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High-Dose Esomeprazole for Treatment of Symptomatic Refractory Gastroesophageal Reflux Disease – A Prospective pH-Metry/Impedance-Controlled Study

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Key Words
Reflux · Gastroesophageal reflux disease · Proton pump inhibitors · Baclofen · Impedance monitoring · Esomeprazole

Abstract
Background/Aims: Combined pH-metry/multichannel intraluminal impedance (pH/MII) measurement enables to measure gastroesophageal reflux despite ongoing proton pump inhibitor therapy. The aim of our study was to evaluate the influence of an escalating medical anti-reflux therapy with 40 mg esomeprazole, 80 mg esomeprazole and 80 mg esomeprazole plus baclofen for the treatment of refractory pathological reflux as determined by pH/MII. ***Methods:*** Symptomatic patients under 40 mg esomeprazole were screened by pH/MII. Patients with normal values in pH/MII were excluded; all others received 2 × 40 mg esomeprazole for another 4 weeks. Thereafter, the treatment effect was controlled by pH/MII. In the case of persistent pathological reflux, therapy was further escalated by adding baclofen and controlled after 3 months by pH/MII. ***Results:*** 45/138 (32.6%) patients showed pathological pH/MII despite ongoing therapy with 40 mg esomeprazole. In these, a significant reduction in liquid/mixed reflux events was observed after administering 2 × 40 mg (mean: 118.3 vs. mean: 66.6; $p < 0.001$), and pH/MII turned to normal in 32/45 (71.1%). Baclofen was additionally administered to 7/13 patients, which did not lead to a remarkable reduction in reflux events. ***Conclusion:*** In patients with abnormal pH/MII and persistent symptoms under 40 mg esomeprazole, we observed a significant reduction in liquid/mixed reflux events after increasing proton pump inhibitor dose up to 80 mg esomeprazole. Further escalation of therapy with baclofen has shown inconclusive results.

Introduction

Gastroesophageal reflux disease (GERD) is a frequent disorder with an increasing incidence and prevalence, involving a considerable economic burden [1]. About 20% of the Western population report GERD symptoms at least once a week [2]. Apart from typical symptoms including heartburn and acid regurgitation, atypical or extraesophageal symptoms like chronic cough, globus sensations in the throat, burning feeling on the tongue and hoarseness can be associated with gastroesophageal reflux [3, 4].

Proton pump inhibitors (PPIs) are the most effective medical therapeutic approach. They lead to a remarkable

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symptom relief, are well tolerated, provide the best healing rates for acute esophagitis and maintain remission better than H_2-blockers [5, 6]. However, it has been estimated that about 30% of GERD patients remain symptomatic on standard dose of PPIs [7]. Treatment failure of GERD may be caused by fast metabolization of the substance, visceral hyperalgesia, delayed gastric emptying, or psychological diseases. In addition, it has been mentioned that, despite effective acid suppression, nonacidic reflux might persist causing symptoms [8]. Combined pH-metry/multichannel intraluminal impedance (pH/MII) monitoring enables to measure the quantity and quality of acidic and nonacidic reflux episodes into the esophagus likewise [9–12]. However, for patients with objectively documented GERD during ongoing PPI therapy, there are no clear recommendations how to proceed further. The influence of escalating PPI dosage is a subject of controversy. We have previously been able to show that escalating PPI therapy can lead to a considerable improvement of symptoms in more than 90% of patients with pathological pH/MII despite treatment with PPIs in standard dosage [13]. However, recent studies showed that the total number of reflux episodes is not affected by PPI therapy [14]. Baclofen, a GABA receptor agonist, has been identified as a potent inhibitor of transient lower esophageal sphincter relaxations and has therefore the potential to be used as an add-on therapy for treatment of PPI failures [15]. However, apart from symptom evaluation, there is no prospective study in which such a treatment success is objectively assessed by pH/MII in GERD patients who objectively failed on PPI treatment. We therefore attempted to further evaluate a step-up therapy regimen consisting of a single-dose, followed by a high-dose treatment with esomeprazole and finally an additional therapy with baclofen if re-treatment failure was observed. The main aim was to determine treatment success solely by counting ongoing reflux episodes (mixed and liquid) by means of pH/MII monitoring.

