

Baclofen decreases acid and non-acid post-prandial gastro-oesophageal reflux measured by combined multichannel intraluminal impedance and pH

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SUMMARY

Background: Omeprazole controls acid but not non-acid reflux. The GABA B agonist baclofen decreases acid reflux through the inhibition of transient lower oesophageal sphincter relaxations (TLESRs) and should similarly decrease non-acid reflux. Using combined multichannel intraluminal impedance and pH (MII/pH), we compared acid and non-acid reflux after placebo and baclofen.

Methods: Nine healthy volunteers and nine heartburn patients underwent two 2-h studies of combined MII/pH in right lateral decubitus after a refluxogenic meal in random order: on placebo and after baclofen 40 mg p.o. Tracings were analysed for acid and non-acid reflux episodes, re-reflux and symptoms in the heartburn patients.

Results: In normal subjects baclofen significantly reduced the median number of episodes of acid (7 vs. 1, $P = 0.02$), non-acid (2 vs. 0, $P = 0.005$), and all reflux combined (10 vs. 2, $P = 0.006$); re-reflux was not reduced (0 vs. 0, $P = \text{N.S.}$). In heartburn patients, baclofen significantly decreased the median number of episodes of acid (15 vs. 6, $P = 0.004$), non-acid (4 vs. 2, $P = 0.003$), re-reflux (2 vs. 0, $P = 0.02$), and all reflux combined (23 vs. 8, $P = 0.004$); it also reduced the median number of acid-related (9 vs. 1, $P = 0.008$) and non-acid-related (1 vs. 0, $P = 0.04$) symptoms.

Conclusions: Baclofen reduces post-prandial acid and non-acid reflux and their associated symptoms. GABA B agonists may have a role in treating GERD.

INTRODUCTION

When the contents of the stomach are buffered, as occurs in the post-prandial period, a significant proportion of gastro-oesophageal reflux is non-acid, and therefore not detectable by conventional pH-metry.^{1–4} Using combined multichannel intraluminal impedance and pH measurement (MII/pH), we have previously shown that although post-prandial acid reflux is

markedly reduced after acid suppression with a proton pump inhibitor, non-acid reflux is unaffected by such treatment; furthermore, more symptoms can be produced by this type of reflux.¹

Since transient lower oesophageal sphincter relaxations (TLESRs) constitute the primary mechanism underlying gastro-oesophageal acid^{5–7} and non-acid² reflux, a medication acting to decrease them would be expected to reduce both acid and non-acid reflux. A decrease in transient lower oesophageal sphincter relaxations has been demonstrated after treatment with baclofen^{8–10} and other GABA B agonists¹¹ in animal studies. In two studies which evaluated the effect of a GABA B agonist on TLESRs in humans, baclofen was

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shown to reduce the rate of post-prandial TLESRs and acid reflux episodes per hour in healthy volunteers¹² and patients with reflux oesophagitis.¹³ Using the Bilitec probe, a decrease in bile reflux after treatment with baclofen has been reported in abstract form.¹⁴ To our knowledge, quantification of non-acid reflux through MII/pH after administration of a GABA B agonist has not been carried out.

Detection of reflux of gastric contents with a pH above 4.0 through pH-metry is achievable through measurement of pH falls of greater than one unit. However, pH-metry is unable to detect the non-acid reflux that occurs in the absence of pH changes, which may happen particularly in the post-prandial period when the stomach contents are buffered by a meal. Intraluminal impedance, which bases the detection of fluid or gas in the oesophagus on changes in electrical conductivity across pairs of electrodes placed within the oesophageal lumen, has been used as a technique for studying bolus movement in the oesophagus.^{1, 2, 15, 16} When the technique is combined with a pH electrode, it enables the detection of both acid and non-acid reflux.¹⁷ Combined multichannel intraluminal impedance and pH measurement (MII/pH) has been used to study acid and non-acid reflux in adults^{1, 2, 18} and infants.^{19, 20} The detection of additional reflux episodes during an ongoing acid reflux episode, i.e. re-reflux, has been described in a study using combined manometry and pH-metry.²¹ The use of MII/pH for measuring re-reflux—i.e. impedance-detected reflux of volume while oesophageal pH is already below 4.0—has been reported in abstract form.²² The aim of our study was to use this technology to compare the frequencies of post-prandial gastro-oesophageal reflux in all its forms (acid, non-acid and re-reflux) and associated symptoms, after treatment with placebo and the GABA B agonist baclofen.

