Evaluation of Elevation of the Head of the Bed, Bethanechol, and Antacid Foam Tablets on Gastroesophageal Reflux

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To ascertain how elevation of the head of the bed, bethanechol, and antacid foam tablets affect gastroesophageal reflux, we used prolonged intraesophageal pH monitoring in 55 symptomatic patients. Acid exposure was separated into reflux frequency and esophageal acid clearance time and recorded during the day in the upright posture and recumbent at night. Values before and during each therapy were compared to physiologic reflux in 15 asymptomatic controls. Ten patients slept with the head of the bed elevated and had a 67% improvement in the acid clearance time ($P < 0.025$); however, the frequency of reflux episodes remained unchanged. Twelve patients given 25 mg of bethanechol 4 times a day had a 50% decrease in recumbent acid exposure only ($P < 0.05$), due to a trend towards decreased reflux episodes and acid clearance time. Bethanechol combined with head of bed elevation in 19 other patients decreased both reflux frequency (30%) and acid clearance time (53%, all $P < 0.05$). Antacid foam tablets failed to significantly diminish acid exposure. Nocturnal reflux responded the best to those therapies tested.

Prolonged distal esophageal pH monitoring provides a quantitative assessment of gastroesophageal reflux in a near physiologic setting by directly measuring distal esophageal acid exposure. The pattern of this exposure can be separated into reflux frequency and esophageal acid clearance time. Previous studies have shown that both posture and sleep influence this reflux pattern. While awake, reflux in the upright posture was characterized by frequent episodes rapidly cleared from the esophagus. In contrast, while asleep, recumbent reflux was characterized by infrequent episodes slowly cleared from the esophagus (1, 2). The purpose of the present study was to examine the effect of medical therapy on the reflux pattern of symptomatic patients while awake and asleep. In order to gain insight into the clinical relevance or desirability of a given pattern change, reflux during medical therapy was also compared to physiologic reflux present in asymptomatic volunteers.

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MATERIALS AND METHODS

Study Population. Fifteen asymptomatic volunteers with no history of gastroesophageal reflux symptoms or antacid use gave informed consent and served as the control population. All were elective admissions to Tripler Army Medical Center for inguinal hernia repair and other nongastroenterologic illness.

Fifty-five patients with heartburn and symptoms of postural regurgitation comprised the treatment group.

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Their acid reflux as determined by 24-hr pH monitoring exceeded two standard deviations above the mean observed for the asymptomatic control volunteers (1).

Intraesophageal pH Monitoring. Distal esophageal pH monitoring was performed in all individuals by passing a Beckman pH probe (#39042) through the nose and placing it 5 cm above the proximal margin of the manometrically located lower esophageal sphincter (LES) in accordance with a previously published technique (1). The 24-hr record was divided into two periods: upright and recumbent. During the upright period, all individuals maintained a sitting or standing position and ate three meals in which the pH of all food and beverage was 5 or above to avoid stimulating a reflux episode. During the recumbent period, all individuals slept with no restrictions as to the prone, supine, or lateral positions. All individuals had an intragastric pH less than 4.

A reflux episode was defined as a drop in intraesophageal pH to a value less than 4.0. The number of reflux episodes were recorded. The time required for the intraesophageal pH to return to 4 or greater after each reflux episode was measured in minutes and defined as the esophageal acid clearance time. Distal esophageal acid exposure during either the upright or recumbent period was expressed as percent time the pH was less than 4.0 (No. of min pH < 4.0/min-in-posture, X100). Reflux frequency (number of episodes pH < 4.0/hr) was determined for both the upright and recumbent period by dividing the number of episodes by the hours spent in the respective postures. The mean esophageal acid clearance time was determined by dividing the total duration of acid exposure (minutes), either upright or recumbent, by the number of reflux episodes. A 24-hr pH score was used to define each individual's reflux status by a composite score that incorporated six components from the record (percent acid exposure for periods: 24-hr, upright and recumbent, as well as reflux episodes: total number, those equal to or greater than 5 min and longest). A score that exceeded two standard deviations above the mean observed in 15 asymptomatic control volunteers was considered abnormal (1).

