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Effects of Oral Calcium Blocker, Diltiazem, on Esophageal Contractions

Studies in Volunteers and Patients with Nutcracker Esophagus

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Animal studies have shown that calcium blocking drugs decrease lower esophageal sphincter pressure and inhibit peristaltic amplitude and duration. In a single-dose acute study, we compared the effects of a new oral calcium blocker, diltiazem (90, 120, 150 mg) with placebo in five volunteers and 10 patients with chest pain/dysphagia and high amplitude peristaltic contractions in the distal esophagus—nutcracker esophagus. In volunteers, diltiazem had no effect on esophageal contractions when compared to baseline values or placebo. In contrast, most doses of diltiazem significantly (<0.05) decreased amplitude and duration of peristaltic contractions in patients with nutcracker esophagus. Despite adequate blood levels, interstudy analysis was not statistically significant because placebo also decreased these parameters. During an eight-week open-labeled study, diltiazem 90 mg QID significantly ($P < 0.01$) improved symptoms of chest pain and dysphagia. Side effects were minimal. Although oral diltiazem has minimal effect on baseline esophageal contractions, our chronic study suggests it may modify transient increases in neuromuscular tone associated with esophageal chest pain. These observations warrant further placebo-controlled studies.

The new calcium channel blocking drugs, verapamil, nifedipine, and diltiazem, relax smooth muscles by inhibiting membrane fluxes of calcium. These drugs have been shown to be potent dilators of coronary and peripheral arteries as well as effective antiarrhythmic agents (1). Since the distal esophagus is primarily composed of smooth muscle, drugs of this class might also be expected to effect esophageal contraction pressures. Animal studies in the opossum (2) and baboon (3, 4) have shown that verapamil and diltiazem strongly inhibit lower esophageal sphincter (LES) pressure and decrease amplitude and duration of contractions in the distal esophagus. These data suggest a potential role for calcium channel blocking drugs in the treatment of esophageal motility disorders characterized by excessive smooth muscle contractions. European studies in humans suggest that nifedipine may be beneficial in the treatment of achalasia (5, 6) and possibly in diffuse esophageal spasm (7). A recent American case report (8) also suggests the

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efficacy of nifedipine in the medical treatment of achalasia.

Despite advances in gastroenterology and pharmacology, the diagnosis and management of patients with chest pain and dysphagia associated with esophageal motility disorders remains a problem. Our group has been extensively studying these patients for the last several years and recently defined a large subset identified by manometric studies as having high-amplitude peristaltic contractions in the distal esophagus; the nutcracker esophagus (9). Patients with chest pain and/or dysphagia having this manometric abnormality account for up to 45% of the esophageal motility disorders encountered in several different laboratories across the United States (10–13). Unfortunately, we currently have no effective medical therapy for these patients. Anticholinergics, nitrates, and tranquilizers have been tried, but without universal success. Esophageal dilatation and surgery have also been advocated, but again with inconsistent results.

The present studies were undertaken to evaluate the effects of the oral calcium channel blocking drug, diltiazem, on esophageal function in normal volunteers and in patients with the nutcracker esophagus. Following manometric studies to assess the effect of a single dose of diltiazem on LES and esophageal peristaltic pressures, an open labeled drug study was performed to monitor prolonged effectiveness and side effects.

MATERIALS AND METHODS

Subject Selection. Studies were performed on five healthy volunteers (five males, ages 30–46), who had normal esophageal motility tracings and no esophageal symptoms, and on 10 symptomatic patients (four males, six females, ages 39–67), who had an abnormal esophageal motility tracing consistent with the nutcracker esophagus. This latter group is defined by the presence of high-amplitude peristaltic contractions in the distal esophagus with mean amplitude induced by ten wet swallows greater than 120 mm Hg (9). Normal mean pressures of peristaltic contractions in the distal esophagus, for our laboratory, are 80 ± 30 mm Hg ($\bar{X}$ ± 2 SD). All patients had suffered from severe recurrent chest pain for at least two years, although only two had chest pains during the actual motility studies. Nine of 10 patients also complained of dysphagia for solids and liquids, while none had frequent heartburn. All had normal upper gastrointestinal x-rays, panendoscopy, and negative Bernstein tests. Cardiac evaluations were variable, but three patients had undergone coronary arteriography which was normal. All patients had been taking long-acting nitrates without consistent improvement. Several had also received anticholinergics, tranquilizers, mercury bougie dilatation and, one patient, nifedipine, without prolonged symptomatic relief. All subjects granted their informed consent for this investigation which was approved by the Institutional Review Board of the National Naval Medical Center, Bethesda, Maryland.