PATIENTS AND METHODS

Patients

The study included nine healthy volunteers (four females and five males, with a mean age of 32 years) and nine heartburn patients (three females and six males, with a mean age of 36 years). Subjects were eligible if they were between the ages of 18 and 70. Premenopausal female subjects had pregnancy excluded through a urine pregnancy test. Patients were enrolled

if they complained of symptoms compatible with heartburn, occurring at least three times weekly; an endoscopic assessment was not carried out. Nursing mothers, subjects with a history of renal failure, seizures, neurological disorder, or intolerance to baclofen were excluded from the study. Patients who were taking medications altering intragastric acidity or oesophageal motility were asked to stop therapy 1 week prior to beginning the study.

METHODS

The study protocol was approved by the Graduate Hospital Institutional Review Board; all subjects gave written informed consent. On the initial visit an interview and physical examination were performed, followed by oesophageal manometry to determine lower oesophageal sphincter (LES) location. Subjects who qualified for the study underwent two 2-h sessions of MII/pH in random order: one session was performed 1 h after receiving placebo, with another session done 1 h after a single oral dose (40 mg) of baclofen. The two sessions were performed at least 48 h but not more than 7 days apart. Studies were performed in the right lateral decubitus position. Subjects ingested a refluxogenic meal, consisting of a sausage-and-egg McMuffin[®] (300 kCal, 60% fat) with an 8 oz (250 mL) cup of coffee, in a 15 min interval immediately preceding the 2 h recording period.

Combined intra-oesophageal impedance and pH measurement

Impedance (in ohms) is a measure of the total opposition to current flow between adjacent electrodes. It is inversely proportional to the electrical conductivity and the cross-sectional area of the material through which the current must travel. The oesophageal muscular wall, air and any given bolus material (such as food, saliva or gastric contents) all have different electrical conductivity, and therefore the presence of each of these substances in the oesophageal lumen produces a different impedance pattern. Impedance will decrease if a highly conductive bolus such as saliva reaches the oesophagus, while it will increase if a poorly conductive material (air for example) enters the oesophageal lumen.^{16, 17}

Combined intraoesophageal impedance and pH measurements were obtained with a MII/pH probe (Sandhill

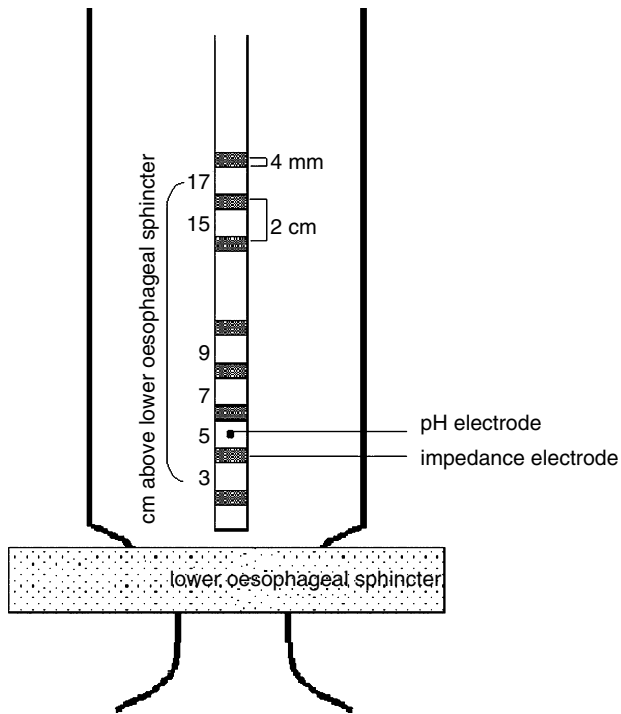


Figure 1. Schematic representation of the MII/pH catheter with impedance electrodes (4 mm long) set in pairs at 2 cm intervals, allowing for six impedance measuring segments, as well as one pH electrode. Once properly positioned, this catheter allows recording of pH 5 cm above the lower oesophageal sphincter and impedance in six measuring segments, with their centres 3, 5, 7, 9, 15 and 17 cm above the LES.

