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MANOMETRIC STUDIES ON THE HUMAN PYLORIC SPHINCTER

Effect of cigarette smoking, metoclopramide, and atropine

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Pyloric sphincter pressure was assessed with water-perfused polyvinyl tubes. Smoking one cigarette significantly decreased the basal pyloric pressure, whereas 10 mg of metoclopramide as an intravenous bolus increased the pyloric pressure in normal subjects and in patients with gastric ulcer with low basal pressure. Duodenal acidification with 0.1 N HCl significantly increased pyloric pressure. Atropine 15 μg per kg, subcutaneously prevented the rise of pyloric pressure in response to acid infusion into the duodenum.

Recent manometric studies on the human pylorus have demonstrated a high pressure zone with the characteristics of a sphincter at the gastroduodenal junction. The sphincter pressure showed relaxation with antral peristalsis, increased with intraduodenal perfusion of hydrochloric acid, and is probably important in the prevention of duodenogastric reflux.[1, 2] The similarities between the pyloric sphincter and the lower esophageal sphincter (LES) were stressed by in vitro studies with muscle strips from both regions[3, 4] that showed distinctive inhibitory innervation.

Dysfunction of the pyloric sphincter and increased duodenogastric reflux have been observed in gastric ulcer patients suggesting that this mechanism may be related to the pathogenesis of gastric ulcer (Reference 5, and J. E. Valenzuela and C. Defilippi, *unpublished data*).

Cigarette smoking,[7] anticholinergics,[8] and metoclopramide[9] have been known to modify the LES pressure. Cigarette smoking is associated with a greater incidence of gastric ulcer,[10] and smoking delays ulcer healing.[11] The purpose of these studies was to examine the effect of these agents on human pyloric pressure.

Methods

Pyloric sphincter pressure. To measure the pyloric sphincter pressure three attached polyvinyl catheters (internal diameter, 1.4 mm) with 3-mm side openings separated by 3 cm and with distal radio-opaque markers were used. A fourth catheter with side opening 10 cm beyond the most distal hole was used to perfuse the duodenum. The catheters were attached to pressure transducers (Statham P23D, Hato Rey, Puerto Rico), connected to an eight-channel Gilson polygraph (model M8PM), and perfused with distilled water at a constant rate of 1.1 ml per min by a peristaltic pump (Harvard Apparatus Co., Dover, Mass.) After an overnight fast the subjects were asked to swallow the assembly which was then advanced to the duodenum under fluoroscopic control with an image intensifier and positioned so that all the markers were in the duodenum. With the subjects in the right recumbent position and when stable readings were observed, the tube assembly was withdrawn in 1-cm increments and left in each position 30 sec, until the openings had all passed into the stomach as monitored by fluoroscopy. Intraduodenal pressure was used as a zero reference. The pyloric pressure was measured as the zone of sustained elevated pressure without considering peak phasic contractions. Two withdrawals within 10 min were performed in each subject before and after all of the study conditions. Reported values are the mean of the two determinations. In rare instances, 3 of 26 studies, it was possible to anchor the assembly with the middle opening within the high pressure zone, and simultaneous recordings were obtained from the antrum, pylorus, and duodenum for up to 5 min.

The effect of smoking was studied in 7 subjects. There were 2 females and 5 males with a mean age of 41.3 years (range 22 to 45 years). Five of the subjects had been smoking between 10 and 30 cigarettes per day for the last 3 years, the other 2 were nonsmokers. Three patients had a duodenal ulcer, 1 patient had a benign gastric ulcer on the mid lesser curvature, and 3 had no known gastrointestinal disease. The diagnosis of these and subsequent patients with ulcers was made by radiology, endoscopy, and cytology. The subjects did not smoke for 16 hr before the test. After the measurement of basal recordings the subjects were asked to sit up and smoke one cigarette with deep inhalations in less than 4 min. Pressure measurements were made as soon as possible after the cessation of smoking, usually within 3 min.

The effect of atropine on the increase in sphincter pressure induced by perfusing the duodenum with acid was studied in 5 subjects. There were 4 males and 1 female with a mean age of 38.4 years (range 22 to 62 years). Two had a duodenal ulcer, 1 had dyspepsia of unknown cause, and 2 were normal volunteers. Basal pyloric pressure was measured while 0.15 M NaCl was continuously infused (1.1 ml per min) with a Harvard syringe pump into the duodenum through the fourth most distal catheter. The duodenum was then perfused with 0.1 N HCl at the same rate, and 10 min later the sphincter pressure was again measured. Atropine (15 μg per kg) was then given

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subcutaneously, and 10 min later, while the duodenum was still perfused with acid, a third pyloric sphincter profile was again recorded. The pull-through technique was used in all subjects. However, in 1 subject it was possible to anchor the middle sensor in the pyloric high pressure zone (fig. 1).