Medical Treatment. The reflux pattern of the patients during each form of therapy was compared both to that of a similar period (upright or recumbent) during the initial baseline pretreatment record as well as to the pattern of physiologic reflux noted in the 15 asymptomatic volunteers. Some patients were monitored during more than a single therapy: three patients were monitored during three different forms of therapy; 18 during two; and the remaining 34 patients during only a single form of therapy. Only one prescribed therapy was monitored during a 24-hr period. Different forms of therapy sequentially followed each other and were all preceded by the initial pretreatment 24-hr record.

Ten patients whose initial 24-hr pH record showed excessive recumbent acid exposure (> 1.2%) (1) had postural therapy by placing 6-in. blocks under both posts at the head of the bed.

The effect of oral bethanechol (25 mg) on distal esophageal acid exposure was ascertained in three consecutive groups of patients. The first group given bethanechol consisted of 15 patients whose initial 24-hr pH score was abnormal (1). They had 25 mg of oral bethanechol 4 times a day (8 AM, 2 PM, 6 PM, 10 PM) without regard to timing of meals or bedtime. They slept horizontal on both study nights and, during each 24-hr period, ate three meals.

The second group given bethanechol consisted of six additional patients whose initial 24-hr pH record showed excessive recumbent acid exposure. They took only 25 mg of oral bethanechol 1 hr prior to bedtime and then slept horizontal. This group provided an opportunity to determine if the therapeutic response of a single evening dose of bethanechol would occur independent of the three doses of bethanechol given earlier in the day.

The third group given bethanechol consisted of 23 additional patients whose initial 24-hr pH record showed either excessive upright acid exposure (>6.2%), excessive recumbent acid exposure, or both (1). The four patients whose initial 24-hr pH record showed only excessive upright acid exposure had only 25 mg of oral bethanechol given 1 hr before each meal. The six patients whose initial 24-hr pH record showed only excessive recumbent acid exposure had only 25 mg of bethanechol given 1 hr before bedtime and slept with the head of the bed elevated. The 13 patients whose initial 24-hr pH record showed both excessive upright and recumbent acid exposure had 25 mg bethanechol given 1 hr before each meal and 1 hr before bedtime and slept with the head of bed elevated. This third group provided the opportunity to observe the effect of bethanechol given 1 hr before each meal on excessive upright acid exposure in 17 patients as well as the effect of bethanechol combined with elevation of the head of bed on excessive recumbent acid exposure in 19 patients.

The effect of antacid foam tablets (Gaviscon®: alginic acid, $AloH_3$ dried gel, $NaHCO_3$, Mg trisilicate) on distal esophageal acid exposure was ascertained in two consecutive groups of patients with abnormal 24-hr pH scores. In the first group, 12 patients chewed and then swallowed 4 foam tablets followed by ½ glass of water 1 hr after each meal and just prior to bedtime. In the second group, 12 additional patients ingested 4 foam tablets in an identical manner every 2 hr and just prior to bedtime. The patients in both groups slept horizontal on each study night.

Statistical Evaluation of Data. All data are expressed in mean values with 1 SE of the mean shown on the bar graphs. The differences between the pretreatment reflux pattern (% acid exposure, reflux frequency, acid clearance time) and that observed during a specific therapy was examined for statistical significance by the paired *t* test. Student's *t* test for unpaired values was used to determine the difference between the reflux patterns during a specific therapy and that of the asymptomatic controls. Only those comparisons with a *P* value less than 0.05 were considered significant and are shown in either the legends or figures.

RESULTS

Postural Therapy. Elevation of the head of the bed resulted in a significant improvement in the esophageal acid clearance time. The clearance time during this therapy approached that of controls

