Effect of Naproxen on Gastroesophageal Reflux and Esophageal Function: A Randomized, Double-Blind, Placebo-Controlled Study

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Objectives: Gastrointestinal symptoms, particularly pyrosis, complicate nonsteroidal anti-inflammatory drug (NSAID) use. NSAIDs cause esophageal injury, and H_2 blockers are often prescribed for, and successfully control, NSAID-related symptoms. To determine whether NSAIDs can induce gastroesophageal reflux, we studied the effect of a commonly used NSAID, naproxen, on reflux parameters and esophageal function. *Methods:* Nine healthy volunteers (five males, four females, age 23–34 yr) were studied. After basal measurements were taken, the subjects randomly received naproxen 500 mg *p.o. b.i.d.* or placebo for 1 wk. On day 6, the subjects underwent esophageal manometry with a water-perfused system and Dent sleeve. Body pressures, contraction velocity, and duration of contraction were recorded in the distal 7 cm of the esophagus. The lower esophageal sphincter pressure (LESP) and number of transient relaxations (TLESRs) were monitored. This was followed by 24-h pH monitoring. The subjects then crossed over to the other drug after a minimum 14-day wash-out period. *Results:* No subject experienced any GI symptoms during the study. One subject developed reflux-induced symptoms a few months after completing the study and was excluded from the analysis. The total fraction of time (pH < 4) was 4.9 ± 1.0% in the basal state, 5.5 ± 1.4% on placebo, and 5.4 ± 1.5% on naproxen. These differences were not significant. The number of reflux episodes and the esophageal clearance time were not affected by naproxen. The LESP in the basal state was 32.1 ± 5.6 mm Hg, 32.3 ± 4.2 mm Hg on placebo, and 29.9 ± 3.3 mm Hg on naproxen (p = NS). The number of TLESRs per 30 minutes in the basal state was 3.5 ± 0.9, 4.6 ± 1.2 on placebo, and 5.8 ± 1.0 on naproxen (p = NS). The speed and duration of contractions were not affected by naproxen. The excluded subject had marked basal reflux (total fraction of time pH < 4 = 10.7%), low LESP (8 mm Hg), and a marked increase in reflux on naproxen (total fraction of time pH < 4 = 53%). *Conclusions:* Naproxen did not induce reflux in normal subjects, although reflux did increase in some subjects. Naproxen had no significant effect on motility parameters. Our data suggest that NSAIDs do not impair the anti-reflux barrier or induce reflux. Pyrosis experienced during NSAID use may not arise from the esophagus or may reflect altered esophageal sensitivity. A single subject with decreased LESP and asymptomatic increased acid exposure in the basal state had a marked increase in reflux on naproxen. This person subsequently developed symptomatic gastroesophageal reflux. The effect of NSAIDs on individuals with a propensity to reflux deserves further study.

INTRODUCTION

Gastrointestinal side effects frequently complicate the use of nonsteroidal anti-inflammatory drugs (NSAID) in clinical practice. NSAID-induced gastric and duodenal ulcers have received the greatest attention, but esophageal complications of NSAID are also recognized. NSAIDs have been linked to the development of benign esophageal strictures and esophageal ulceration (1, 2). Endoscopic investigation of chronic NSAID users has observed the presence of esophagitis in 20% of the users (3). In addition to the life-threatening complications, such as bleeding or perforated ulcers, NSAIDs commonly induce dyspepsia, heartburn, nausea, and vomiting. Up to 50% of subjects report these symptoms in short term clinical trials, and chronic users may experience such symptoms less frequently (4). Mucosal injury correlates poorly with dyspeptic symptoms, and many symptomatic patients have a normal upper GI endoscopy (5).

Symptomatic NSAID users are frequently prescribed H_2 receptor antagonists to control symptoms, despite evidence that standard doses of these drugs cannot prevent NSAID-induced gastric ulcers (6). Recent clinical trials have confirmed the efficacy of cimetidine 400 mg *b.i.d.* in patients with endoscopy-negative NSAID-induced symptoms (7, 8), suggesting a relationship between acid secretion and dyspeptic symptoms. Prostaglandins are known to affect both the lower esophageal sphincter and body smooth muscle (9, 10), so we hypothesized that NSAIDs may induce symptoms by increasing esophageal
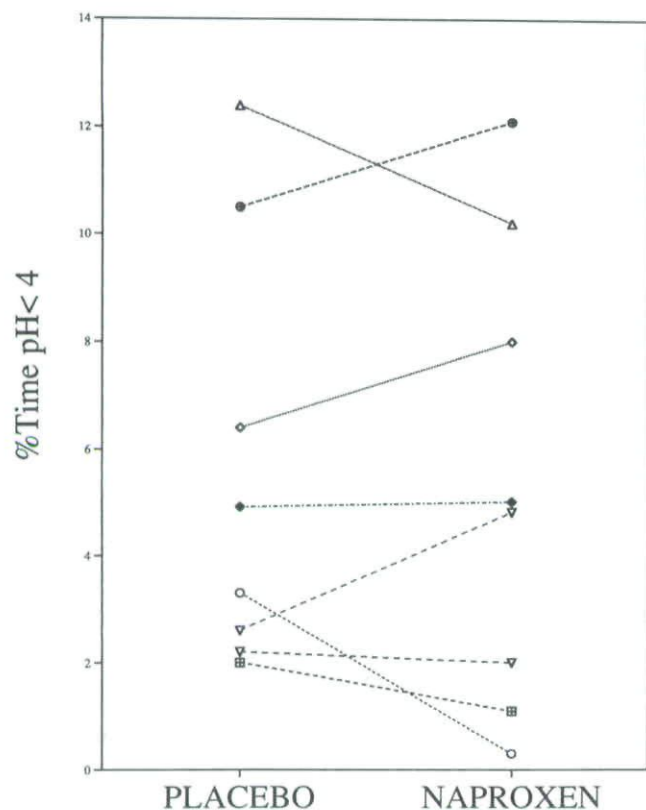
FIG. 1. Esophageal acid exposure time for each volunteer during placebo and naproxen administration. Each data point reflects the percentage of time esophageal pH was less than 4 during each monitored period.

