Cisapride Improves Nicotine-evoked Antral Hypomotility in Smokers

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Summary: It has recently been shown that nicotine administration reduces antral motor function. The aim of this study was to test whether cisapride administration can improve nicotine-evoked antral hypomotility in humans. Eight healthy smoking volunteers were selected for the study. After an overnight fast, manometric recordings and electrogastrographic recordings were performed before and after the ingestion of a mixed solid meal. The measurements (manometric and electrogastrographic protocols) were carried out on two separate days. In each protocol, the measurements were made under three different conditions on three separate days; a placebo day, a nicotine day [nicotine patch (14 mg/day)], and a nicotine plus cisapride day (the nicotine patch and 5 mg cisapride) in a crossover randomized design. The number of antral phase III complexes, antral phase III motility indexes (the sum of the highest of all antral phasic contractions >10 mmHg in 10 min), and postprandial antral motility indexes (the sum of the highest of all antral phasic contractions >10 mmHg for the duration of 30 min) were significantly lower on the nicotine day than on the placebo day (P<0.01, P<0.05, and P<0.01). However, the values obtained on the nicotine plus cisapride day were significantly higher in comparison with those obtained on the nicotine day (P<0.05, P<0.05, and P<0.01) and were similar to those obtained on the placebo day (P=0.92, P=0.79, and P=0.36). The frequency stability index (maximal signal amplitude for a given 2-minute recording segment occurring at a frequency of ≥2 cycle/min and ≤4 cycle/min) was similar on the placebo day, the nicotine day, and the nicotine plus cisapride day in both the fasting (P=0.69) and postprandial periods (P=0.22). These results indicate that (a) transdermal nicotine administration reduces antral gastric motor function without modification of slow wave rhythmicity and (b) cisapride administration improves nicotine-evoked antral hypomotility.

Key words cisapride, electrogastorography, manometry, nicotine

Introduction

Cigarette smoking leads to inhibition of gastric motor activity. In canine models, intravenous nicotine administration reduces gastric and duodenal contractile activity in both fasting and fed states (Carlson et al. 1970). Similarly, recent
human studies have shown that acute smoking decreases antral phase III activity and delays gastric emptying of liquids and solid meals (Muller-Lissner, 1986; Nowak et al. 1987; McDonnell and Owyang, 1989; Miller et al. 1989; Scott et al. 1993). On the other hand, phasic antral motor activity is regulated by an electrical pacemaker located in the proximal gastric corpus (Sarna, 1975). In clinical settings, abnormal pacemaker frequencies, such as tachygastria and bradygastria, are usually associated with impaired gastric motor activity (Telander et al. 1978; You and Chey, 1984; Chen and McCallum, 1992). A recent study has suggested that smoking may also impair gastric electrical activity particularly in subjects without a smoking history (Kohagen et al. 1996). The clinical relevance of the smoking-induced gastric motor function disorder may in part account for the increased incidence of peptic ulcer complications (Piper et al. 1982; McIntosh et al. 1985; Ainley et al. 1986).

Drug therapy is the most effective approach in patients with reduced gastric motor activity. Many studies have shown that cisapride accelerates gastric emptying in patients with various types of gastroparesis or patients with functional dyspepsia (Camilleri et al. 1986; Corinaldesi et al. 1987; Feldman and Smith, 1987; Horowitz et al. 1987a,b; Stacher et al. 1987; Camilleri et al. 1989; Testoni et al. 1990). In addition, cisapride, unlike metoclopramide, appears to be associated with few side effects (McCllum et al. 1988). However, there is no study dealing with the effect of cisapride on the smoking-induced gastric motor function disorder. Although the mechanisms underlying the inhibition of gastric motor function by smoking are not fully understood, Kohagen et al. (1996) have recently shown that transdermal nicotine administration evokes fasting and postprandial antral hypomotility. This finding suggests that transdermal nicotine administration is a useful model to produce the smoking-induced gastric motor function disorder.

The aim of this study was to examine whether cisapride improves nicotine-evoked antral hypomotility in subjects with a smoking history. For this purpose, intraluminal pressures were measured in three different conditions (placebo, nicotine, or nicotine plus cisapride) using a crossover technique in eight healthy smokers. In addition, gastric electrical activity was measured by electropastrography (EGG).

Materials and Methods

Study population

Eight healthy smoking volunteers (five men and three women) with a mean age of 32 years (range; 28-42 years), who had no history of gastrointestinal disease and were not taking any medication, were selected for this study. They smoked at least 1 pack of cigarettes/day (range, 1-2 packs/day). Informed consent was obtained from each patient and the study protocol was approved by the School Ethics Committee.