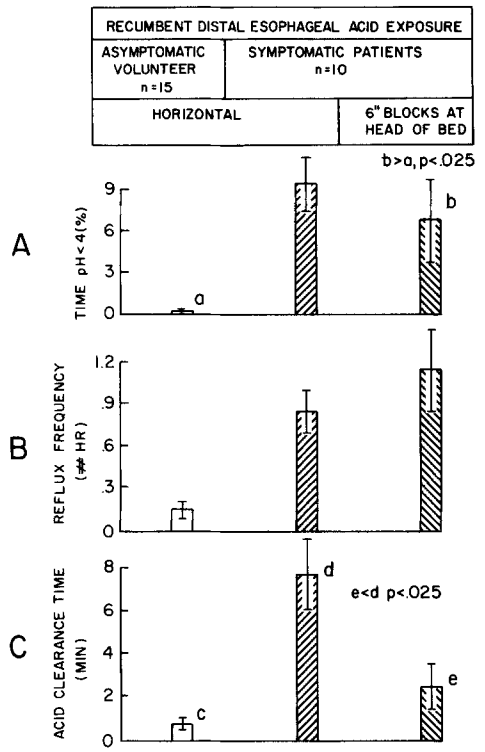

Fig 1. Effect on recumbent distal esophageal acid exposure when patients slept with the head of bed elevated compared to acid exposure found in the asymptomatic controls sleeping horizontal. *N* = number of individuals. All bars show mean and 1 SEM. Controls are open bars; patients are hatched (up: pretreatment; down: during treatment).

sleeping horizontal (Figure 1C). The acid exposure time (Figure 1A) and reflux frequency (Figure 1B) during postural therapy still significantly exceeded that of the asymptomatic volunteers sleeping recumbent.

Bethanechol. Oral bethanechol, given 4 times a day to 15 patients (group I), resulted in a significant improvement in only recumbent acid exposure. Upright acid exposure was essentially unchanged (Figure 2A). The improvement in recumbent acid exposure resulted from both a diminished reflux frequency (Figure 2B) and improved esophageal acid clearance time (Figure 2C), although neither change was statistically significant.

A single tablet of oral bethanechol given to six patients (group II) 1 hr before bed resulted in a significant improvement in the mean esophageal acid clearance time that approached that observed in the asymptomatic controls (Figure 3C). This resulted in a decrease in recumbent acid exposure (Figure 3A). Recumbent reflux frequency had a diminished trend, although this change was not statistically significant (Figure 3B).

Bethanechol and Postural Therapy. Recumbent distal esophageal acid exposure significantly diminished in 19 patients (group III) given 25 mg of oral bethanechol 1 hr before sleeping with the head of the bed elevated (Figure 4A). This diminished acid exposure resulted from both a significant improvement in reflux frequency (Figure 4B) as well as esophageal acid clearance time (Figure 4C).

Bethanechol Taken before Meals. Upright acid exposure (Figure 5A) and reflux frequency (Figure 5B) was essentially unchanged in 17 patients taking oral bethanechol 1 hr before each meal. However, the upright esophageal acid clearance time, both before and during bethanechol therapy, was comparable to that of the asymptomatic controls (Figure 5C).

Antacid Foam Tablets. There was no significant difference in acid exposure (% time at pH < 4), either upright or recumbent, in: (1) 12 patients ingesting 4 antacid foam tablets 1 hr after meals and at bedtime (upright 9 ± 2 vs 11 ± 3 SE; recumbent 9 ± 2 vs 10 ± 4 SE); or (2) 12 patients ingesting 4 antacid foam tablets every 2 hr while awake and at bedtime (acid exposure: upright 13.7 ± 3 vs 11.0 ± 3 SE; recumbent 10 ± 2 vs 14 ± 3 SE, respectively).

DISCUSSION

Symptom improvement denotes the beneficial effect postural therapy, bethanechol, and antacid have on gastroesophageal reflux when concomitantly employed (3). An increase in esophagogastric junction competency may account for this symptom improvement, since these agents enhance LES pressure (4). However, manometric studies do not distinguish how the three forms of medical therapy actually affect the reflux pattern or how they complement each other. What is needed is a study that objectively determines how standard medical therapy actually affects the reflex pattern and how changes in the pattern during the prescribed therapy relate to both physiologic reflux in asymptomatic controls and the reflux pattern associated with esophagitis (2, 5).

Sleeping with 6-to 8-in. blocks under the head of the bed has been widely held to benefit patients with gastroesophageal reflux. However, it is not entirely clear whether this therapy allows gravity to minimize reflux into the esophagus (6, 7) or improves esophageal acid clearance (8). The present

