after meals	38.2	
Nausea	32.5	
Pain relieved by vomiting	16.1	
Pain in the morning	17.4	
Morning vomiting	2.1	
Loose stools	16.1	
Bloating	33.8	
Pain relieved by stools or flatus	9.3	
Horizontal upper abdominal pain	14.9	
Constipation	9.6	
Incomplete rectal evacuation	4.2	
Other abdominal pain	2.8	
Ingestion of H2-blockers or antacids, latest month	39.3	
Smoking	49.6	
Alcohol drinking	56.3	
Stomach pain during the day, latest wk		
Mild	25.7	
Moderate	57.0	
Severe	8.5	
Heartburn, latest wk		
Mild	18.3	
Moderate	37.4	
Severe	11.3	
Response after 2 wk of treatment	43.5	

RESULTS

The prognostic and therapeutic influence of single variables in the model sample is summarized in Table 2. The results

Table 2. Therapeutic and Prognostic Influence of Single Variables as Obtained by Logistic Regression Analysis of the Data of 236 Patients With Dyspepsia (Model Sample*)

Variable	Influence of Variable on Therapeutic Gain of Omeprazole Treatment ("Therapeutic Influence")	Influence of Variable on Placebo Response ("Prognostic Influence")
High body mass index	↑ ↑	↓ ↓
Pain at night time	↑	↓ ↓
Antacids or H2-blocker in the latest month	↑	
Pain relieved by antacids	(↑)	
Heartburn during the last 7 days	(↑)	
High alcohol consumption	(↑)	
High age	(↑)	
Pain relieved by food		(↑)
Incomplete rectal evacuation		(↓)
Present episode long lasting		↓ ↓
Female gender	(↓)	
Pain in the morning	(↓)	(↑)
Pain after meals	(↓)	
Pain during the day last 7 days	↓	
Nausea	↓ ↓ ↓	↑ ↑

* Only variables showing some indication of therapeutic or prognostic influence ($p \leq 0.20$) are included.
(↑) or (↓): $p \leq 0.20$.
↑ or ↓: $p \leq 0.05$.
↑ ↑ or ↓ ↓: $p \leq 0.01$.
↑ ↑ ↑ or ↓ ↓ ↓: $p \leq 0.005$.
Upward arrow = higher therapeutic gain (therapeutic influence) or higher placebo response probability (prognostic influence).
Downward arrow = lower therapeutic gain (therapeutic influence) or lower placebo response probability (prognostic influence).

are based on logistic regression analysis including terms for the variable in question ("prognostic" effect), the treatment and interaction between the variable and the treatment ("therapeutic" effect). Only variables showing some indication of "prognostic" and/or "therapeutic" influence are included. The most influential variables were: nausea, duration of the present episode of dyspepsia, body mass index, pain at nighttime, pain during the day, and use of antacids or H2-blockers within the last month. The direction of the influence is indicated in Table 2. The final model obtained by multiple logistic regression analysis is presented in Table 3.

Based on the model a prognostic index for placebo treatment can be expressed as follows (see Appendix for technical details):

$Y_{placebo} = -0.21 - 1.16$ (for pain at night time) $- 0.12 \times$ (body mass index $- 25$) $+ 0.10$ (for antacids or H2-blockers ingested within the last month) $+ 1.19$ (for nausea) $+ 0.86$ (for pain relieved by food) -2.99 (for incomplete rectal evacuation).

In a similar way a prognostic index for omeprazole can be expressed as follows:

$Y_{omeprazole} = -0.21 - 0.67 + (-1.16 + 1.69)$ (for pain at nighttime) $+ (-0.12 + 0.16) \times$ (body mass index $- 25$) $+$ $(0.10 + 1.30)$ (for antacids or H2-blockers ingested within the last month) $+ (1.19 - 1.83)$ (for nausea) $+ 0.86$ (for pain relieved by food) $- 2.99$ (for incomplete rectal evacuation).