Esophageal Manometry. An eight-lumen polyvinyl manometry catheter (diameter, 4.5 mm; internal diameter, 0.8 mm; Arndorfer Specialities, Inc., Milwaukee, Wisconsin) was used in all studies. The four proximal orifices were spaced at 5-cm intervals and 90° angles while the distal four orifices were at the same level in radial orientation at 90° angles. A low-compliance pneumohydraulic capillary infusion system (Arndorfer Specialities, Inc.) was used for continuous infusion at 0.5 ml/min, giving a pressure rise rate greater than 400 mm Hg/sec (14). Each manometric catheter lumen was connected to a transducer (model 267 BC, Hewlett-Packard Co., Rockville, Maryland) and in turn to a direct-writing recorder (model 7700, Hewlett-Packard).

All subjects were studied after an overnight fast. The manometry catheter was passed through the nose and the patient studied in the supine position. After a 15-min acclimation period, LES pressure was recorded utilizing the distal four radial orifices and the station pull-through technique. The LES pressure recorded for each subject represented the mean of the four individual pressures at midexpiration compared to the gastric baseline. The catheter was then positioned to record from one distal orifice in the sphincter and the four proximal orifices 5, 10, 15, and 20 cm above the sphincter. Ten "wet swallows" (3 to 5-cc water bolus) were administered, each separated by a 30-sec interval, to assess peristaltic activity. Amplitude (mm Hg) was measured from the mean of the esophageal baseline to the peak of the peristaltic wave. Duration of each peristaltic wave (sec) was measured from the initial positive deflection of the peristaltic wave to the return to esophageal baseline. Distal esophageal velocity (cm/sec) was calculated by determining the time between the onset of the rapid upstroke of the waves at recording sites 5 and 10 cm above the LES and dividing it into the 5-cm distance between the sites. The amplitude, duration, and velocity for each subject represented the mean values of 10 wet swallows.

Tracings were read blindly for LES pressure, amplitude, duration, and velocity. Mean values recorded 5 cm above the sphincter are described subsequently as distal esophageal contractions. Group responses were compared to placebo. Statistical analyses were performed using both the Student's t test for paired samples and analysis of variance.

Acute Drug Study. The acute drug study was double-blind and performed on four separate days. On each occasion, after basal manometric measurements, each subject ingested five identical-appearing capsules containing either a sugar placebo or 30 mg of diltiazem (Marion Laboratories, Inc., Kansas City, Missouri) to give a total diltiazem dose of 90, 120, or 150 mg. Measurements of LES pressure and esophageal peristaltic activity were repeated every 30 min for a total of 2 hr. Supine blood pressure in the left arm, supine pulse, and electrocardiographic rhythms strips were obtained prior to the

study and repeated every 30 min in association with manometric measurements. Prior to and at the conclusion of the four studies, routine blood work and urinalysis were obtained. Ninety minutes into each acute study, blood was drawn for diltiazem drug levels for comparison with established therapeutic levels of 50–250 ng/ml. Patients were also questioned about side effects noted during the study and for 12 hr after drug ingestion.

Chronic Drug Study. After completion of the acute study, all patients with the nutcracker esophagus who could tolerate diltiazem were asked to participate in an eight-week open labeled study. This study was designed to evaluate the efficacy of diltiazem (90 mg QID; meals and bedtime) in the treatment of chest pain and dysphagia. Symptoms were assessed weekly by the patients for two weeks prior to therapy and for eight weeks on diltiazem. Symptom scores were recorded and summarized in a diary at the end of each week. Average frequency and intensity of each symptom for the past week was scored using a 6-cm bar graph. From these graphs a symptom "index" was calculated by multiplying the frequency times the intensity of each symptom over the week (maximum potential score = 36). Patients were seen at the beginning of the study, after two weeks on no drug, and after four and eight weeks on drug therapy. During each session patients were examined and questioned about symptoms and side effects. At the end of each four-week drug period, returned tablets were counted to assess drug compliance. Routine blood work, urinalysis, and electrocardiograms were obtained before and at the end of the study period.