Scientific Inc.). The 2.1 mm catheter, illustrated in Figure 1, has six pairs of ring electrodes, each of them 4 mm in length, set at 2 cm intervals. Since impedance is measured between adjacent electrodes, this set-up allows for six measuring segments, the centres of which lie at 2, 4, 6, 8, 14 and 16 cm from the tip of the catheter. A single pH electrode is located 4 cm from the tip. The probe was connected directly to a computer that continuously recorded pH and impedance events.

On the days of combined MII/pH, the subjects came to the laboratory after a fasting period of at least 5 h. The MII/pH catheter was passed into the oesophagus transnasally and positioned with the pH electrode 5 cm above the lower oesophageal sphincter, and the centres of the impedance measuring segments 3, 5, 7, 9, 15 and 17 cm above the LES.

Symptom association was evaluated in the heartburn patients, who were asked to alert the investigator (who was present at all times during the recording) of the presence of heartburn, regurgitation or acid taste, for

real-time labelling on the tracing. The severity of symptoms was not recorded. Subjects were not reminded to report symptoms once recording began.

Analysis

All tracings were analysed manually by two separate investigators who were blinded to the study conditions (i.e. baclofen or placebo). Tracings were analysed for: (a) number of acid (pH < 4.0 for at least 5 s) and non-acid (MII-detected volume reflux without accompanying pH < 4.0) reflux episodes, (b) number of re-reflux episodes (MII-detected volume reflux while pH already < 4.0), and (c) association of symptoms with acid and non-acid reflux.

Symptoms were considered to be associated with reflux, either acid or non-acid, if they occurred in a 5 min interval immediately following a reflux event. This is the time interval that is customarily used in our laboratory, based on a prior description of the symptom index.^{2,3}

Statistics were calculated using the SPSS 10.0 Base software package of statistical programs. Given the small number of patients, nonparametric tests were used. The Wilcoxon signed rank test was used to compare the number of reflux episodes and number of symptom events with placebo vs. baclofen. A Mann-Whitney *U*-test was used to compare the number of reflux episodes in healthy volunteers vs. heartburn patients. A χ^2 analysis was used to compare side-effects. Significance was established at $P < 0.05$.

RESULTS

Examples of gastro-oesophageal reflux of three types: acid, non-acid and re-reflux, are shown in Figure 2.

Reflux episodes in normal volunteers

Normal volunteers had a total of 74 MII-detected reflux events (55 acid, 17 non-acid and 2 re-reflux events) on placebo compared to 18 MII-detected reflux events on baclofen (14 acid, 4 non-acid and no re-reflux events), as shown in Figure 3. Comparisons of number of reflux episodes for each subject as well as group medians, on placebo and baclofen, are shown in Figure 4. The median number of reflux episodes was significantly lower with baclofen for acid reflux (7 vs. 1, $P = 0.02$), non-acid reflux (2 vs. 0, $P = 0.005$), and all reflux