Study protocol

After an overnight fast, manometric and EGG recordings were performed before and after the ingestion of a 300 kcal mixed solid meal. Each recording was carried out on two separate days.
The details of the techniques are described in the later sections. For each subject, both manometric and EGG recordings were made under three different conditions on three separate days (placebo day, nicotine day, nicotine plus cisapride day), one week apart, in a crossover randomized design. All subjects were asked to stop smoking and drinking alcoholic beverages for at least 36 hs before the study and during the study.

**Manometric protocol:** On the placebo day, a placebo patch was placed on a hairless area of the upper arm three hours before the start of the recording and a placebo tablet was administered one hour before the start of the recording. In the same fashion, a nicotine patch (14 mg/day) (Habitrol; Ciba-Geigy Inc, NJ) and a placebo tablet were administered on the nicotine day, and the nicotine patch and 5 mg cisapride were administered on the nicotine plus cisapride day. Venous blood samples were drawn before and after each study day to determine the plasma nicotine levels.

**Manometric measurements**

Intraluminal pressure recordings were made using three semiconductor strain-gauge pressure sensors mounted 5 cm apart in a pressure probe (model P-31-3005DM59; Synectics Medical Inc, Stockholm, Sweden). Before the recordings, the pressure sensors were calibrated by a pneumatic manometer at 0.0 and 50.0 mmHg at 37 °C. The probe was passed transnasally and placed in the antrum under fluoroscopic guidance. The probe was connected to a portable memory recorder (MicroDigitrapper, Synectics Medical Inc). Fasting motor activity was recorded for 3 hs and postprandial motor activity was recorded for 30 min after the ingestion of the test meal. At the completion of the study, each subject underwent fluoroscopy again to ensure that no significant probe migration occurred during the measurements. The data stored on the recorder was downloaded to an IBM-compatible personal computer. A software program was used for the analysis of the intraluminal pressures. In the fasting period, the number of antral phase III complexes per hour was calculated. Antral phase III complexes are characterized by a 5-10 minute period of intense phasic motor activity that begins in the stomach and propagates through much of the length of the small intestine (Vantrappen et al. 1978). Furthermore, antral phase III motility indexes were also calculated as the sum of the highest of all antral phasic contractions > 10 mmHg in 10 min.

In the postprandial state, antral motility indexes were calculated as the sum of the highest of all antral phasic contractions > 10 mmHg for the duration of the 30-minute postprandial recordings.

**Cutaneous EGG measurements**

The cutaneous EGG techniques are described elsewhere (Lindberg et al.
In brief, three standard silver-silver chloride adhesive electrodes (Cleartrace, Medtronic Andover Medical Inc, Haverhill, Mass) were placed on the upper abdominal wall over the region of the stomach. The first electrode was placed in the midclavicular line below the left costal margin. The second electrode was placed midway between the xiphoid and the umbilicus. A third reference electrode was affixed in the right upper quadrant of the abdomen. Electrodes were connected to a portable memory recorder (Digitrapper EGG, Synectics Medical Inc). The recording device included a one-channel EGG preamplifier, a bandpass analog filter, an analog-to-digital (8-bit precision) converter, and 96 kbyte of memory. The filter had a 1.8- to 12-cpm passband with a roll-off of 6 dB/octave. The EGG signal was sampled at a rate of 4 Hz. Fasting EGG recordings were obtained for 30 min and postprandial recordings were obtained for 30 min after the ingestion of the test meal. Then, the data stored on the recorder was down-loaded to an IBM-compatible personal computer. The software program performed a running power spectral analysis in which fast Fourier transforms were calculated across the frequency range from 0.5 to 10 cycle/min in 2-minute intervals in an overlapping fashion. Each line in the running power spectral analysis plot represented the amplitude of the signal at the different frequencies. Data from the power spectral analysis was imported into a spreadsheet where the dominant frequency was determined by assessment of the largest signal amplitude. If the maximal signal amplitude for a given 2-minute recording segment occurred at a frequency of ≥2 cycle/min and ≥4 cycle/min, the dominant frequency was defined as within the normal range. To provide a quantitative measure of slow wave rhythmic activity, a frequency stability index (%) was calculated in each 2-minute recording segment during both fasting and postprandial periods.

Plasma nicotine determinations
Venous samples for nicotine determinations were drawn before and after each recording, collected in a pre-chilled tube, and centrifuged at 4°C. The plasma was kept frozen at –20°C until the assay. Plasma nicotine levels were measured by a high-performance liquid chromatographic method (Hariharan et al. 1988). The mean coefficient of variation for the plasma nicotine levels was 4%.