RESULTS

Acute Drug Study. For the five normal volunteers, the basal mean amplitude of peristaltic contractions in the distal esophagus was 87 ± 9 mm Hg ($\bar{X}$ ± SE) with a range of 66–101 mm Hg. Over the 2-hr study period, the three doses of diltiazem had no significant effect on amplitude in the distal esophagus whether compared to basal values or placebo response (Figure 1). Likewise, diltiazem did not significantly alter the duration or velocity of esophageal contraction from basal mean values of 3.2 ± 0.8 sec and 3.5 ± 0.4 cm/sec, respectively. Basal mean LES pressure was 18.4 ± 2.1 mm Hg and was not significantly changed by diltiazem or placebo (Figure 2).

Despite the absence of measurable effect on esophageal pressures, adequate serum drug levels were obtained. In all subjects, drug levels were found to be in the therapeutic range after the three doses of diltiazem. Side effects confirming a direct effect on cutaneous and vascular smooth muscle were common. Transient frontal headaches occurred in four of five patients after 120 mg diltiazem and five of five patients after 150 mg diltiazem.

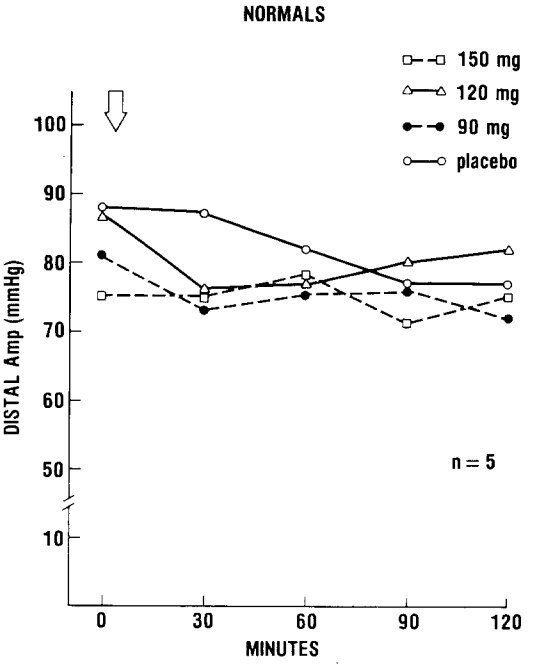

Fig 1. Effects of placebo and diltiazem on amplitude (Amp) of peristaltic contractions in the distal esophagus of normal volunteers. Each point represents mean amplitude in mm Hg. $N = 5$ subjects.

Flushing was observed in three patients after the higher dose schedule. Supine blood pressure, pulse, and laboratory values were unchanged during the studies. Resting electrocardiograms revealed prolongation of PR interval in all patients which did not exceed 0.2 sec. No rhythm disturbances were recorded.

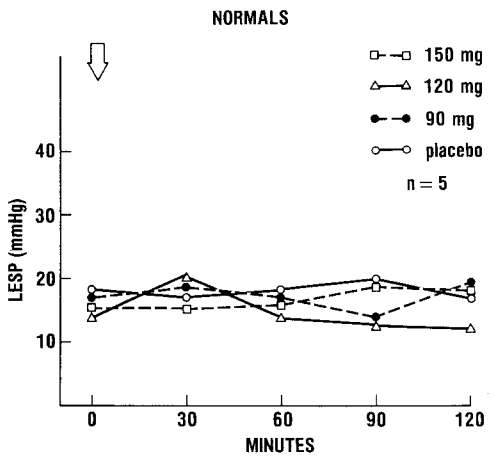

Fig 2. Effects of placebo and diltiazem on lower esophageal sphincter pressure (LESP) in normal volunteers. Each point represents means sphincter pressures in mm Hg. $N = 5$ subjects.