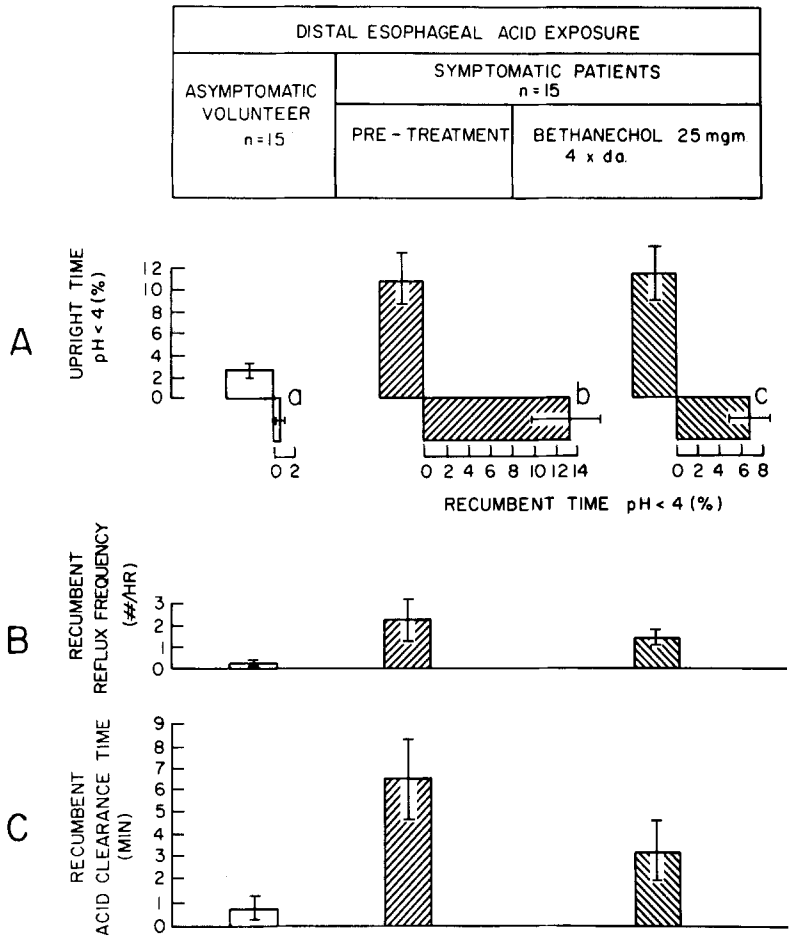

Fig 2. Effect of bethanechol (25mg, 4 times a day) on distal esophageal acid exposure, both upright (vertical bar) and recumbent (horizontal bar), in patients compared to acid exposure found in the controls. N = number of individuals. All bars show mean and 1 SEM. $c < b$, $P < 0.05$. $c > a$, $P < 0.005$. Controls are open bars; patients are hatched (up: pretreatment; down: during treatment).

study showed that elevation of the head of the bed significantly improved the esophageal acid clearance time. Since the upright posture has been associated with both lower LES pressure (9) and an increased gastroesophageal pressure gradient (10, 11) that would encourage reflux, it was not surprising that when patients assumed a more upright position with elevation of the head of the bed there was a trend for a small increase in reflux episodes. Thus, the beneficial effect of elevating the head of the bed would not appear to result from stopping acid exposure or reflux episodes. Instead, it alters the nocturnal reflux pattern from one of infrequent episodes poorly cleared to that of a comparable number of episodes now more rapidly cleared. Given a comparable degree of acid exposure, frequent, rapidly cleared reflux episodes evoked less histologic reaction and less severe forms of endoscopic esophagitis than infrequent episodes slowly cleared (2, 5).

Cholinergic agents, such as bethanechol, increase lower esophageal sphincter pressure and diminish heartburn and antacid requirement in patients with reflux (3, 4). Since incremental increases in LES pressure have been shown to decrease the number of reflux episodes (12), the first group that received bethanechol was given 25 mg 4 times a day without regard to timing of meals as was prescribed in an earlier study (3). It was interesting that only recumbent acid exposure significantly diminished, even though three doses of bethanechol were given during the upright period. As anticipated, the decrease