Table 3. Final Multiple Logistic Regression Model for Prediction of Therapy-Dependent Response in Dyspepsia

Variable	Scoring	Coefficient	SE	*p* Value
Prognostic variable				
Pain at nighttime	Present: 1; Absent: 0	−1.16	0.43	0.008
Body mass index	$kg/m^2 - 25$	−0.12	0.052	0.03
Antacids or H2-blockers ingested within the last month	Yes: 1; No: 0	0.10	0.47	0.83
Nausea	Present: 1; Absent: 0	1.19	0.47	0.01
Pain relieved by food	Present: 1; Absent: 0	0.86	0.30	0.005
Incomplete rectal evacuation	Present: 1; Absent: 0	−2.99	0.88	0.0008
Therapeutic variable				
Treatment	Omeprazole: 1; Placebo: 0	−0.67	0.55	0.23
Pain at nighttime × treatment		1.69	0.61	0.006
Body mass index × treatment		0.16	0.069	0.02
Antacids or H2-blockers ingested within the last month × treatment		1.30	0.65	0.05
Nausea × treatment		−1.83	0.64	0.005
Constant		−0.21	0.42	0.61

Thus, for a placebo treated patient, the model predicts that the likelihood of a positive response (no symptoms) after 2 wk would be relatively higher in the presence of nausea and pain relief by food (both having positive coefficients), and relatively lower in the presence of pain at nighttime, a high body mass index, and incomplete rectal evacuation (all having negative coefficients). The predicted likelihood of a positive response after 2 wk of omeprazole treatment is significantly influenced by the therapeutic coefficients.

The therapeutic index (TI) is a measure of the predicted therapeutic effect and is the difference between $Y_{omeprazole}$ and $Y_{placebo}$. (see Appendix for technical details):

TI = −0.67 + 1.69 (for pain at nighttime) + 0.16 × (body mass index − 25) + 1.30 (for antacids or H2-blockers ingested within the last month) − 1.83 (for nausea).

Thus the model predicts that the therapeutic gain of omeprazole treatment will be relatively increased by the presence of pain at night time, a high body mass index, and ingestion of antacids or H2-blockers within the last month, and will be relatively decreased by the presence of nausea (the therapeutic variables contributing to the therapeutic index).

The results of the validation of the model are shown in Figures 1 and 2. Figure 1 shows the observed response in percentages in the test sample patients according to the value of the calculated therapeutic index, classified into three groups: TI <0, 0–1.5, and >1.5. The response after placebo therapy is rather constant around 30% and independent of the therapeutic index, whereas the response after omeprazole therapy increases highly significantly with increasing therapeutic index.

Figure 2 shows the observed therapeutic gain (omeprazole response minus placebo response) in percent according to the therapeutic index. There is a highly significant increase in the therapeutic gain with increasing therapeutic index. In the group with TI <0 (39%) the therapeutic gain is not significantly different from zero. By contrast, for the group with TI >1.5 (24%), the therapeutic gain is highly significantly positive (39.4%) ($p = 0.005$). In the group with TI between 0 and 1.5 (37%), the therapeutic gain is intermediate (19.3%) ($p = 0.05$). Thus, TI holds highly significant information about the omeprazole effect in independent patients.

For clinical use a pocket chart (Table 4) has been developed, by which the therapeutic points (*i.e.*, the therapeutic index × 10) can easily be calculated for any patient based on the following information: pain at nighttime, body weight and height, ingestion of antacids or H2-blockers within the last month, and nausea. The pocket chart has been developed from the therapeutic coefficients as described in the Appendix.