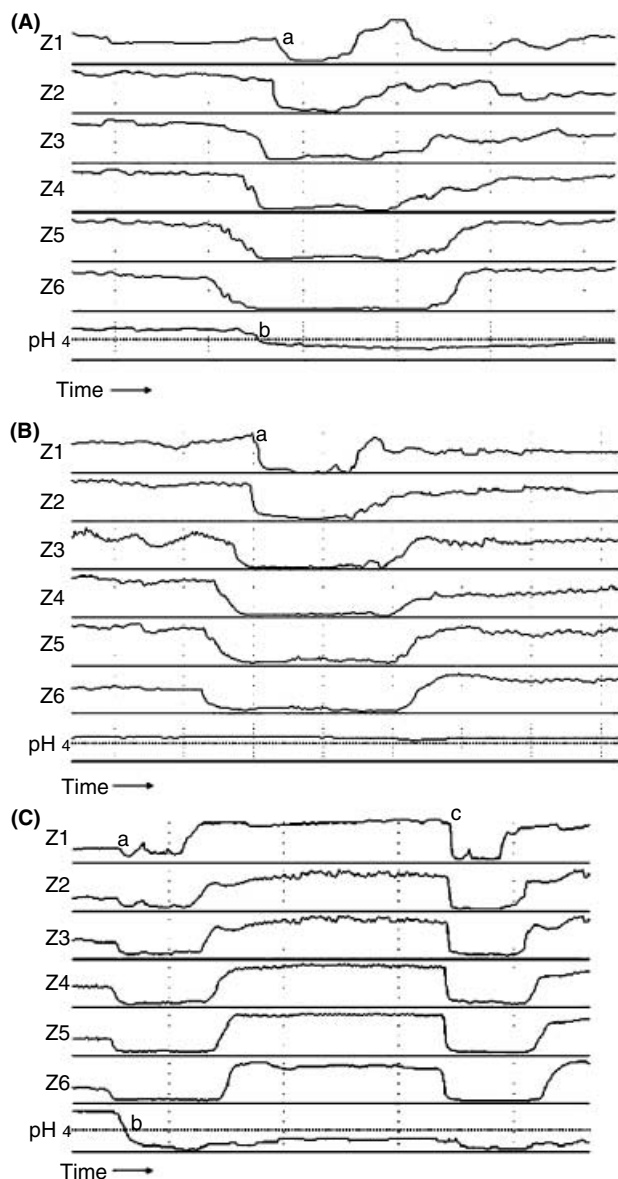


Figure 2. Impedance changes in ohms during three episodes of reflux. The six impedance measuring segments (Z1–Z6) and pH changes are shown on the *y* axis. The dotted line marks a pH of 4.0. (A) Acid reflux. Point a indicates the most proximal level of this impedance pattern of reflux. It is preceded by a sequential drop in impedance starting at the most distal measuring segment that proceeds toward the proximal oesophagus. Arrival of the refluxate into the distal oesophagus causes a fall in pH to below 4.0, an acid reflux episode. (B) Non-acid reflux. The level of this typical impedance pattern of reflux is indicated by point a. This is not accompanied by a fall in pH to below 4.0 and is thus considered an episode of non-acid reflux. (C) Re-reflux. Reflux detected by impedance (a) causes a fall in pH to below 4.0 (b). A second impedance-detected reflux episode (re-reflux, c) occurs before pH returns to 4.0.

combined (10 vs. 2, $P = 0.006$); re-reflux was not reduced on treatment (0 vs. 0, $P = \text{ns}$).

Reflux episodes in heartburn patients

As illustrated in Figure 3, patients complaining of heartburn had more reflux episodes compared to normal volunteers. The median number of MII-detected episodes was significantly higher for patients both on placebo (23 vs. 10, $P = 0.0005$) and baclofen (8 vs. 2, $P = 0.01$). Comparisons of the number of reflux episodes for each patient, as well as group medians, on placebo and baclofen, are shown in Figure 4. In this group of patients, treatment with baclofen resulted in a statistically significant reduction in the median number of episodes of acid reflux (15 vs. 6, $P = 0.004$), non-acid reflux (4 vs. 2, $P = 0.003$), re-reflux (2 vs. 0, $P = 0.02$), and all reflux combined (23 vs. 8, $P = 0.004$).

Symptom frequency with placebo and baclofen

One of the heartburn patients reported no symptoms, despite having both acid and non-acid reflux. The remaining eight heartburn patients reported a total of 118 symptom events during the two sessions. 85 of these were associated with acid reflux, 25 with non-acid reflux. Eight of the 118 (6.8%) symptom events were not associated with either acid or non-acid reflux. As shown in Table 1, in the untreated state acid reflux was more frequently symptomatic ($P = 0.005$) than non-acid reflux. This difference was not significant after treatment with baclofen, most likely due to a type-two statistical error resulting from the small number of symptoms.

Figure 5 illustrates the pooled symptom results for all eight patients on placebo and baclofen, with individual patient values shown in Figure 6. Baclofen produced a significant decrease in the median number of total (11 vs. 1, $P = 0.004$), acid-related (9 vs. 1, $P = 0.008$) and non-acid-related (1 vs. 0, $P = 0.04$) symptoms.