Data analysis
The results are reported as mean±S.E. Effects of placebo, nicotine, and nicotine plus cisapride on manometric and EGG variables were compared by means of ANOVA. If this analysis showed a statistical significance, the Schaffer’s test was used for multiple comparisons. Plasma nicotine levels (mean values before and after the study) in the manometric protocol and in the EGG protocol were compared using the Mann-Whitney U test. All data analyses were performed using computer software (StatView, Abacus Concepts Inc, Berkeley, CA). Significance was established at P<0.05.

Results
Manometric protocol
The number of antral phase III
complexes, antral phase III motility indexes, and postprandial motility indexes were significantly different on the placebo day, the nicotine day, and the nicotine plus cisapride day (P<0.01, P<0.01, P<0.01). The number of antral phase III complexes was significantly lower on the nicotine day than on the placebo day (P<0.01). However, the number of antral phase III complexes obtained on the nicotine plus cisapride day was significantly higher than those observed on the nicotine day (P<0.05) and were similar to those obtained on the placebo day (P=0.92). The antral phase III motility indexes were significantly lower on the nicotine day than on the placebo day (P<0.01). However, the antral phase III motility indexes obtained on the nicotine plus cisapride day were significantly higher in comparison with those obtained on the nicotine day (P<0.05) and were similar to those obtained on the placebo day (P=0.79). Similarly, the postprandial antral motility indexes were significantly lower on the nicotine day than on the placebo day (P<0.01). However, the postprandial antral motility indexes obtained on the nicotine plus cisapride were significantly higher as compared with those obtained on the nicotine day (P<0.01) and were not significantly different from those obtained on the placebo day (P= 0.36) (Table 1 and Fig. 1).

**EGG protocol**

In the fasting period, no significant difference in the frequency stability index was found on the placebo day, the nicotine day, and the nicotine plus cisapride day (P=0.69). The postprandial frequency stability index was also similar on the three study days (P=0.22) (Table 1).

**Plasma nicotine levels**

The plasma nicotine levels are summarized in Table 2. On both the nicotine day and the nicotine plus cisapride day, the plasma nicotine levels with the manometric protocol were similar to those in the EGG protocol.

### Table 1.

**Motility parameters obtained on the placebo, nicotine, and nicotine plus cisapride days**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo day</th>
<th>Nicotine day</th>
<th>Nicotine plus cisapride day</th>
<th>P value (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Manometric protocol</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of antral phase III/hr</td>
<td>0.67±0.63</td>
<td>0.29±0.76(^{a})</td>
<td>0.63±0.76(^{x})</td>
<td>0.002</td>
</tr>
<tr>
<td>Antral phase III motility index (min. mmHg)</td>
<td>1168±106</td>
<td>498±150(^{a})</td>
<td>1054±87(^{x})</td>
<td>0.001</td>
</tr>
<tr>
<td>Postprandial antral motility index (min. mmHg)</td>
<td>798±49</td>
<td>416±58(^{a})</td>
<td>693±44(^{y})</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>EGG protocol</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of fasting 3 cpm (%)</td>
<td>74±5</td>
<td>72±3</td>
<td>76±2</td>
<td>0.692</td>
</tr>
<tr>
<td>Frequency of postprandial 3 cpm (%)</td>
<td>82±2</td>
<td>76±2</td>
<td>79±2</td>
<td>0.219</td>
</tr>
</tbody>
</table>

\(^{a}\), P<0.01 vs. placebo day.  
\(^{x}\), P<0.05, \(^{y}\), P<0.01 vs. nicotine day.
Fig. 1. Fasting and postprandial manometric recordings obtained from one subject on the placebo day (upper panel), the nicotine day (middle panel), and the nicotine plus cisapride day (lower panel).

TABLE 2.
Plasma nicotine and cisapride levels obtained on the nicotine and nicotine plus cisapride days

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nicotine day</th>
<th>Nicotine plus cisapride day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Manometric protocol</td>
<td>EGG protocol</td>
</tr>
<tr>
<td>Plasma nicotine level (ng/mL)</td>
<td>11.5±1.4</td>
<td>9.8±0.8</td>
</tr>
</tbody>
</table>

Note: The plasma nicotine levels were zero on the placebo day.