Some examples of calculating the therapeutic points in individual patients using the pocket chart are as follows: 1) If a patient presents with pain at nighttime, a body weight of 100 kg, a body height of 175 cm, ingestion of antacids or H2-blockers within the last month, and no nausea, the therapeutic points, using Table 4, would be 17 + 6 + 13 + 0 = 36, suggesting a highly beneficial effect of omeprazole. 2)

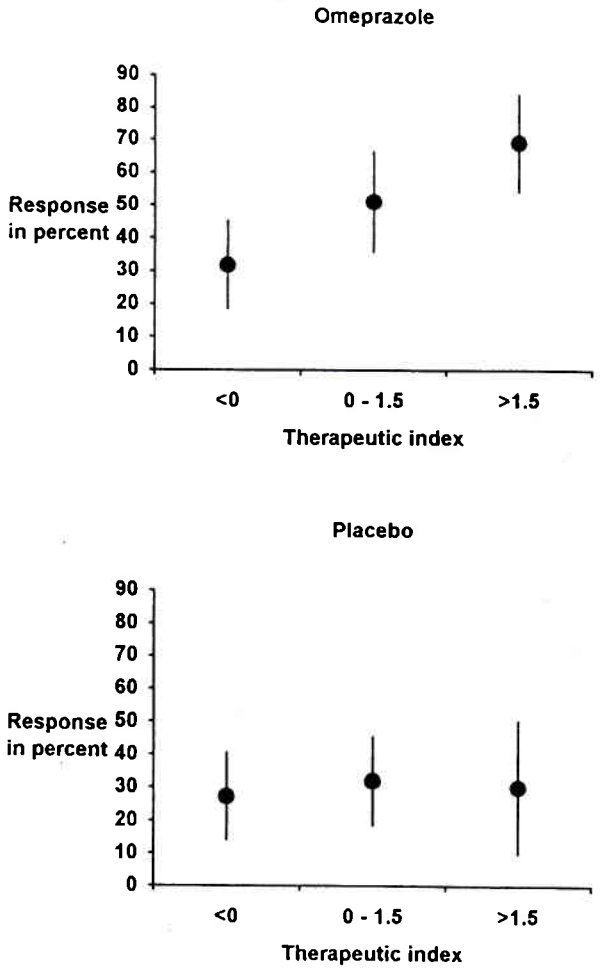

Figure 1. Observed response in percent (with 95% confidence limits) as a function of the therapeutic index in 235 independent test sample patients with dyspepsia. For omeprazole treatment (upper panel) the responses were: TI ≤ 0: 15/47 = 31.9%; 0 < TI ≤ 1.5: 21/41 = 51.2%; TI > 1.5: 25/36 = 69.4%; test for increasing trend: $p = 0.0003$. For placebo treatment (lower panel) the responses were: TI ≤ 0: 12/44 = 27.3%; 0 < TI ≤ 1.5: 15/47 = 31.9%; TI > 1.5: 6/20 = 30.0%; test for increasing trend: $p = 0.36$. Test for difference between trends for omeprazole and placebo treatment: $p = 0.013$.

For a patient presenting with pain at nighttime, a body weight of 70 kg, a body height of 165 cm, no ingestion of antacids or H2-blockers within the last month and no nausea, the therapeutic points, using Table 4, would be 17 − 6 + 0 + 0 = 11, suggesting a some beneficial effect of omeprazole. 3) If a patient presents with no pain at nighttime, a body weight of 61 kg, a body height of 179 cm, having ingested antacids within the last month and having nausea, the therapeutic points would be 0 − 17 + 13 − 18 = −21, suggesting no beneficial effect of omeprazole.

DISCUSSION

The proton pump inhibitor omeprazole has been shown to be highly effective in the treatment of peptic ulcer disease and