In the 10 nutcracker esophagus patients, the basal mean amplitude of peristaltic contractions in the distal esophagus was 183 ± 22 mm Hg with a range of 128–368 mm Hg. During the four studies, two patients were observed to have isolated episodes of "spasm" activity characterized by simultaneous, repetitive distal esophageal contractions. This activity was brief, unrelated to drug administration, and occurred only once in each patient during a single recording interval. Figure 3 summarizes the effect of diltiazem on the amplitude of esophageal contractions. Placebo had no significant effect on amplitude, but did show a gradual decrease in amplitude over the 120-min study period. Oral diltiazem (90 mg) had its maximal effect on amplitude after 60 min. At that time, peristaltic pressures had decreased significantly ($P < 0.05$) from a basal value of 171 ± 23 to 142 ± 14 mm Hg. The effects of 150 mg diltiazem were more striking and prolonged. Amplitude decreased significantly ($P < 0.01$) from 190 ± 32 to 154 ± 19 mm Hg at 60 min, and this diminution in amplitude persisted for the study duration. Diltiazem, 120 mg, had no effect on amplitude. When compared to placebo controls, however, the diltiazem-induced decline in amplitude approaches, but does not reach, statistical significance at any dose because of the similar decline in amplitude after placebo ingestion.

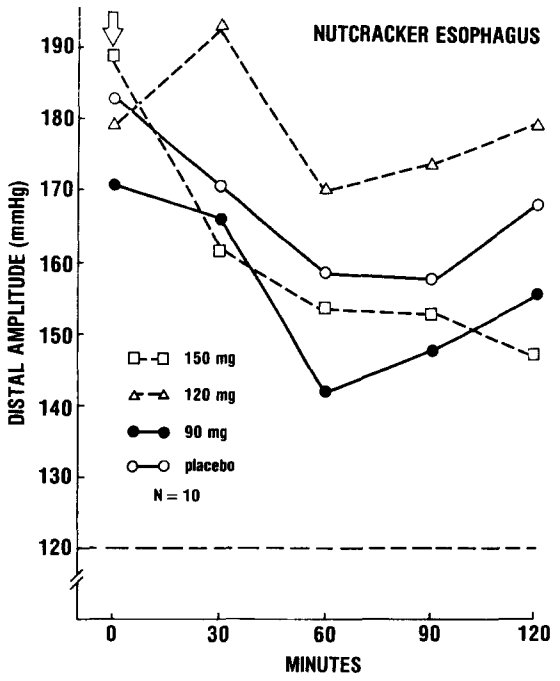

Fig 3. Effects of placebo and diltiazem on amplitude of peristaltic contractions in the distal esophagus of patients with the nutcracker esophagus. Each point represents mean amplitude in mm Hg. The horizontal broken line represents the upper limit of normal for amplitude in our laboratory. $N = 10$ subjects.

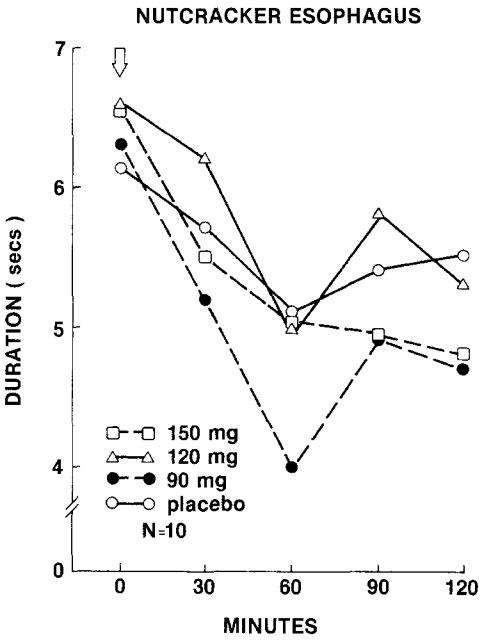

Fig 4. Effects of placebo and diltiazem on duration of peristaltic contractions in the distal esophagus of patients with the nutcracker esophagus. Each point represents mean duration in secs. $N = 10$ subjects.