Discussion

Several studies using experimental animal models and human models have suggested that cigarette smoking leads to an inhibition of gastric motor activity (Carlson et al. 1970; Sarna, 1975; Muller-Lissner, 1986; Nowak et al. 1987; McDonnell and Owyang, 1989; Miller et al. 1989; Scott et al. 1993). In this study, in keeping with a recent study (Kohagen et al. 1996), transdermal nicotine administration was found to decrease antral gastric motor activity. Indeed, the number
of phase III motor complexes, antral phase III motility indexes, and postprandial antral motility indexes were significantly reduced on the nicotine day as compared to the placebo day. In contrast, Miller et al. (1989) have shown that the effects of nicotine chewing gum on gastric emptying in humans is minimal. One explanation of this finding, however, may be that the peak plasma nicotine levels are lower and delayed by up to 30 minutes when chewing nicotine gum as compared to smoking (Russel et al. 1976). In this study, the plasma nicotine levels were 11.5±4 ng/mL on the nicotine day and 12.3±1.7 ng/mL on the nicotine plus cisapride day (manometric protocol). These values are similar to those observed in individuals who smoke 1 pack/day of cigarettes (Pomerleau et al. 1989). Thus, the previous (Kohagen et al. 1996) and current observations strongly indicate that nicotine from smoking plays an important role in the inhibition of gastric motor activity.

Phasic antral motor activity is regulated by an electrical pacemaker located in the proximal gastric corpus, which produces slow waves at a frequency of 0.05 Hz (3 cycles/min) (Sarna, 1975). Slow wave dysrhythmias, such as bradygastria and tachygastria, have been reported in patients with antral hypomotility, suggesting a possible pathogenic role in the antral motor dysfunction. This is further supported by a recent experimental study in which glucagon-evoked dysrhythmias and delayed gastric emptying were reversed by electrical pacing of the stomach (Bellahsene et al. 1992). In this EGG protocol, a substantial elevation of plasma nicotine levels was observed on both the nicotine day (9.8±0.8 ng/mL) and the nicotine plus cisapride day (10.3±1.1 ng/mL). Nonetheless, transdermal nicotine administration appeared to have very little effect on gastric slow wave rhythmicity in the healthy smokers. Indeed, both the fasting and postprandial frequency stability indexes obtained on the placebo day were not significantly different from those obtained on the nicotine day. Kohagen et al. (1996) have reported similar results in subjects with smoking histories. These previous and current results therefore indicate that gastric dysrhythmias are not essential for nicotine-evoked antral hypomotility in smokers.

The most important finding in this study was that cisapride improved the nicotine-evoked antral hypomotility. This was supported by the results in which the number of phase III motor complexes, antral phase III motility indexes, and postprandial antral motility indexes obtained on the nicotine plus cisapride day were significantly higher in comparison with those obtained on the nicotine day. Furthermore, these motility variables obtained on the nicotine plus cisapride day were similar to those obtained on the placebo day.

The present study does not give insights into the mechanisms underlying the stimulating effect of cisapride on the nicotine-evoked antral hypomotility. Disturbances in gastric pacemaker potentials have been demonstrated in patients with gastroparesis (Telander et al. 1978; You and Chey, 1984; Chen and McCallum, 1992). Rothstein et al. (1993) has shown that long-term cisapride administration improves both dysrhythmias and delayed gastric emptying in
patients with idiopathic and diabetic gastroparesis. This finding indicates that cisapride ameliorates electrical activity, resulting in the improvement of antral hypomotility in these patients. However, as stated earlier in this article, gastric dysrhythmias are not essential for nicotine-evoked antral hypomotility. Furthermore, both the fasting and postprandial stability indexes obtained on the nicotine plus cisapride day were similar to those obtained on the nicotine day. Thus, it is unlikely that the stimulating effect of cisapride on nicotine-evoked antral hypomotility is due to an improvement of slow wave rhythmicity. Rather, effects on serotonergic pathways are more plausible. According to the results of an in vitro study, cisapride has a blocking effect on both 5-HT1 and 5-HT3 receptors and a stimulating effect on 5-HT4 receptors (Taniyama et al. 1991). Due to these effects, cisapride may stimulate gastrointestinal smooth muscles indirectly via the release of acetylcholine from myenteric nerves (McCallum et al. 1988). Thus, one can speculate that nicotine-evoked antral hypomotility may be due to a stimulating effect on either 5-HT1 and/or 5-HT3 receptors or a blocking effect on 5-HT4 receptors. The precise mechanism will be a subject for future studies.

In conclusion, these results indicate that transdermal nicotine administration reduces antral gastric motor function without modifying slow wave rhythmicity, and that cisapride administration improves nicotine-evoked antral hypomotility. The smoking-induced gastric dysmotility may increase the incidence of complications from peptic ulcers (Piper et al. 1982; Mcintosh et al. 1985; Ainley et al. 1986). Therefore, it would be of interest to determine whether continuous cisapride administration is useful in the prevention of peptic ulcer diseases in the smoking population. This hypothesis should be tested in an appropriate controlled trial.

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