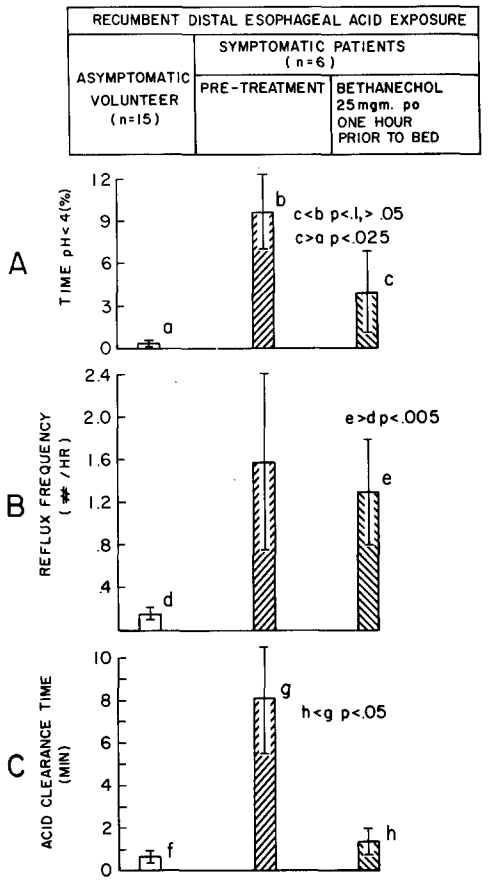

Fig 3. Effect of only 25 mg of bethanechol given 1 hr before bedtime on recumbent distal esophageal acid exposure in patients compared to acid exposure in controls. N = number of individuals. All bars show mean and 1 SEM. Controls are open bars; patients are hatched (up: pretreatment; down: during treatment).

in recumbent acid exposure resulted in part from a decrease trend in reflux frequency possibly related to pharmacologic enhancement of LES pressure by bethanechol, although improved gastric emptying cannot be excluded (13).

A trend for improvement in the esophageal acid clearance time was also partially responsible for the significant decrease in recumbent esophageal acid exposure noted in the first group treated. Subcutaneous bethanechol has previously been shown to enhance the clearance time of 15 cc of 0.1 N HCl instilled into the esophagus of recumbent patients while awake (14). The present study showed that oral bethanechol will improve the esophageal acid clearance time even while patients sleep horizontal. This effect does not appear dependent upon three doses given during the day, since only a single 25 mg dose of bethanechol given 1 hr prior to bedtime to six additional patients in group II achieved a significant improvement in the acid clearance time. These patients also had a 50% reduction in recumbent acid exposure along with a decrease trend in reflux episodes. The improvement in esophageal acid clearance time may result from the peristaltic pressure increase and velocity decrease associated with bethanechol (15, 16).

Since head of bed elevation failed to decrease reflux frequency, and bethanechol failed to decrease acid exposure in the upright posture in the first group, we studied the reflux pattern both upright and recumbent in a third group of 23 patients treated with bethanechol. Bethanechol combined with elevation of the head of the bed resulted in a significant decrease in reflux frequency in those 17 patients with excess recumbent acid exposure. This decrease in reflux episodes may have occurred due to an augmentation in LES pressure previously reported with bethanechol (4). It is important to note that bethanechol obviated the trend for an increase in reflux frequency when elevation of the head of the bed was employed alone. As anticipated, this combined therapy improved the esophageal acid clearance time, since both therapies were previously found to do so individually. Since bethanechol combined with postural therapy resulted in both a significant decrease in the recumbent reflux frequency and acid clearance time, one would anticipate that chronic use of this treatment program would improve esophagitis, especially since nocturnal reflux episodes that are slowly cleared have been associated with reflux esophagitis (2, 5, 17). Indeed, bethanechol has been shown in a double-blind study to be more effective than placebo when combined with postural therapy to heal esophagitis (18).

Since patients have a high frequency of reflux episodes in the postprandial period (2), bethanechol was given 1 hr before each meal to those 19 patients with excessive upright acid exposure (group III). This would afford cholinergic enhancement of LES pressure at a time when frequent episodes of reflux were expected (2). Bethanechol again failed to significantly improve upright acid exposure, because no significant decrease in reflux frequency occurred. Gravity assists fluid transit through the upright esophagus (19). Therefore, the asymptomatic controls as well as the symptomatic patients, both before and during bethanechol, all had comparable upright acid clearance times despite their