Patients and Methods

As a research project that prospectively assigned human subjects to study the cause-effect relationship between a medical intervention and a health outcome, the study was preliminarily announced in ClinicalTrials.gov (Identifier: NCT00461604) and was approved by the Ethics Committee of the Technical University of Munich.

Patients

Patients were eligible for inclusion if they did not have a history of previous gastric or esophageal surgery, severe esophageal motility disorders or discontinuous PPI (40 mg esomeprazole) intake within the last 4 weeks prior to initial (screening) pH/MII measurement. All patients complained of persistent typical reflux-associated symptoms like heartburn or regurgitation and/or atypical symptoms such as globus sensations, chronic cough, a burning feeling on the tongue, hoarseness or chest pain and were aged between 18 and 85 years. They did not suffer from any condition that contraindicated safe medication with baclofen such as seizure disorder, renal insufficiency, and current therapy with antidepressants, anticoagulative or anticholinergic agents. All patients completed a symptom-based standardized questionnaire that had already been used in a previous study detailing all abovementioned reflux symptoms [13]. The frequency of the most bothersome symptom was noted on a 6-point scale and its intensity on a 10-point scale. Significant symptom relief was defined as a reduction of a minimum of 2 points in the questionnaire.

pH/MII Monitoring and Data Recording

Combined pH/MII monitoring was performed using an ambulatory, multichannel intraluminal impedance system, consisting of a portable data logger and a combined pH-impedance catheter (Tecnomatix ZAN S61C01E; Sandhill Scientific, Inc., Highlands Ranch, Colo., USA). Six impedance electrodes as well as a distal pH-antimon probe were placed at defined spots (3.0, 5.0, 7.0, 9.0, 15.0 and 17.0 cm; pH probe 5.0 cm). The catheter was placed with the pH-antimon probe located 5 cm above the manometrically predefined lower esophagus sphincter. Data were recorded for at least 22 h. Stored data were then uploaded on a personal computer and analyzed using a commercially available software system (BioView, Sandhill Scientific, Denver, Colo., USA). Reflux events detected by impedance changes were defined on the basis of a previous study and MII was considered pathological when more than 73 fluid and/or mixed reflux episodes occurred in the esophagus during 22–24 h [16]. pH monitoring of the esophagus was considered pathological when the percentage of time the pH was below 4 was more than 4% [17]. Reflux episodes were defined as acidic or nonacidic if a retrograde bolus movement was detected by impedance and pH was below or above 4, respectively. Furthermore, the content of the reflux episode was characterized according to its composition (gas, liquid or mixed). The patients were asked to indicate the 3 most bothersome symptoms (typical and/or atypical reflux symptoms).

Study Design

Patients with reflux-associated symptoms and pathological pH/MII results despite 40 mg esomeprazole (30 min prior breakfast) received an escalated medical therapy by doubling the dosage for 4 weeks (40 mg esomeprazole b.i.d.). In the case of normalized pH/MII, patients did not receive a further therapy modification. Patients with persistent pathological pH/MII results were additionally treated with baclofen for another 3 months. Initial baclofen dosage was 15 mg (3 × 5 mg) and aimed to be increased up to 60 mg/day (weekly escalation of 15 mg) for a total of 3 months. Combined pH/MII and clinical follow-up by means of a standardized questionnaire were performed at 3 time points (screening with ongoing therapy with 40 mg esomeprazole, control under 2 × 40 mg esomeprazole and under 2 × 40 mg esomeprazole with 60 mg baclofen).