The effect of metoclopramide was studied in three groups of patients. The first group consisted of 6 volunteers with a mean age of 38.1 years (range 16 to 59 years). The second group consisted of 4 male patients with benign gastric ulcers on the mid lesser curvature; mean age of 50.0 years (range 35 to 83 years). The third group consisted of 4 patients, all male, with duodenal ulcers and a mean age of 37.2 (range 30 to 45 years). Pyloric sphincter pressure measurements were made in each subject before and 10 min after a bolus intravenous injection of 10 mg of metoclopramide.

All subjects were informed and gave full consent for the studies. The Student's t-test for paired data was used in the statistical analysis.[12]

Results

Cigarette smoking: Basal pyloric sphincter pressures in these subjects were within the range previously reported from this laboratory (table 1).[6] In the small number of subjects studied, there was no relationship between smoking history and basal pyloric pressure (table 1). The mean resting pressure decreased after smoking one cigarette from 10.2 ± 1.2 to 7.9 ± 1.1 mm Hg ($P < 0.05$).

Atropine. Pyloric sphincter pressure during perfusion of saline into the duodenum was 11.4 ± 1.8 mm Hg. The pressure was almost doubled during the perfusion of acid into the duodenum, 20.2 ± 1.8 mm Hg ($P < 0.001$). However, this increase in pressure induced by acid was completely prevented when atropine was given, 9.1 ± 1.3 mm Hg (fig. 1 and table 2).

Metoclopramide. Metoclopramide increased pyloric sphincter pressure in all subjects studied (table 3; fig. 2). In the volunteer group the pyloric pressure was doubled, from 10.2 ± 0.8 mm Hg to 20.0 ± 2.2 mm Hg. The basal pyloric pressure in gastric patients, 6.2 ± 0.8 mm Hg, was significantly lower than normal subjects ($P < 0.05$) and within the range of similar patients previously studied.[6] After metoclopramide the mean pressure increased significantly ($P < 0.05$) almost to normal level 9.3 ± 1.5 mm Hg. Basal pyloric pressure of duodenal

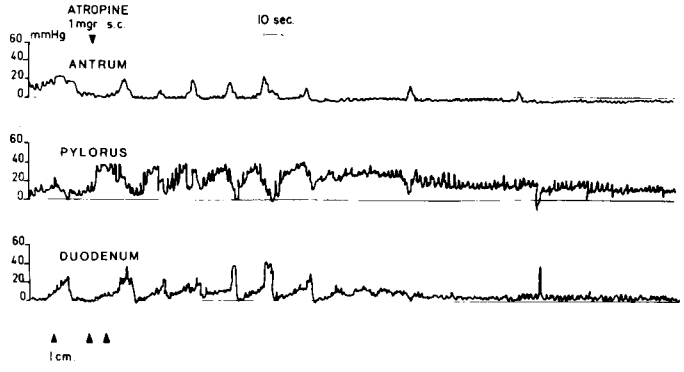

FIG. 1. Effect of atropine on pyloric pressure after 0.1 N HCl infusion, 1.1 ml per min, into the duodenum. Pressure sensors are 3 cm apart, and proximal catheter is recorded on the *upper line*. Fluoroscopic monitoring indicated that the middle opening was positioned at the pylorus. It was possible to anchor middle sensor in the pylorus in this subject. One-centimeter withdrawals are indicated by the *arrows*. Paper speed is shown by the *horizontal line*.

TABLE 1. *Effect of cigarette smoking on the pyloric sphincter pressure on individual subjects*

Subjects	Sex	Age	Diagnosis	Pyloric pressure: Basal	Pyloric pressure: After smoking	Smoking pattern
				mm Hg		
1	M	22	Volunteer	12.3	9.3	None
2	F	32	Volunteer	8.2	7.3	None
3	F	40	Volunteer	10.0	5.0	20 a day
4	M	34	DU[a]	15.0	8.2	30 a day
5	M	40	DU	8.3	11.0	10 a day
6	M	45	DU	12.0	11.0	10 a day
7	F	44	GU[b]	5.6	3.3	10 a day
				10.2 ± 1.2	7.9 ± 1.1[c]	

[a] DU, duodenal ulcer.
[b] GU, gastric ulcer.
[c] Mean ± SEM ($P < 0.05$).

TABLE 2. *Effect of atropine (15 μg per kg subcutaneously) on pyloric sphincter pressure stimulated by intraduodenal infusion 0.1 N HCl (1.1 ml per min)*

Subject	Sex	Age	Diagnosis	Pyloric pressure: Basal	Pyloric pressure: After HCl	Pyloric pressure: After HCl and atropine
				mm Hg		
1	M	34	DU	15.3	21.3	7.3
2	M	26	DU	15.8	34.1	14.0
3	F	22	Volunteer	8.2	15.0	6.6
4	M	62	Dyspepsia	11.2	17.7	9.0
5	M	48	Volunteer	6.4	12.8	8.8
				11.4 ± 1.8[b]	20.2 ± 3.7[b]	9.1 ± 1.3[b]

[a] DU, duodenal ulcer.
[b] Mean ± SEM ($P < 0.01$).