Side-effects

Seven (39%) subjects experienced side-effects on baclofen: five subjects reported mild to moderate dizziness (subsiding in less than 6 h); one complained of mild nausea lasting for 10 min after completion of the recording session, and one developed nausea with two episodes of vomiting, which resolved 6 h after dosing.

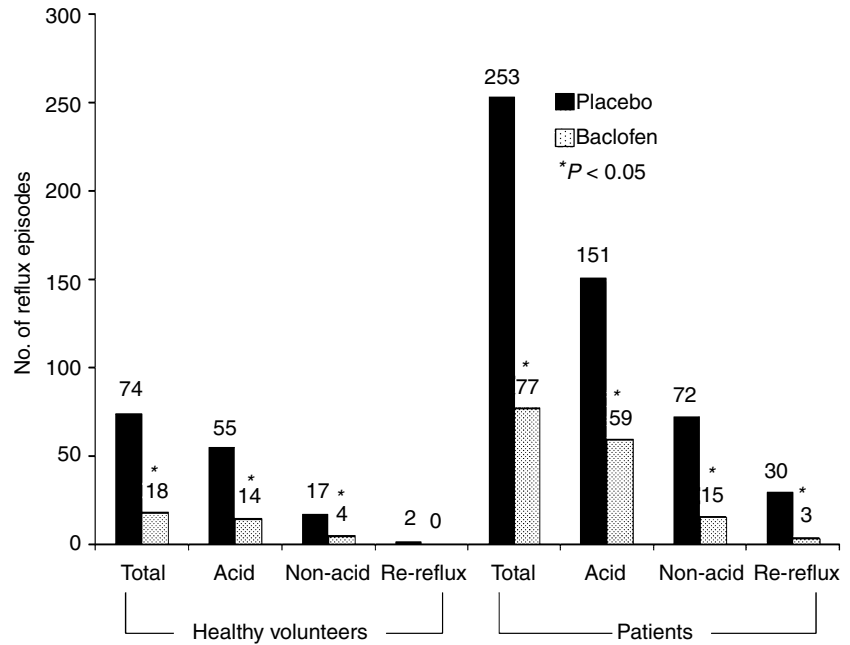


Figure 3. Pooled results of types of reflux episodes for the nine healthy subjects and the nine heartburn patients, taking placebo or baclofen.