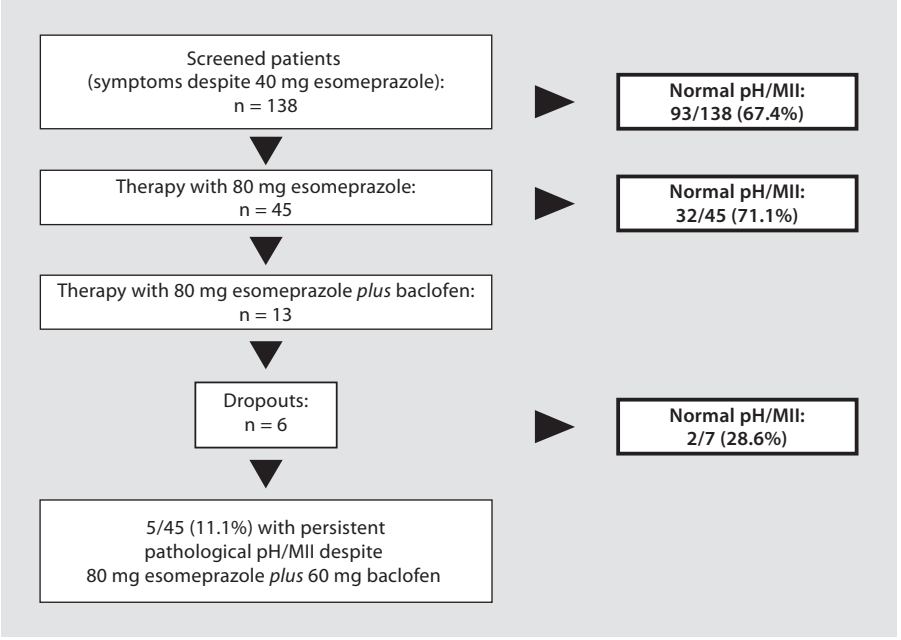

Fig. 1. Study course presented as a flowchart.

Statistics

Simon's two-stage optimal design was chosen for calculation of number of patients needed for inclusion. The hypothesis was based on an estimated response rate of 60% after doubling the esomeprazole dosage and a further response of 20% after adding baclofen. A minimum number of 43 patients were therefore requested for inclusion.

Data are shown in a descriptive manner. For all calculations, SPSS for Windows 14.0 software package (SPSS, Chicago, Ill., USA) was used. The t test was applied where appropriate, and a p value below 0.05 was considered statistically significant.

Results

The results of the study course after escalating therapy on pH/MII monitoring and the subdivided results of pH/MII monitoring are summarized in figures 1 and 2.

Screening Results of pH/MII Monitoring

A total of 138 patients meeting the inclusion criteria were screened. Examinations were well tolerated in all subjects, and we did not experience technical failures. 93/138 patients (67.4%) had normal values on combined pH/MII (<73 liquid/mixed reflux episodes and/or relative reflux time derived from pH-metry <4%) and were therefore excluded from further investigation. Patients' characteristics and their most bothersome symptoms are summarized in table 1.

Table 1. Characteristics and symptoms of screened patients

	Male	Female	Total
Patients	71	67	138
Age, years			
Median	55	62	60
Range	19–78	25–85	19–85
Body mass index			
Median	25	24	24.5
Range	17–31.5	16.5–36	16.5–36
Symptoms			
Heartburn	33	25	58
Regurgitation	9	5	14
Globus	10	14	24
Chronic cough	8	14	22
Burning tongue	8	6	14
Hoarseness	2	3	5
Chest pain	1	0	1

Results of pH/MII Monitoring under Treatment with 2 × 40 mg Esomeprazole

In accordance with the study protocol, esomeprazole was doubled to 40 mg b.i.d. in 45 patients. All of them received pH/MII monitoring 4 weeks after escalated therapy. 32/45 patients (71.1%) had normal values on combined pH/MII at this time point. The results of combined pH/MII measurement comparing patients under 40 and 80 mg esomeprazole within the follow-up are

