Rationale for the Use of Anticholinergic Agents in the Management of Duodenal Ulcer

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ANTICHOLINERGIC AGENTS have been recommended for the treatment of every disorder of the gastrointestinal tract, whether functional or organic in origin. The spasmolytic and antisecretory potential of these compounds has led to the assumption that they have a beneficial effect in a wide variety of conditions. Despite their adoption into the physician's therapeutic armamentarium, it must be noted that acute pancreatitis and the watery diarrhea of the irritable colon syndrome are the only gastrointestinal conditions in which general agreement exists about the value of using anticholinergic drugs.[1]

A discussion of the rationale for the use of anticholinergic therapy in the treatment of duodenal ulcer would be simple and of little practical concern if incontrovertible proof existed that these drugs favorably affect the course of peptic ulcer disease. The first question is: Do anticholinergics, used alone or in addition to a regimen of bland diet, antacids, and sedation, shorten individual attacks of duodenal ulcer symptoms and do they speed the healing of the ulcer crater? The second question to be raised is: Does the continued administration of anticholinergic drugs to patients with duodenal ulcer disease reduce the recurrence rate of the ulcer, the incidence of complications such as perforation and hemorrhage, or the percentage of patients eventually requiring surgery? The number of reports dealing with these two questions is legion, but it is obvious that a report by Dr. X stating that 92% of his patients with duodenal ulcer responded favorably to Compound Y does not supply the needed answers. There are only a few well-designed studies where patients with duodenal ulcer disease were randomly assigned to treatment with adequate doses of an anticholinergic agent or to no such treatment. In one such

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recent investigation,[2] treatment with an anticholinergic drug of a small group of patients with healed duodenal ulcer reduced the recurrence rate of ulcer symptoms from 45% to 8% during a 2-year observation period. The majority of investigatiors have, however, come to the conclusion that the value of anticholinergic drugs in the treatment of duodenal ulcer remains uncertain,[1, 3–6] although it cannot be categorically denied.

A few points appear well established:

1. The unit dose in which anticholinergic agents are manufactured, the therapeutic dose recommended by the pharmaceutical houses, and the dose usually prescribed by physicians are far too low to affect gastrointestinal function. In general, gastric secretion is not significantly reduced unless doses are given which cause mild to moderate dryness of the mouth or which are just one dosage increment below the dose causing uncomfortable side effects. This dose is called the optimal effective dose and shows wide individual variations.[7] The optimal effective dose is usually several times higher than the unit dose; this should be established for each patient by a stepwise increase in the amount of the drug until dryness of the mouth appears. Thus, dryness of the mouth is not a side effect, but an indication of effective anticholinergic therapy. In view of the variable dosage which is required to achieve an optimal effective dose, the routine use of drugs combining the unit dose of an anticholinergic agent with a sedative or tranquilizer has no rational basis.

2. Anticholinergic drugs are rather safe and are well tolerated in over 90% of patients.[3] The most frequent complication is urinary retention in men with prostatic enlargement. Glaucoma remains a contraindication to the use of anticholinergic agents, but glaucoma crises are precipitated only rarely by their use. In patients with narrowing of the gastric outlet these drugs are contraindicated, since they may precipitate or aggravate pre-existing gastric retention through inhibition of gastric motor function. There is no evidence suggesting a cumulative effect of, nor the development of tolerance to, anticholinergic agents.[3]

3. Thus far, no synthetic anticholinergic agent has been demonstrated to have a selective ability to suppress gastric secretion. It is not yet possible to exert an anticholinergic effect on the stomach without also producing signs of cholinergic inhibition in other organs.[3, 8] At optimum effective doses, atropine causes greater inhibition of intestinal motility[9] and higher incidence of diplopia[3] than the newer, synthetic agents.

4. It is common clinical experience that anticholinergic drugs often are promptly effective in relieving ulcer pain. This welcome effect may occur without a concomitant reduction in gastric acidity.[3]

Cholinergic activity, mediated by excitation of the vagus, or arising within the intramural ganglia of the gastrointestinal tract, affects most aspects of gastric secretory and motor function.[10] The vagus nerves may be stimulated centrally (e.g., sham feeding response), by hypoglycemia, and by gastric distention. Under the influence of vagal stimulation, gastric motor function becomes more active, and the stomach secretes an increased volume of juice containing large amounts of acid, pepsinogen, and mucoprotein. Vagal activity enhances the amount of gastrin released from the gastric antrum, and it potentiates the action of gastrin and of an intestinal hormone on the parietal cells of the stomach promoting secretion of hydrochloric acid. Cholinergic excitation is the most potent stimulus known for the secretion of pepsinogen from the gastric chief cells.