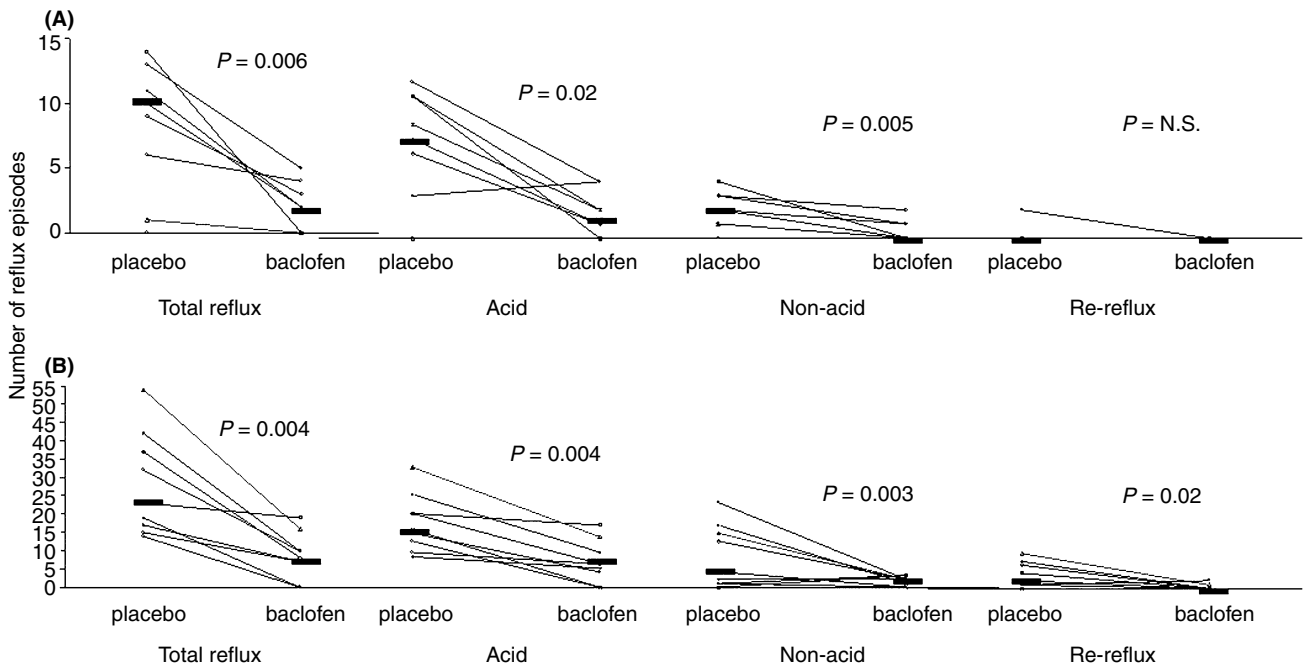


Figure 4. Individual subject values for reflux episodes (total, acid, non-acid and re-reflux) in (A) normal volunteers and (B) heartburn patients taking placebo or baclofen. Medians are represented by the horizontal bars. Significance established at $P < 0.05$ (Wilcoxon signed rank test).

One (6%) subject complained of short-lived dizziness after receiving placebo. Although side-effects were numerically higher on medication, the differences were

not statistically significant when comparing placebo and baclofen for dizziness (1 vs. 4, $P = \text{N.S.}$), nausea (2 vs. 0, $P = \text{N.S.}$), and vomiting (1 vs. 0, $P = \text{N.S.}$).

	Placebo		Baclofen		Placebo + baclofen	
	Acid GER	Non-acid GER	Acid GER	Non-acid GER	Acid GER	Non-acid GER
Sx present	70	20	15	5	85	25
Sx absent	73	50	39	8	112	58
<i>P</i>	0.005		> 0.05		0.04	

Sx = symptoms, GER = gastro-oesophageal reflux.

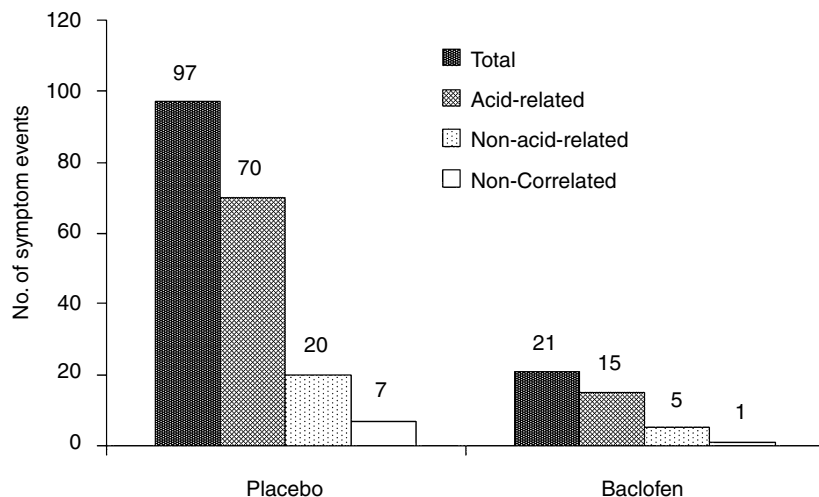


Table 1. Pooled results from the eight heartburn patients in whom symptoms were recorded, showing symptomatic and asymptomatic acid and non-acid reflux episodes, on placebo, baclofen, and for both recording sessions combined

Figure 5. Pooled results of types of total symptom events for all heartburn patients taking placebo or baclofen.

DISCUSSION

Suppression of gastric acid constitutes the mainstay of medical treatment of gastro-oesophageal reflux. Using combined MII/pH, we have recently shown that after acid suppression with a proton pump inhibitor, the total number of post-prandial reflux episodes is unchanged: although acid reflux becomes rare after treatment with omeprazole, reflux continues to occur but becomes predominantly non-acid. Furthermore, non-acid reflux is responsible for at least some symptoms in the untreated state and for the majority of post-prandial reflux symptoms after acid suppression.¹ In the group of patients who continue to complain of reflux symptoms despite acid suppression, an alternative approach to treatment is desirable.