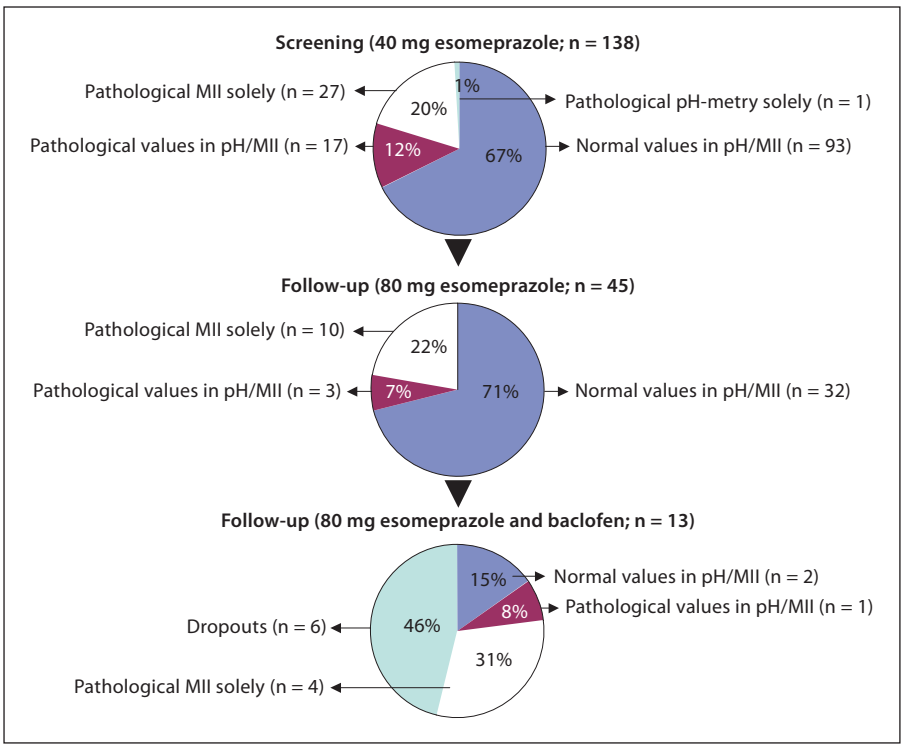

Fig. 2. Subdivided results of pH/MII monitoring within the study course presented as a flowchart.

Table 2. Results (including mean values ± SD of mean, t test) of combined pH/MII measurement comparing patients before and after doubling esomeprazole dose (n = 45)

	Esomeprazole		t test
	40 mg	80 mg	
Mixed/liquid reflux events	118.3 ± 44.8	66.6 ± 35.6	<0.0001
Relative acid reflux time, %	4.3 ± 4.8	0.9 ± 17	<0.0001
Acid reflux events	47.7 ± 42.1	15 ± 17.4	<0.0001
Nonacid events	101.9 ± 57	81.7 ± 41.8	0.041
Liquid reflux events	71.8 ± 40.5	37.5 ± 29.5	<0.0001
Mixed reflux events	46.5 ± 21.1	29 ± 16.8	<0.0001

summarized in table 2. 20% (27/138) of the measured patients under 40 mg esomeprazole had pathological values as determined by impedance (fig. 2). The reflux events generally decreased in patients with pathological liquid/mixed reflux episodes as defined by pH/MII after PPI dose was doubled up to 80 mg esomeprazole/day. Here, the mean number was 115 before versus 64.3 after the administration of doubled dose of esomeprazole ($p < 0.0001$).

With respect to symptom assessment as derived from the questionnaire, 38/45 (84.4%) perceived a significant relief according to both symptom intensity and frequency. Moreover, 24/45 (53.2%) were free of symptoms after 4-week treatment with double dose of esomeprazole.

pH/MII Monitoring Results under 2 × 40 mg Esomeprazole and Baclofen

Pathological findings on pH/MII monitoring despite ongoing PPI therapy with 2 × 40 mg esomeprazole were identified in 13/45 (28.9%) patients. According to the study protocol, additional baclofen therapy was intended in these patients. However, 3 from those patients refused baclofen therapy due to loss of symptoms under 80 mg esomeprazole, one decided to undergo surgery (fundoplication) and was excluded, and 2 patients had to discontinue additive baclofen because of adverse reaction of the GABA agonist (drowsiness) and were therefore excluded. The comparison of the combined pH/MII measurement of the 7 patients who completed the study according to the protocol is summarized in table 3.