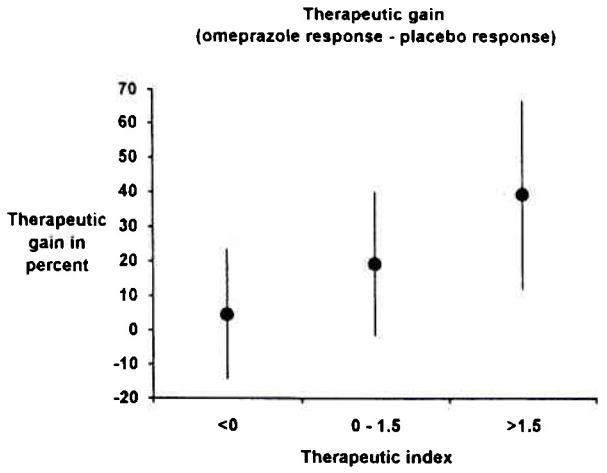

Figure 2. The observed therapeutic gain (% response with omeprazole minus % response with placebo) with 95% confidence limits as a function of the therapeutic index in 235 independent test sample patients with dyspepsia. The response in the 3 groups was: TI ≤ 0: 4.6%; 0 < TI ≤ 1.5: 19.3%; TI > 1.5: 39.4%, test for increasing trend: $p = 0.013$ (see legend to Fig. 1).

reflux esophagitis (9). By contrast, the effect in nonulcer dyspepsia patients has been shown to be very modest (10). In uninvestigated patients with dyspepsia presenting with predominantly acid-related symptoms, the benefit of omeprazole compared to antacids has been shown to be modest (4, 5). This study deals with uninvestigated patients with dyspepsia, presenting in general practice with acid-related symptoms, in whom a randomized clinical trial comparing omeprazole and placebo has been performed (6). The study endpoint was a total relief of symptoms after 2 wk. Several studies have been performed in patients with nonulcer dyspepsia to evaluate which symptoms respond to acid-reducing treatment. As reviewed by a working party (3), the studies have demonstrated an occasional effect of H2-blockers in reducing the pain severity or the number of pain episodes. The effect on other symptoms has not been consistent. In a single subject trial model involving patients with nonulcer dyspepsia, it was shown that women responded better to treatment with cimetidine than did men (11). In a recent study a high body mass index has been shown to be related to a high level of acid exposure in the esophagus (12). According to several guidelines (3, 13, 14) patients with dyspepsia without alarm symptoms should be empirically treated, and only in patients in whom the symptoms do not improve or rapidly recur should endoscopy be

Table 4. Pocket Chart for Calculation of Therapeutic Points for Omeprazole Effect in a Given Patient With Predominantly Reflux-Like or Ulcer-Like Dyspepsia

Variable													Points
Pain at Nighttime								Present					17
								Absent					0
Influence of body mass index (BMI) (Select the number corresponding to the body weight and height combination of the patient)													
	Height (cm)												
Weight (kg)	150	155	160	165	170	175	180	185	190	195	200	205	210
40	−18	−20	−22	−23	−25	−26	−27	−28	−29	−30	−31	−31	−32
45	−15	−17	−19	−20	−22	−23	−24	−26	−27	−28	−29	−30	−30
50	−11	−13	−15	−17	−19	−21	−22	−23	−25	−26	−27	−28	−29
55	−8	−10	−12	−14	−16	−18	−20	−21	−22	−24	−25	−26	−27
60	−4	−7	−9	−11	−13	−15	−17	−19	−20	−21	−23	−24	−25
65	0	−3	−6	−8	−11	−13	−15	−16	−18	−19	−21	−22	−23
70	3	0	−3	−6	−8	−10	−12	−14	−16	−17	−19	−20	−21
75	7	3	0	−3	−5	−8	−10	−12	−13	−15	−17	−18	−19
80	10	7	3	0	−2	−5	−7	−9	−11	−13	−15	−16	−18
85	14	10	6	3	0	−2	−5	−7	−9	−11	−13	−14	−16
90	17	13	10	6	3	0	−2	−5	−7	−9	−11	−12	−14
95	21	17	13	9	6	3	0	−2	−5	−7	−9	−11	−12
100	24	20	16	12	9	6	3	0	−2	−5	−7	−9	−10
105	28	23	19	15	11	8	5	2	0	−3	−5	−7	−9
110	32	27	22	18	14	11	8	5	2	0	−3	−5	−7
115	35	30	25	21	17	13	10	7	4	2	−1	−3	−5
120	39	33	28	24	20	16	13	9	6	4	1	−1	−3
Antacids or H2-blockers ingested within the last month									Yes				13
									No	0			
Nausea									Present				−18
									Absent				0
Total of therapeutic points =													