Theoretically, anticholinergic agents should be able to abolish all these manifestations of vagal or cholinergic activity, but the situation is more complicated than that. As expected, anticholinergics prevent the increase in gastric acid output following injections of cholinergic agents such as Urecholine* and Mecholyl.† But, paradoxically, they have no[3] or only a slight[8, 11] depressive effect, in conventional doses, on two forms of gastric secretory stimulation mediated by the vagus: insulin-induced hypoglycemia and an ordinary meal, both of which produce secretion rich in pepsinogen and acid. The conclusion that can be drawn from these observations is that anticholinergic agents cannot effectively interfere with some manifestations of vagal activity that are caused by endogenous stimulation of the parasympathetic system. Basal gastric secretion, on the other hand, is consistently reduced by anticholinergic drugs, as is secretion following the injection of histamine or Histalog.* There is much evidence to suggest that a therapeutic dose taken at bedtime will suppress nocturnal acid secretion,[3] especially if given together with a dose of an antacid.[4, 12] In patients without gastric outlet obstruction, anticholinergic therapy does not consistently lead to a measurable delay in gastric emptying.[13]

The clinician inquiring about the rationale of anticholinergic therapy for peptic ulcer has but slight interest in the effects that these drugs exhibit in the gastric secretory laboratory under various experimental conditions. He needs to know what these drugs accomplish under the actual conditions of use, that is, in an active patient who is following an ulcer regimen for some period of time.[1, 4] With this question in mind we conducted the study described below.

*Merck Sharp & Dohme, West Point, Pa.
†Eli Lilly and Company, Indianapolis, Ind.

TABLE 1. MEAN VALUES OF GASTRIC SECRETION IN 6 FASTING PATIENTS WITH DUODENAL ULCER ON GLYCOPYRROLATE*

	Basal secretion (1 hr.)				*Post-Histalog (1 hr.)* †			
	Vol. (ml.)	*pH*	*Free acid (mEq./L.)*	*Total acid (mEq./L.)*	*Vol. (ml.)*	*pH*	*Free acid (mEq./L.)*	*Total acid (mEq./L.)*
No drug	122	1.7	32	45	232	1.4	66	90
Glycopyrrolate	51	1.9	20	41	136	1.5	56	86

*Gastric contents were continuously aspirated by hand. One-third of the daily optimal effective dose of glycopyrrolate had been taken by mouth 2 hr. before collection of basal secretion started and 3 hr. before Histalog injection.

†Dose: 0.5 mg./kg. body weight.

METHOD

In 6 patients suffering from a symptomatic recurrence of duodenal ulcer disease the dose of the anticholinergic, glycopyrrolate (Robinul),* which caused mild dryness of the mouth was determined; this varied from 15 to 24 mg. daily, given in 3 divided doses at 9:00 A.M., 3:00 P.M., and 9:00 P.M. This dose was sufficient to reduce the volume of basal gastric secretion and the volume after Histalog injection by about 50%, but it did not reduce gastric acid concentration markedly (Table 1). The patients were then admitted to a metabolic ward, where they received throughout the study a six-meal bland diet (7-10-12-3-5-8), 1 oz. of Gelusil† every hour on the hour between feedings from 7:00 A.M. to 10:00 P.M., and one dose of antacid at 2:00 A.M. The optimal effective dose of glycopyrrolate tablets, divided in 3 daily doses, was given for 3 days and an equal number of placebo tablets for another 3-day period. The sequence of the 3-day drug and placebo period was alternated. The patients were ambulatory on the ward and had an indwelling nasogastric polyvinyl tube (1.8 mm. internal diameter) with its tip in the most dependent portion of the stomach. Hourly aspirations of 3–5 ml. of gastric contents, just prior to the next meal or antacid dose, were performed during the entire period of 6 days. In 5 patients, samples were aspirated every 30 min. on the second day of the drug and the placebo period. The pH of the samples was measured after food particles had been removed by centrifugation at 2000 r.p.m. Mean pH values were calculated by

*A. H. Robins Co., Inc., Richmond, Va.

†Warner-Chilcott Laboratories, Morris Plains, N. J.

conversion of individual pH measurements into milliequivalents per liter of hydrogen ion.

RESULTS

In none of the 6 patients was gastric acidity consistently reduced during the day, but the pH tended to be slightly higher in the evening and night hours during the glycopyrrolate period. The results of hourly aspirations on the hour for the entire study are shown in Fig. 1. For each hour, the p-value of the difference in pH between drug and placebo period was calculated; in no instance did this difference reach statistical significance ($p<0.05$). Figure 1 also reveals that the gastric contents 59 min. after food or antacid intake during the day and also during the night had a pH of less than 3.5 for most of the time. This is of some concern since the activation of gastric pepsinogen to active, proteolytic pepsin occurs mainly between pH 1.0 and 3.5.

The results of the gastric aspirations on the half hour are shown in Fig. 2; pH values during drug and placebo periods were very similar. If glycopyrrolate had caused significant gastric retention of food and antacids at 30 min. after oral intake, consistently higher pH values than during the placebo periods should have been present in these samples taken on the half hour.