Pathological findings on pH/MII monitoring despite ongoing PPI therapy with 2 × 40 mg esomeprazole and 60 mg baclofen were identified in 5/7 (71.4%) patients. With respect to symptom assessment, no patient experienced a significant resolution of symptoms after additional treatment with baclofen.

Table 3. Results (mean values ± SD of mean) of combined pH/MII measurement comparing patients before and after doubling esomeprazole dose, and before and after adding baclofen (n = 7)

	Esomeprazole		
	40 mg	80 mg	80 mg + baclofen
Mixed/liquid reflux events	112.6 ± 28.3	115.4 ± 34.5	92.4 ± 43.5
Relative acid reflux time, %	3.7 ± 2.5	2.5 ± 2.7	2.2 ± 3.8
Acid reflux events	44 ± 22.2	23.9 ± 26.3	21.3 ± 25.8
Nonacid events	100 ± 40.4	121.1 ± 42.5	100.3 ± 31.5
Liquid reflux events	81 ± 27.1	78.6 ± 38.5	59.9 ± 45.6
Mixed reflux events	31.6 ± 14.4	36.9 ± 22.8	32.6 ± 10.1

Except for the total numbers of acidic reflux events before and after doubling esomeprazole, no significant p values were observed. No significant values were observed before and after adding baclofen.

Discussion

The treatment of refractory GERD with objectively determined pathological reflux under ongoing acid-suppressive therapy is discussed controversially. In addition, PPIs in treating nonacidic or weakly acidic reflux have been claimed ineffective [18]. The crucial information given by our prospective study is that escalating esomeprazole up to the double standard dosage (2 × 40 mg) leads to a significant reduction in pathological acidic and nonacidic reflux episodes. In other words, in our study, more than 70% of patients with pathological findings on pH/MII monitoring and persistent reflux-associated symptoms despite 40 mg esomeprazole had their values return to normal, as determined by counting reflux episodes with pH/MII, and experienced a significant relief of their symptoms after doubling the PPI dosage. The symptomatic benefit and the decrease in the number of reflux events might be related to further inhibition of acid perhaps leading to a decreased gastric volume and gastric distension [19, 20] which might result in fewer transient lower esophageal sphincter relaxations (TLESRs). In contrast, persistence of acidic reflux episodes despite ongoing acid suppression might be a consequence of rapid metabolization of PPI in few patients [7].

Generally, it is recommended that patients not responding to PPI therapy should modify the medication to a second-generation PPI [21]. To overcome this factor, we solely used esomeprazole already in the screening and in the further course of our study, as esomeprazole has been shown to be highly effective even in standard dosage [22]. The screened population of symptomatic patients showed a treatment failure in 32% on standard-dose PPI (40 mg) which was objectified by pH/MII. Hence, in approximately 2/3 of the cases, the symptoms despite ongoing PPI therapy could not be sufficiently explained on the basis of the counted reflux episodes.

In daily routine, the Symptom Index (SI) is supposed to be a useful parameter to identify GERD patients. However, the SI was not taken into our calculation since its value in evaluating treatment effect is not proven. Even the definition of the SI is discussed controversially [23, 24]. One might argue that the underlying pathomechanism of persistent reflux-related symptoms despite ongoing PPI can be determined by SI as well, and we therefore underdiagnosed refractory GERD. But as defined by our study design and inclusion criteria, we only focused on patients with pathologically accumulated reflux events in pH/MII in order to have clear measurable parameters.

Before pH/MII was integrated into the diagnostic workup for identification of reflux patients, flawed diagnostic tools mostly resulted in the overdiagnosis of GERD. In addition, the presence of various atypical GERD symptoms is increasingly questioned to have a reflux-related origin, whenever concomitant typical reflux-symptoms are absent [25, 26]. Interestingly, in the cohort of 91 screened and excluded patients with potentially nonreflux-related complaints, persistent symptoms were typical and atypical likewise. In our trial, we therefore focused on patients with an objectified pathological pH/MII despite ongoing therapy with PPI in standard dosage and to a lesser extent on the character of perceived symptoms. However, the most bothersome symptom remained similar in all patients under escalating medical therapy.