Circle the relevant number for each of the four variables and add the points to obtain the total therapeutic points.
Interpretation: >15 points: good response to omeprazole; 1–15 points: fair response to omeprazole; ≤0 points: no response to omeprazole.

performed. Consequently, empirical treatment would be cost-saving if the potential responders could be identified.

In this study we have developed a model for identification of responders to omeprazole treatment. This model has been successfully tested in a comparable group of independent patients. In the final model, four variables were independently related to the magnitude of the therapeutic gain of omeprazole treatment: pain at nighttime, a high body mass index (BMI), the use of antacids or H2-blockers within the last month, (all associated with an increased therapeutic gain of omeprazole treatment) and the presence of nausea (associated with a decreased therapeutic gain of omeprazole treatment). These associations are biologically reasonable: symptoms of reflux are known to be correlated to a high BMI; pain at night time is a classic symptom in ulcer patients and a recent use of antacids or H2-blockers indicates that the dyspepsia possibly has an acid-related component. The presence of nausea reduces the beneficial effect of omeprazole. In patients with nausea a favorable response to placebo is more likely, indicating that nausea is not an acid-related symptom but, rather, a symptom related to a dysmotility type of dyspepsia, with a reasonably good spontaneous short-term prognosis that may inadvertently be influenced by omeprazole as it may cause nausea as a side effect.

The final model has been tested in a sample of independent patients. This testing showed that the model could, to some degree, identify the omeprazole responders. Testing of the therapeutic aspects of the model could be performed only by comparing the response in subgroups defined by the therapeutic index, not on an individual basis, because each individual received only one of the two treatments. The testing in independent patients showed that the model could identify the patient group having a particularly high therapeutic gain of omeprazole treatment.

The model predicts no effect (or even a harmful effect) of omeprazole when the therapeutic index is negative. However, as shown in Figures 1 and 2, a negative effect of omeprazole therapy in the patients with negative therapeutic index was not found in the test sample patients. Thus, we have found no direct evidence of any harmful effect of omeprazole therapy, although this is a theoretical possibility because of the potential side effects of the drug (headache, nausea, diarrhea, constipation, flatulence), that rarely occur.

This study was based on patients presenting with reflux-like or ulcer-like dyspepsia (6). These subgroups of dyspepsia were recognized at the time of the trial (7). Later on, other classifications were applied (15, 16), and the use of subgrouping was discouraged (17). Recently, however, subgroups defined by the predominant symptom have been reintroduced (3). Treatment of uninvestigated patients with dyspepsia will necessarily have to be based on symptoms. Patients in this study had predominantly acid-related symptoms and, therefore, the results should be applied on such patients only: the therapeutic index should be used to identify potential omeprazole responders in patients with acid-related (ulcer-like or reflux-like) dyspepsia.

A placebo-controlled trial of omeprazole in a more broadly defined population of dyspepsia patients having just one or a few acid-related symptoms without excluding patients with other dyspepsia symptoms could lead to a more comprehensive model for prediction of the response to omeprazole, and such results could be applied to dyspepsia patients in general.

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APPENDIX

The logistic regression analysis studied the association between the response and the descriptive variables, the treatment (omeprazole or placebo), and variable–treatment interactions.