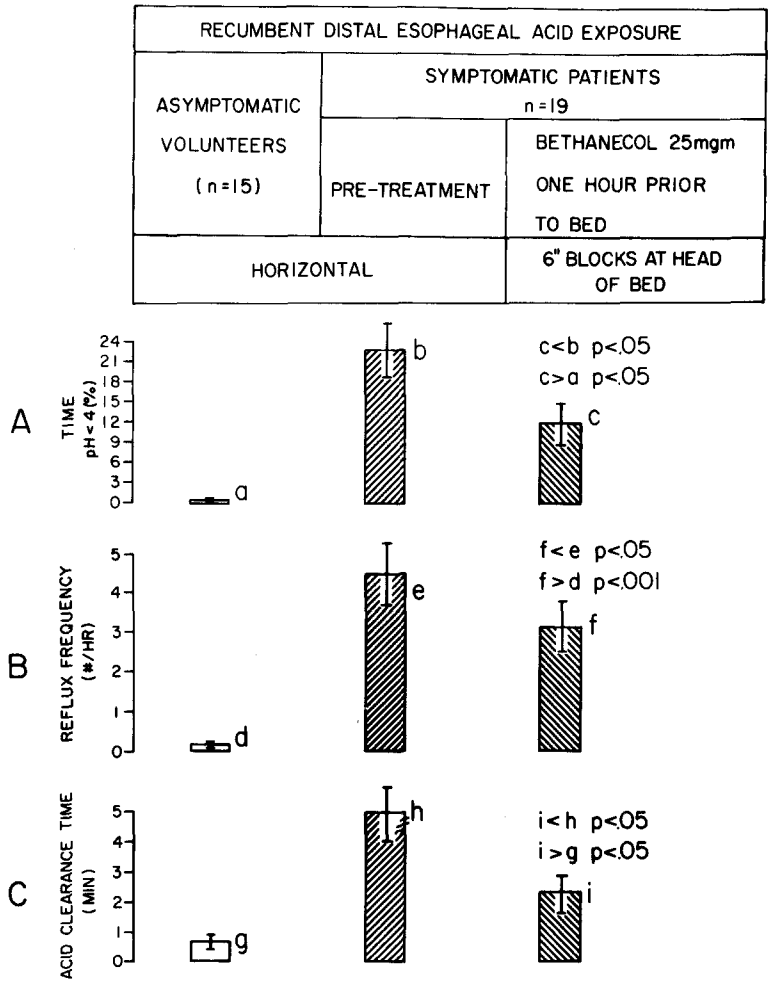

Fig 4. Effect of 25 mg of bethanechol given 1 hr before sleeping with head of bed elevated on recumbent distal esophageal acid exposure in patients compared to acid exposure found in controls. N = number of individuals. All bars show mean and 1 SEM. Controls are open bars; patients are hatched (up: pretreatment; down: during treatment).

marked desparity in degree of upright acid exposure and reflux frequency.

It was not surprising that bethanechol failed to affect the upright reflux frequency during the day as opposed to resulting in a significant decrease while recumbent at night. Simultaneous pH and motility tracings have shown precipitation of reflux episodes after deglutition (20). The frequent swallowing rate while awake (21) along with the attendant relaxation of the LES would make pharmacologic enhancement in LES pressure less likely to be effective as an antireflux barrier, especially since a 12-mm pressure gradient, that would facilitate reflux, exists from stomach to mid-esophagus in the upright posture (22). In contrast, pharmacologic enhancement in LES resting tone would be expected to be more effective in diminishing reflux episodes in recumbency. Associated with this posture would be a diminished swallowing rate during sleep (21), an additional augmentation in LES pressure (9), and a lessened gastroesophageal pressure gradient (10, 11).

Excessive exposure of the esophagus to refluxed acid gastric juice while patients sleep may sensitize the esophagus and result in heartburn. This theory has support, since in an earlier study (3) bethanechol combined with postural therapy significantly diminished both heartburn and antacid requirement. Heartburn is a symptom generally experienced and self-medicated while awake during the