One might argue that we may have underdiagnosed refractory GERD as we considered the normal range of pH/MII of healthy subjects 'off-PPI' as reference for the normal range of pH/MII in GERD 'on-PPI'. However, presently there are no reliable data or normal values for patients under ongoing therapy with standard-dosage PPI. Hence, we chose the well-established cut-off level of 73 liquid/mixed reflux episodes. Regarding the follow-up of pH/MII and the clinical outcome of proven refractory GERD patients (i.e., those meeting our inclusion criteria) after doubling standard-dosage, we have to point out that those patients indeed suffered from refractory GERD on single PPI dosage.

One third of the patients treated with 80 mg esomeprazole did not show a normalized pH/MII and most of

them perceived persistent reflux-associated symptoms. This rather high rate of 'nonresponders' may be a consequence of our selected patient population, as we represent a high volume center in which mostly GERD patients are presenting after previous failure of other treatment options (other PPI or additive adjustment of lifestyle factors). Treatment of these patients is not well established. Theoretically, nonacidic and acidic reflux should be reduced by intensifying esophageal and gastric motility, i.e., by applying prokinetic agents. Former trials proved an effective therapy using prokinetic drugs. However, they have focused only on clinical symptoms and on solely acidic reflux [27–29]. A causative medical approach for them was initiated by the use of $GABA_1$ agonists. GABA is a major inhibitory transmitter in the central nervous system. Its prototype baclofen is considered as one of the most potent inhibitors of TLESRs [30, 31]. The medical therapeutic concept of administering the drugs at a dose of 5 mg 3 times daily and increasing the dose stepwise to 20 mg 3 times daily showed a significant reduction in TLESRs and subsequently decreased duodenogastroesophageal reflux with an improvement of reflux-associated symptoms [15]. Consecutive studies supported the significant effect of baclofen in the medical antireflux therapy [32, 33]. However, according to our results, baclofen had a rather limited beneficial effect on patients' symptoms, since none of them perceived a significant regression of symptoms. As only 7/13 patients completed the study according to the study protocol within our escalating medical concept, it is noticeable that only 2 patients had a normalization of objectively measured reflux episodes, though the results of pH/MII showed a slight positive treatment effect of baclofen regarding the total fluid and/or mixed reflux episodes. But the p value in this small cohort may reflect a type II error; thus, the effect of baclofen reducing reflux episodes remains unproven. However, the amount of pills (at least 3/day) and the common side effects of baclofen are major drawbacks [34]. Two of 7 patients had to discontinue the medication due to progredient drowsiness. This emphasizes the need for future development of drugs with similar mechanisms but less side effects. As an alternative, a surgical approach should be discussed with the patient if there is a persistent pathological reflux despite high-dose PPI therapy. This has been demonstrated by studies showing that combined pH-metry/impedance measurement can be helpful in selecting good candidates for surgery [35, 36]. Other medical treatment strategies such as additional therapy with H_2 receptor antagonists or antacids are limited since they may not be regarded as useful for long-term maintenance therapy, which is often mandatory in these patients [34].

One might argue that this rather exploratory study is dealing with a highly selected patient population, and the volume of patients treated with baclofen is underpowered. However, to the best of our knowledge, this is the first prospective study evaluating the effect of an escalating medical treatment concept in patients with an insufficient response to 40 mg esomeprazole due to persistent pathological acidic and nonacidic reflux events showing a remarkable treatment success after doubling the dose up to 80 mg.

Based on the data of the present explorative study, we have to assume that doubling standard PPI dosage as the first step in the treatment of persistent gastroesophageal reflux despite therapy with PPI at standard doses as proven by pH/MII is an effective therapeutic approach, even when solely nonacidic reflux episodes are causative, as we observed an objectively measurable reduction in the number of reflux events including those of the nonacidic type. More than 2 thirds of patients benefit from such a procedure. Concerning further escalation with additive baclofen, we observed inconclusive results. New substances acting on reducing the number of TLESRs with fewer side effects than baclofen are currently under investigation. These drugs may be useful as an add-on therapy for the few remaining patients. Placebo-controlled studies are needed to elucidate their effect.

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