acid exposure, thus explaining the efficacy of acid suppression in ameliorating symptoms.

Detailed studies of the effect of NSAIDs on the esophageal function and gastroesophageal reflux have not been performed. A prior study in humans has demonstrated that a single rectal dose of indomethacin actually increased lower esophageal sphincter pressure (LESP), consistent with animal data that certain prostaglandins, especially PGE_2, decrease LESP (11). Histological studies have suggested that NSAID ingestion may actually reduce the severity of esophageal inflammation in both experimental esophagitis (12) and in rheumatic patients *versus* control subjects (13).

Endoscopic studies confirm that NSAID users have far less esophagitis than gastric or duodenal injury and that local irritative toxicity, not esophageal reflux, is the presumed predominant mechanism of esophageal injury. Cyclooxygenase inhibition could potentially effect the antireflux barrier via effects on either the LES or esophageal clearance mechanisms, so we studied normal volunteers to determine whether a commonly prescribed NSAID, naproxen, taken for 1 wk, could induce reflux or significantly affect esophageal motility parameters.

METHODS

Nine healthy, nonsmoking volunteers (five males, four females), mean age 25 yr (range 23–34), without a past

history of heartburn or intolerance to NSAIDs, were studied. None of the subjects was taking any medication. Subjects who were pregnant, tobacco- or heavy alcohol-users and individuals with recent use of, or allergy to, nonsteroidal anti-inflammatory drugs were excluded.

This study used a randomized, double-blind, placebo-controlled, crossover design. After a basal esophageal manometry study and 24-h pH monitoring, each subject received, on separate occasions 2 wk apart, either placebo or naproxen 500 mg *b.i.d.* for 1 wk.

A symptom diary was completed by all subjects. On day 6 of study medication, the subjects underwent esophageal manometry and placement of a 24-h pH probe. The pH probe was removed within 12 h of last dose of naproxen. After a minimum 2-wk wash-out period, the volunteers crossed over to the other study medication. They returned on day six for repeat evaluation with esophageal manometry and placement of a 24-h pH probe.

Esophageal manometric studies and ambulatory 24-h pH monitoring were performed using standard techniques (14, 15). Contractions were recorded from an 8-lumen polyvinyl catheter with attached Dent sleeve (Arndorfer Medical Specialties, Greendale, WI). The distal four openings were 1 cm apart at 90° angles, and the four proximal openings were at 5-cm intervals. Each lumen was continuously perfused with distilled water at a rate of 0.5 ml/minute from a low compliance, pneumohydraulic capillary-infusion system. The catheter was connected to external transducers with output to a physiograph (Beckman 611, Sensormedics, Anaheim CA). LESP was recorded using the Dent sleeve. Esophageal peristalsis was assessed after 10 wet swallows (5 ml of water given at 30-s intervals). After each swallow, the amplitude, velocity, and duration of esophageal body contractions were measured at 2 and 7 cm above the lower esophageal sphincter. The frequency of transient lower esophageal sphincter relaxations were also recorded over a 30-minute basal period.

The 24-h pH monitor probe (Synectics Medical Inc., Irving TX) was placed 5 cm above the manometrically defined lower esophageal sphincter and was connected to a belt-held computer. The frequency and duration of reflux events were measured. The results were analyzed for percent time pH <4 (total, supine, upright), number of reflux events (total, supine, upright), esophageal clearance time per reflux event (total, supine, upright), and number of reflux events greater than 5 minutes.

Statistical analysis

The effect of naproxen on the 24-h pH monitor and esophageal manometry study data were compared to the placebo data using the Student's *t* test for paired data. A *p* value of <0.05 was considered significant. This research study was approved by the Institutional Review Board at University of Michigan Medical Center.