TABLE 3. *Resting pyloric sphincter pressure and effect of metoclopramide (10 mg intravenous) on 14 subjects*

	Resting pressure	10 min after metoclopramide
	mm Hg	
Controls	10.0	17.0
	8.0	26.0
	13.2	23.7
	12.3	14.3
	9.6	25.0
	8.2	14.5
Mean ± SEM	10.2 ± 0.8	20.0 ± 2.2
Gastric ulcer	5.2	6.7
	7.0	12.0
	4.6	6.5
	8.3	12.0
Mean ± SEM	6.2 ± 0.8	9.3 ± 1.5
Duodenal ulcer	7.6	9.3
	15.0	23.0
	8.3	17.3
	12.0	18.0
Mean ± SEM	10.7 ± 1.7	16.9 ± 2.8
Grand mean ± SEM ($P < 0.01$)	9.2 ± 0.8	16.1 ± 1.7

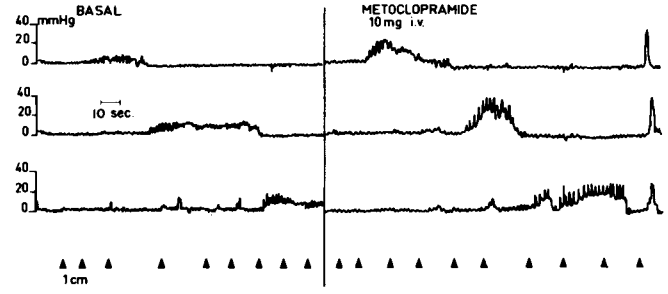

FIG. 2. An example of metoclopramide effect on basal pyloric pressure. On the *left*, the basal pressure is recorded, whereas recordings on the *right* were obtained 10 min after a bolus injection of 10 mg of metoclopramide. Withdrawals, sensors, and speed as indicated in figure 1.

ulcer patients (10.7 ± 1.7 mm Hg) was also significantly increased by metoclopramide to 16.9 ± 2.83 mm Hg ($P < 0.01$).

Discussion

A positive correlation has been found between cigarette smoking and the incidence of peptic ulcer.[10] Bynum et al.[13] suggested that this is due to the reduced bicarbonate secretion by the pancreas caused by cigarette smoking. These findings however do not elucidate the relationship between smoking and gastric ulcer. One of the current hypotheses concerning the etiology of gastric ulcer emphasizes the importance of the increased duodenogastric reflux.[14] Although the mechanisms that prevent duodenal reflux to the stomach have not been fully studied, the presence of a high pressure zone at the pylorus seems important in creating a barrier to duodenal content.[1, 5] Read and Grech[15] using a radiological technique observed that smoking increased duodenogastric reflux in normal volunteers and dyspeptic patients. Our results suggest that smoking-induced decrease in pyloric sphincter pressure may contribute to this reflux. Presumably nicotine is the agent which produces the reduction in sphincter pressure and may act directly or through the release of chemical intermediaries, e.g., catecholamines, histamine, 5-hydroxytryptamine, etc.[16-18]

Anuras et al.[4] did not observe any effect of nicotine on muscle relaxation in in vitro studies from the gastroduodenal junction. They also reported that muscle relaxation was not affected by antagonists of catecholamines and suggested a nonadrenergic inhibitory innervation of the pylorus.[4] A similar neural control mechanism has been proposed for the LES[3] where nicotine in vivo also exerts an inhibitory role.[7] A recent in vivo study[19] on the LES pressure in opossums suggested that nicotine may produce its inhibitory effect by action on the intramural ganglia in the wall of the LES. Further studies are needed to clarify the nicotine effect on the pyloric sphincter.

Atropine produced a prompt fall of the pyloric pressure stimulated by perfusion of duodenum with acid (fig. 1). This atropine effect may be either the result of a direct action on the pyloric muslce or by inhibition of duodenal hormone release. Although the atropine effect was very rapid, and therefore more likely to be a direct effect, the present evidence does not permit discarding other effects. Whatever the mechanism, a similar reduction in pressure after the administration of other anticholinergics used in the treatment of gastric ulcer may enhance the duodenogastric reflux.

Metoclopramide produced an increase in pyloric pressure even in patients with gastric ulcer that had low-resting pyloric pressure. However, the increase in pyloric pressure after metoclopramide in the gastric ulcer patients was of less amplitude than in controls and duodenal ulcer patients. A pyloric sphincter dysfunction has been already reported in gastric ulcer patients.[5, 6] These results might suggest that metoclopramide may be effective in the therapy of gastric ulcer to restore pyloric pressure and decrease duodenogastric reflux. However, this needs to be tested.

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