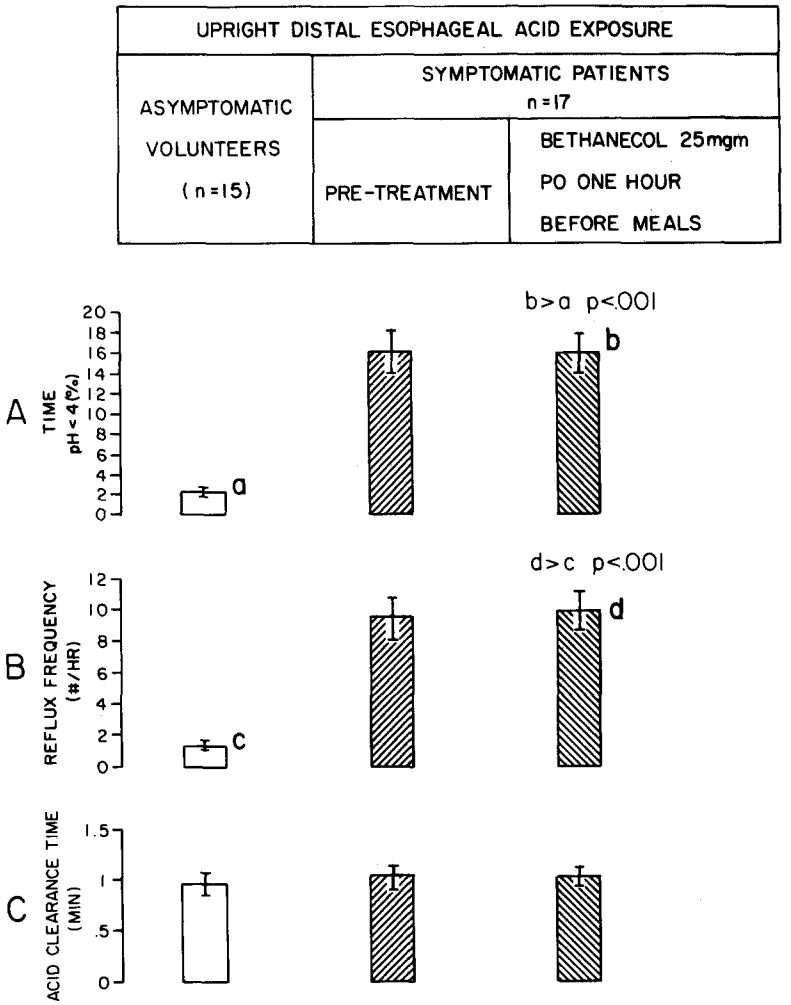

Fig 5. Effect of 25 mg of bethanechol given 1 hr before each meal on upright distal esophageal acid exposure in patients compared to acid exposure found in controls. N = number of individuals. All bars show mean and 1 SEM. Controls are open bars; patients are hatched (up: pretreatment; down: during treatment).

day. The present study showed that bethanechol only significantly affected nocturnal acid exposure. These data suggest a more effective treatment of gastroesophageal reflux while patients sleep may improve daytime symptoms that are quite distressing because of the frequency of reflux episodes but cause little histologic reaction because of rapid clearance (2, 5). Additionally, it may be prudent to record changes in nocturnal reflux in future clinical studies that assess patient response to a given treatment. This concept is particularly important since heartburn poorly correlates with esophagitis (5, 23) and patients are asleep during the time that the most detrimental reflux occurs and would be less likely to accurately notice changes in reflux based upon heartburn.

The alginic acid antacid foam tablets (Gaviscon) affect reflux by forming a neutral viscous sodium alginate gel that floats on the surface of the gastric contents. To find that Gaviscon failed to significantly affect distal esophageal acid exposure in the present study was contrary to the findings of Stanciu et al. (24), who noted a small decrease in acid exposure when patients were studied after two weeks of medical treatment with Gaviscon. Perhaps the reason for the difference in the results of these two studies was the two-week time interval during which other concomitant medical therapy may have assisted Gaviscon to cause a small reduction in acid exposure. In the present study, even large doses of Gaviscon, such as four tablets every 2 hr and at bedtime, failed to significantly reduce acid expo-

sure. This was in contrast to the immediate effect combined postural and bethanechol therapy had on distal esophageal acid exposure. Perhaps an immediate reduction in distal esophageal acid exposure would result if the neutralizing capacity of the antacid foam tablets were strengthened (25).

In conclusion, prolonged distal esophageal pH monitoring can be used to determine diurnal changes in the reflux pattern of patients during a given medical or surgical therapy (26, 27). It is clinically encouraging that improvements in the reflux frequency and esophageal acid clearance time found at night during bethanechol and postural therapy are identical to those parameters previously associated with severe esophagitis and pulmonary aspiration (28, 29). Based on the findings reported here, we speculate that additional clinical investigation involving pharmacologic enhancement of LES competency and the mechanism of esophageal acid clearance during sleep may possibly lead to further improvement in the medical therapy of gastroesophageal reflux.

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