Diltiazem had a similar although more consistent effect on peristaltic duration (Figure 4). The 150-mg dose of diltiazem had the most striking and prolonged effect on duration. Mean duration decreased significantly ($P < 0.01$) from a baseline of 6.6 ± 0.9 to 4.8 ± 0.4 sec at 30 min, and this shortened duration was maintained for the 120-min study. Diltiazem (90 mg) had a significant ($P < 0.05$) reduction in duration at 60 and 120 min. The 120-mg dose of diltiazem, which did not decrease amplitude, significantly ($P < 0.05$) decreased the duration of distal esophageal contraction at 60, 90, and 120 min (baseline: 6.6 ± 0.7 to 5.3 ± 0.6 sec at 120 min). Here again the decrease in duration by diltiazem did not reach statistical significance compared to placebo, because the placebo also gradually decreased duration, although not significantly. Velocity was not affected by diltiazem at any of the given doses.

The mean LES pressure in the nutcracker esophagus patients, 17.5 ± 2.3 mm Hg, was similar to our controls. LES pressure, like velocity, was unaffected by the three doses of oral diltiazem studied (Figure 5).

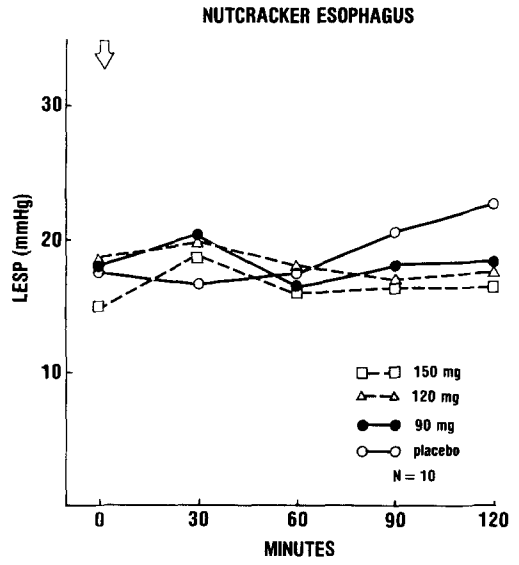

Fig 5. Effects of placebo and diltiazem on lower esophageal sphincter pressure (LESP) in patients with the nutcracker esophagus. Each point represents mean sphincter pressure in mm Hg. N = 10 subjects.

Therapeutic drug levels were obtained at all doses in nine of 10 patients. The last and oldest patient (67 years) had drug levels in the toxic range 90 min after the ingestion of the two higher doses of diltiazem. Either headaches or flushing were experienced by seven of 10 patients at some dose of diltiazem. Supine blood pressure, pulse, and laboratory parameters were unchanged. All patients had a minimal prolongation of PR intervals on their electrocardiograms. Unlike controls, two patients had potentially important arrhythmias. One patient developed a 10-sec sinus pause 90 min after the ingestion of diltiazem (120 mg). The second patient, whose drug levels were in the toxic range, developed transient first-degree heart block after diltiazem (120 mg) and second-degree (Mobitz I) heart block after diltiazem (150 mg) at 60 min into each study. These arrhythmias were unassociated with symptoms or decreased blood pressure and resolved untreated over 10–20 min.

Chronic Drug Study. Nine of 10 patients with the nutcracker esophagus participated in the eight-week open labeled study. The tenth patient was excluded because diltiazem induced cardiac arrhythmias. Seven patients completed the study. One man, who experienced marked symptomatic improvement the first month on drug therapy, dropped out at the end of six weeks after a nine-day hospitalization for "noncardiac" chest pain. The second patient, an alcoholic, experienced intolerable flushing necessitating discontinuation of drug therapy.

Six of seven patients experienced global symptomatic improvement and requested continued drug therapy. Specifically, six of seven patients noted improvement in chest pain frequency and index, while five of six noted similar improvement in dysphagia. As illustrated in Figure 6, significant ($P < 0.01$) improvement in the chest pain index for the group occurred within the first week of initiating diltiazem and persisted unchanged throughout the study. Similar results were seen for chest pain frequency, dysphagia frequency, and index.