The particular model used can be illustrated by considering only one descriptive variable, as follows:

$$Y = b_0 + b_{tr} \times z_{tr} + b_{var} \times z_{var} + b_{var \times tr} \times z_{var} \times z_{tr}$$

where Y can be considered a therapy-dependent prognostic index for prediction of response being dependent on the therapy and the variables (characteristics) of the patient. Technically Y is the logit, *i.e.*, $Y = \log_e(P/(1 - P))$, P being the probability of the response (*i.e.*, $P = e^Y/(1 + e^Y)$), b_0 is a constant, z_{tr} is the treatment variable score (placebo: 0 or omeprazole: 1), b_{tr} is the regression coefficient for the treatment, z_{var} is the scoring of the variable in question, b_{var} is the regression coefficient for the variable. This regression coefficient expresses the so-called "prognostic" association of the variable with the response obtained with placebo. $z_{var} \times z_{tr}$ is the interaction variable score (product of the scores for the therapy and the variable in question), $b_{tr \times var}$ is the regression coefficient for the interaction variable. Because this regression coefficient expresses the influence of the variable on the omeprazole effect or, more precisely, the *therapeutic gain* (the response with omeprazole minus the response with placebo), it is called the "therapeutic" regression coefficient. If the coefficient is significant, it means that the omeprazole effect varies with—or depends on—the descriptive variable. A positive therapeutic regression coefficient means an association of a high interaction score (*i.e.*, omeprazole treatment and a high score of the variable) with a larger therapeutic gain.

The defined logistic regression model allows estimation

of Y (which can be considered a *prognostic index* for obtaining the response) in a given patient for each of the two treatment alternatives. For one variable having both prognostic and therapeutic influence, this can be stated as follows (keeping the scores for the treatments in mind):

$$Y_{omeprazole} = b_0 + b_{tr} \times 1 + b_{var} \times z_{var} + b_{tr \times var} \times z_{var} \times 1 = b_0 + b_{tr} + b_{var} \times z_{var} + b_{tr \times var} \times z_{var}$$

$$Y_{placebo} = b_0 + b_{tr} \times 0 + b_{var} \times z_{var} + b_{tr \times var} \times z_{var} \times 0 = b_0 + b_{var} \times z_{var}$$

A simple expression for the therapeutic effect, or therapeutic gain (still presented for one variable), is obtained as the *therapeutic index* (TI) (see Ref. 18), defined as the difference between $Y_{omeprazole}$ and $Y_{placebo}$:

$$TI = b_0 + b_{tr} + b_{var} \times z_{var} + b_{tr \times var} \times z_{var} - (b_0 + b_{var} \times z_{var}) = b_{tr} + b_{tr \times var} \times z_{var}.$$

A positive therapeutic index indicates a therapeutic gain of omeprazole treatment. All the expressions can be expanded to include more than one descriptive variable.

Individual variables showing signs of prognostic (therapy-independent) and/or therapeutic (therapy-dependent) association with the response ($p \leq 0.20$) were analyzed together in a multiple logistic regression model including both prognostic and therapeutic terms as defined above, but expanded to include more descriptive variables. Variables were selected using stepwise backward elimination ($p < 0.05$). However, for each significant therapeutic variable, the corresponding prognostic term was maintained in the model (even if statistically insignificant) to provide a clear definition of the therapeutic influence of the variable in question. The final model also included the therapy variable and the significant prognostic variables. To fulfill the model assumptions and to avoid collinearity, a modified scoring had to be used for the body mass index (BMI) (*i.e.*, subtraction of 25 being the mean value).

A pocket chart (presented in Table 4) was derived from the final logistic regression model (Table 3), by transforming the regression terms to integer points to be added together to the total therapeutic points. For the variables (pain at nighttime, antacids or H2-blockers ingested within the last month, and nausea), the points were obtained as the regression term times 10 and then rounded to the nearest integer. For the BMI, the pocket chart uses the body weight and height directly, and to reduce further the number of points to be added, the therapeutic term (−0.67) have been subtracted at the same time. Thus, each BMI point in the pocket chart have been obtained as follows: ({[weight (kg)/height^2 (m^2)] − 25} × 0.16 − 0.67) × 10 and then rounded to the nearest integer. Thus, the total points obtained by using the pocket chart corresponds to the therapeutic index times 10.

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