Control of gastro-oesophageal reflux by GABA B agonists has been described in healthy volunteers and GERD patients by the same group.^{12, 13} Both of these studies, as well as studies in animals,⁸⁻¹¹ used manometry and pH-metry to document a reduction in the rate of TLESRs, with a corresponding decrease in the rate of acid reflux episodes. Our study is the first attempt

to quantify both acid and non-acid reflux before and after treatment with a GABA B agonist.

We chose to use combined MII/pH for this study because the technique enables a quantification of all forms of reflux (acid, non-acid and re-reflux). We believe that combined MII/pH should be considered the procedure of choice for reflux quantification, because it measures the final step in the sequence of events leading to gastro-oesophageal reflux (i.e. the presence of refluxate in the oesophageal lumen) regardless of the underlying mechanism (i.e. TLESR, swallow related lower oesophageal sphincter relaxation or low basal LES pressure) and in a pH independent fashion. In order to increase the yield of the study, we monitored subjects in conditions which have been shown to be conducive to reflux and to induce TLESRs, i.e. after a high fat meal and in the right lateral decubitus position.²⁴⁻²⁷

Not surprisingly, the patients exhibited a significantly higher number of reflux episodes when compared with the healthy volunteers. The frequency of reflux episodes was significantly decreased by baclofen in both groups. A closer analysis showed that the reduction was seen separately for acid, non-acid and re-reflux. This clearly

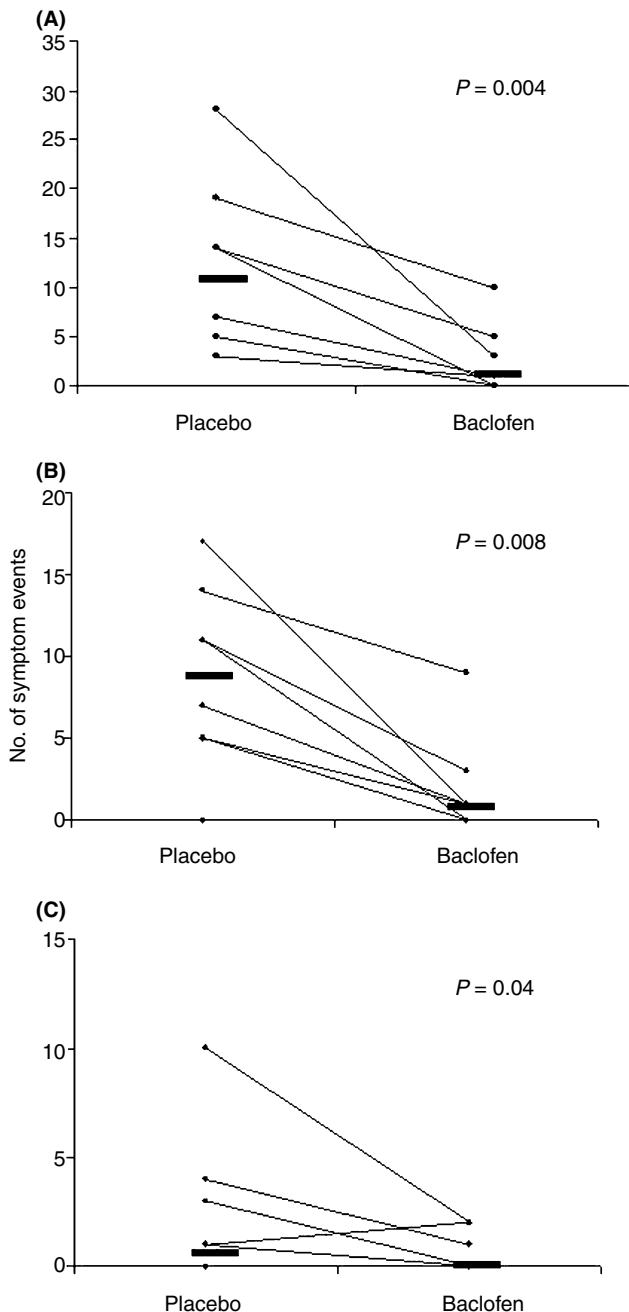


Figure 6. Individual patient values taking placebo or baclofen, for reflux symptoms: (A) all symptoms, (B) acid-related symptoms, and (C) non-acid-related symptoms. Medians are represented by the horizontal bars. Significance established at $P < 0.05$ (Wilcoxon signed rank test).