Except as previously noted, side effects were tolerable and infrequent. Headaches in three of nine patients resolved in several days without adjustment of diltiazem dose. One patient experienced edema of the hands and feet, requiring low-dose diuretic therapy. No patient complained of syncope, palpitations, or dyspnea. Resting blood pressure, pulse, electrocardiogram, and laboratory data were unchanged.

DISCUSSION

The pathogenesis of chest pain associated with esophageal motility disorders continues to elude our understanding. Since its initial description by Osgood in 1889, diffuse esophageal spasm has been associated with chest pain and dysphagia (15). It is still unknown, however, whether these symptoms are the results of the simultaneous contractions, repetitive waves, high-amplitude pressures, prolonged durations, or some unrelated factor. In support of the latter hypothesis is the observation that similar esophageal abnormalities can be found in healthy subjects without esophageal symptoms (16). In addition, cold-induced chest pain, long attributed to esophageal "spasm," has only recently been shown to result in the decrease and/or total absence of esophageal contractions (17).

In our laboratory, we have described a subset of patients with recurring chest pain and/or dysphagia having a manometric abnormality characterized by peristaltic contractions of excessive amplitude in response to wet swallows (9). We have used the descriptive term nutcracker esophagus to identify this phenomena. Since its initial description, this manometric abnormality has been found with a high prevalence in that group of patients being studied for a possible esophageal cause of recurring chest

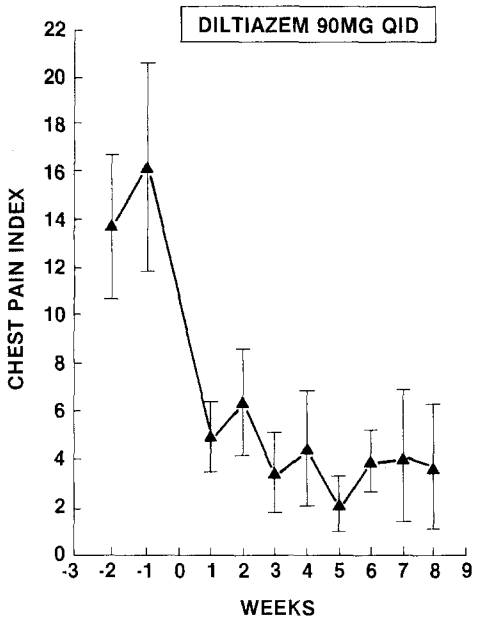

Fig 6. Improvement in chest pain index during the eight-week clinical trial with diltiazem, 90 mg QID. Index score was calculated by multiplying the frequency times the intensity of chest pain over the preceding week (maximum potential score = 36). Significant improvement ($P < 0.01$) occurred within the first week and persists unchanged throughout the study. Each point represents $\bar{X} \pm$ SEM for seven subjects.

pain syndromes. This has been true in our laboratory as well as other laboratories in the country, with an incidence rate up to 45%. It is not clear at this time, however, how this manometric abnormality relates to these patients' recurring chest pain. It is not necessarily the high-amplitude peristaltic waves themselves that are producing pain, for these patients are usually asymptomatic at the time of the manometric study when the nutcracker esophagus is demonstrated. It seems likely that the nutcracker esophagus may represent a manometric "footprint," suggesting a more elusive esophageal motility defect as a cause of pain in these patients. This may even represent a form of what has, for many years, been termed "diffuse esophageal spasm," or that these patients may actually have "spasm" at the time of their chest pain. Much of this is speculative and awaits more long-term manometric monitoring of this group of interesting patients.

Limited by our infant understanding of the origin of esophageal chest pain, it should not be surprising that attempts at treatment of esophageal motility disorders have produced inconsistent results. Anticholinergics, tranquilizers, and bougie therapy have met with minimal success. Nitrates have little effect on esophageal function in normal subjects (18) but may be efficacious in the medical therapy of achalasia (19) or esophageal spasm (20). Hydralazine, which acts primarily on arterial smooth muscles, has recently been suggested for the treatment of painful motility disorders (21). Animal studies in the opossum (2) and baboon (3, 4) have shown conclusively that calcium channel blocking drugs can decrease amplitude and duration of esophageal contractions as well as LES pressure. Several clinical reports have found nifedipine beneficial in the relief of dysphagia associated with achalasia (5, 6, 8). Whether symptom improvement can be attributed to the reduction in LES pressure, decrease in frequency or amplitude of simultaneous contractions, or improved esophageal emptying of a solid meal is unclear. Nifedipine has also recently been found to decrease amplitude of peristaltic waves and the frequency of nonperistaltic contractions in patients with diffuse esophageal spasm (7). The frequency and severity of symptoms were improved but a placebo control was not utilized.