	Basal	Placebo	Naproxen	p Value
Total % pH <4	4.9 ± 1.0	5.5 ± 1.4	5.4 ± 1.5	NS
Reflux events (total)	57.8 ± 21.3	45.4 ± 11.2	36.1 ± 7.1	NS
Esophageal clearance (total) min/reflux event	1.4 ± 0.4	1.3 ± 0.2	1.5 ± 0.4	NS
Total reflux events >5 min	2.4 ± 0.9	2.1 ± 1.0	2.9 ± 1.2	NS

NS, not significant.

TABLE 2
Results of Esophageal Manometric Studies

	Basal	Placebo	Naproxen	p Value
LESP (mm Hg)	32.1 ± 5.6	32.3 ± 4.2	29.9 ± 3.3	NS
Amplitude (mm Hg)	77.9 ± 16.6	83.4 ± 12.6	91.1 ± 15.0	NS
Duration (s)	2.82 ± 0.2	2.8 ± 0.14	2.9 ± 0.1	NS
Speed (cm/s)	9.32 ± 1.0	7.7 ± 1.3	8.5 ± 1.4	NS
TLESR	3.50 ± 0.9	4.6 ± 1.2	5.8 ± 1.0	NS

NS, not significant.

RESULTS

Twenty-four-hour pH monitoring

No subject developed pyrosis or any other GI symptom on naproxen. A number of months after completion of the study, one of the subjects developed hoarseness and sore throat requiring evaluation. Reflux was felt to be the etiology, and the patient was successfully treated with an H_2 receptor antagonist. This subject was excluded from the analysis, and her studies are described in detail separately. The eight remaining subjects had mild, asymptomatic reflux in the basal state with the total percent of time pH <4 = 4.9 ± 1.0% (upper limit of normal for our laboratory 4%). The total percent of time (pH <4) was 5.5 ± 1.4% on placebo and 5.4 ± 1.5% on naproxen treatment (p not significant). As seen in Figure 1, the total percent time pH < 4 on naproxen for each subject was variable. The number of reflux events, percent of time (pH <4) in the supine or upright positions, and esophageal clearance time were not significantly affected by naproxen use (Table 1). The excluded subject had a markedly decreased LESP (8 mm Hg) and reflux (total fraction of time pH <4 = 10.7%) in the basal state. On naproxen, this subject developed marked asymptomatic reflux (total time pH <4 = 53%).

Esophageal motility studies

Esophageal manometry studies determined the LESP, amplitude, duration, and speed of peristaltic contractions, in addition to the number of transient lower esophageal sphincter relaxations (TLESR) over a 30-minute monitoring period. LESP was 32.1 ± 5.6 mm Hg in the basal state, 32.3 ± 4.2 mm Hg on placebo, and 29.9 ± 3.3 mm Hg (p = NS)

on naproxen. The number of TLESRs in the basal state was 3.5 ± 0.9, 4.6 ± 1.2 on placebo, and 5.7 ± 1.0 on naproxen (p = NS). The speed, duration, and amplitude of contractions were not significantly affected by naproxen (Table 2). There was no relationship between the LESP or number of TLESRs and the results of 24-h pH monitoring.

DISCUSSION

Our data have demonstrated that in healthy normal individuals, 1 wk of naproxen does not induce gastroesophageal reflux or significantly affect parameters of esophageal function. Although prostaglandins clearly are implicated in control of esophageal smooth muscle contraction, different prostaglandin subtypes have been reported to either increase or decrease LESP (9, 11). Animal models of reflux esophagitis have demonstrated that esophageal inflammation is associated with increases in local prostaglandin production, which may contribute to further LES incompetence, an effect blocked by indomethacin (12, 16). Our results in humans suggest that when cyclooxygenase is inhibited, existing overlapping control mechanisms (neural, hormonal) maintain esophageal function. This process may represent the esophageal equivalent to gastric adaptation to NSAID injury in the stomach (17).

If NSAIDs do not appear to effect esophageal motility or induce reflux, is the reflux-like dyspepsia and pyrosis experienced during NSAID therapy, which seems to respond to acid inhibition, due to increased gastroesophageal reflux? Although our acute study in healthy subjects who experienced no symptoms cannot directly address this question, two possibilities are suggested by our results. One subject in our study did experience a large increase in reflux on naproxen, so there may be interindividual susceptibility to the effects of NSAIDs, similar to the case for upper GI mucosal injury. Although there was no relationship between LESP and esophageal acid exposure overall, the subject with marked increased reflux on naproxen had the lowest basal LESP of the study group. Further study of patients who experience pyrosis on NSAIDs and the effect of NSAIDs on individuals with a reflux propensity are warranted.

Another possibility is that NSAIDs may affect esophageal sensitivity to physiological levels of reflux, because acid perfusion or balloon distention of the esophagus can identify individuals with normal pH monitoring who have esophageal symptoms (18, 19). Prospective studies using 24-h pH monitoring and studies of esophageal sensitivity in symptomatic NSAID users and reflux patients are required to answer these questions.

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