differs from what we described after acid suppression with a proton pump inhibitor, which reduced post-prandial acid but not non-acid reflux.¹ A successful reduction in reflux after treatment with a GABA B

agonist has been reported in two studies in which 20 healthy subjects¹² and 20 GERD patients¹³ underwent manometry and pH-metry in the post-prandial period for 3 h in the sitting position. In both of these studies, the investigators found that baclofen achieved a reduction in the rate (episodes per hour) of both acid reflux episodes and TLESRs, as well as an increase in basal lower oesophageal sphincter pressure. However, these and our own observations are limited to the post-prandial period, and further studies evaluating the effect of baclofen on gastro-oesophageal reflux over a 24 h period and in ambulatory conditions are needed.

We recorded symptoms in eight patients having a history of frequent heartburn. Symptoms were recorded in an intensive monitoring setting over 2 h in the post-prandial state, with the investigator present at all times. These circumstances are quite different from what is experienced by a subject pursuing normal daily life activities while carrying an ambulatory pH recorder.

Symptoms were caused by both acid and non-acid reflux, with very few symptoms reported in the absence of reflux. Although acid reflux was more frequently symptomatic than non-acid GER, this difference was not seen after treatment with baclofen, likely to be due to a type II statistical error resulting from the small number of symptom events after treatment. Interestingly, 48% of acid reflux events produced symptoms on placebo, compared to 27% on baclofen; although this would suggest that baclofen may alter perception of symptoms, at this time this idea is speculative at best. Most importantly, baclofen treatment achieved a significant reduction not only in acid but also in non-acid post-prandial reflux, with a corresponding decrease in non-acid-related symptoms. This constitutes a striking difference from the ongoing non-acid reflux and non-acid-related symptoms seen after treatment with a proton pump inhibitor, documented recently in our laboratory.¹

The fact that baclofen was effective in reducing all symptoms, whether they were produced by acid or non-acid reflux, suggests that GABA B agonists may have an important role in the treatment of patients with ongoing symptoms after adequate acid suppression. This would be particularly true if their symptoms were associated with non-acid reflux during MII/pH monitoring. However, the patients evaluated in this study should not be considered to be representative of the patient group with symptoms that are refractory to acid suppression, they were merely frequent sufferers of typical heartburn.

The effect of baclofen on patients receiving acid suppressive medication has only been reported in abstract form.¹⁴ Using combined pH and bilitec to monitor 15 symptomatic patients with normal pH-metry but pathological bile reflux while on treatment with proton pump inhibitors, Koek *et al.* documented a baclofen-induced decrease in bile reflux and symptoms.

Side-effects of dizziness, nausea and vomiting were more frequent with baclofen. Some of these untoward effects may be lessened or avoided by utilizing a conventional and more gentle baclofen loading regimen, i.e. starting at 5 or 10 mg t.d.s., rather than administering a single 40 mg dose. Whether the long-term control of gastro-oesophageal reflux is achievable while maintaining an acceptable side-effect profile, with baclofen or other GABA B agonists, remains to be determined.

Our study is limited to the chosen conditions (i.e. lying on the right side after a refluxogenic meal), and cannot be extrapolated outside of this post-prandial monitoring period. However, our observations clearly document a major decrease in both acid and non-acid reflux, with a corresponding improvement in symptoms, following therapy with baclofen. The effect of baclofen on acid and non-acid reflux outside of the post-prandial period is yet to be determined.

In summary, we found that the GABA B agonist baclofen effectively reduces reflux in all its forms (acid, non-acid and re-reflux) as well as symptoms associated with both acid and non-acid reflux. This class of drugs may therefore have a place in the treatment of gastro-oesophageal reflux disease, particularly in patients who continue to complain of symptoms despite adequate acid suppression. These studies also document the effectiveness of combined MII/pH for measuring reflux regardless of the underlying mechanism and independent of the pH of the refluxate.

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