Our current study has attempted to assess the effectiveness of another calcium channel blocking drug, diltiazem, in the treatment of chest pain and dysphagia associated with the nutcracker esophagus. Oral diltiazem, particularly at 90- and 150-mg doses, had a significant effect on the amplitude and duration of esophageal peristalsis compared to pretreatment basal values in this group of patients. This response, however, did not reach statistical significance in interstudy analysis because the placebo control also showed a similar, although not significant, reduction in amplitude and duration over the 120-min study period. We do not, however, believe the placebo is actively inhibiting esophageal contractions. This response has not been observed in previous animal studies (3, 4) or our normal controls, suggesting this effect may be unique to this subset of patients. Emotional tension may be a contributing factor, as we have observed that these patients have personality profiles similar to irritable bowel patients (22). Therefore, our placebo responses could merely represent a slower acclimation to the manometry catheter. This observation reemphasizes the importance of placebo controls and a double-blind study format in this type of acute drug investigation.

The inability of a drug to alter the basal manometry tracing may not, however, preclude its usefulness in treating esophageal chest pain. Prior studies

in our laboratory have shown that approximately 30% of patients with the nutcracker esophagus who are asymptomatic during the baseline manometry study will respond to cholinergic stimulation by intravenous edrophonium with chest pain and a more dramatic abnormality of esophageal pressures, usually simultaneous broad contractions of a "spastic" nature (23). This might also explain why our patients seem to have responded symptomatically to therapy with diltiazem in an open labeled study, although their basal manometric tracings showed a disappointing degree of change in pressure. It is quite likely that their episodic chest pain was related to a more dramatic pressure phenomenon in the distal esophagus which was blunted or prevented by diltiazem.

This hypothesis is supported by the recent study by Mellow using hydralazine as a smooth muscle relaxing agent to treat patients with painful esophageal motility disorders (21). He showed that hydralazine had no significant effect on basal esophageal contraction but did decrease the responsiveness to the cholinergic drug bethanechol. These same patients seemed to respond symptomatically in an uncontrolled clinical trial with this drug. The only other reported clinical study of the effects of diltiazem on esophageal contractions also confirms our observations. LES pressures were not effected by diltiazem, yet six of seven patients with esophageal motility disorders other than achalasia experienced symptomic relief during a six-month drug trial (24). These separate observations suggest that an event associated with increased neuromuscular tone may be occurring transiently in some of these patients at the time of their chest pain.

Other calcium channel blocking drugs may also be effective in the treatment of esophageal motility disorders, but diltiazem may be the best tolerated of the calcium blockers. Verapamil is a potent negative inotropic drug that also depresses conduction in the atrioventricular node and depresses sinus-node automaticity. The drug should not be given to patients with heart failure or serious diseases of the sinus or atrioventricular nodes. Nifedipine is a potent pansystemic arteriolar dilator with no negative inotropic effect at even the highest doses used clinically. Diltiazem has components of both drugs. It slows sinus rate and has a weaker negative effect on cardiac conduction as well as being a more selective coronary artery dilator. The incidence of side effects is lowest with diltiazem (4%) and is as high as 17% with nifedipine (25).

The potential use of calcium channel blocking drugs in the therapy of conditions associated with excessive contractions in gastrointestinal smooth muscle is an exciting prospect. The results obtained in our acute study with diltiazem were somewhat disappointing and indicate that it seems unlikely that a dramatic effect on resting esophageal contractions will be seen with acceptable doses of these drugs. The striking symptomatic improvement in the open labeled trial, however, suggests a beneficial clinical effect and indicates the need for further clinical studies with drugs of this type. Given the effect of placebo on the manometric parameters of esophageal contractions, future studies should utilize placebo controls and double-blind crossover study designs.

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