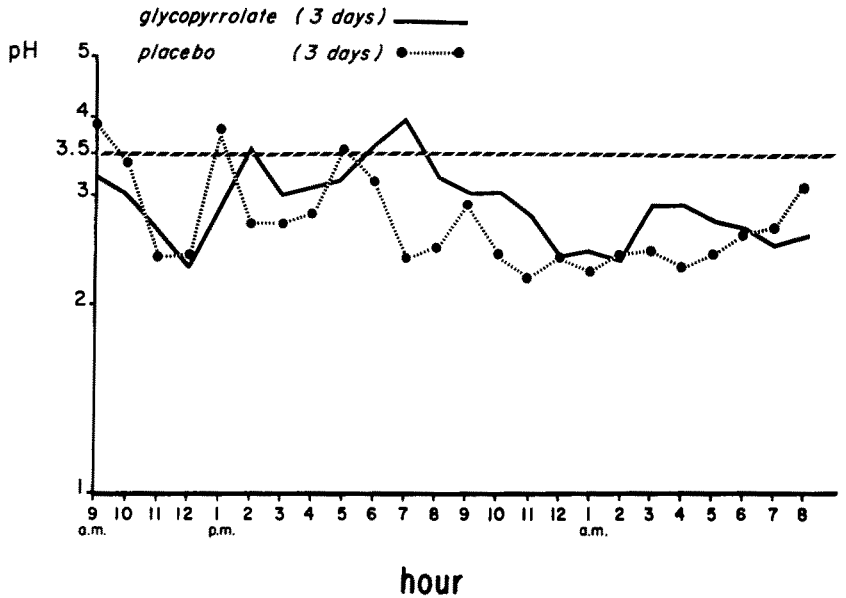

Fig. 1. Mean pH of hourly gastric aspirates in 6 patients during a 24-hr. period.

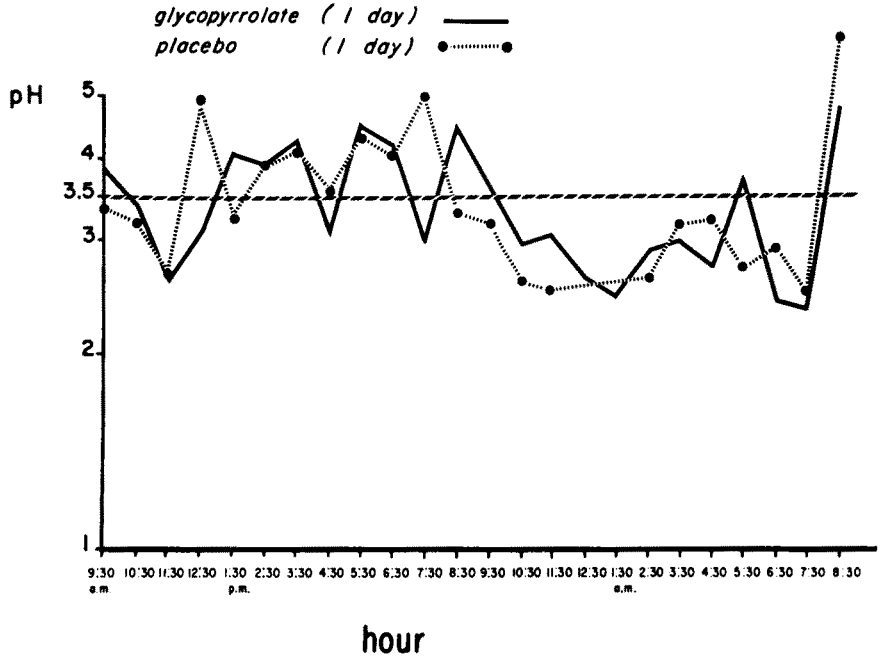

Fig. 2. Mean pH of gastric aspirates on the half hour during a 24-hr. period in 5 patients.

DISCUSSION

The result of this study is not particularly surprising since other potent anticholinergic drugs used in a similar experimental design were equally ineffective in decreasing gastric acidity.[4, 12, 13] Indeed, there is no indication that the addition of anticholinergic therapy to a regimen of regularly scheduled meals and antacids causes an impressive decrease in the acidity of gastric contents in the patient with duodenal ulcer. In one recent report,[8] however, the anticholinergic agent, poldine, caused considerable reduction in gastric acid concentration from 30 to 105 min. after a meal, but the design of this investigation differed from ours. Despite these negative findings, it is entirely possible that under the conditions of actual clinical use, anticholinergic drugs may significantly decrease the volume of gastric juice, with concomitant decline in total acid and pepsinogen[14] secretion. To our knowledge, definite information on these points is not available for any anticholinergic agent. As long as it is not known whether gastric acid concentration, total acid output, pepsinogen secretion rate, or yet another factor is the critical parameter which governs healing and recurrence of peptic ulcer, we cannot draw any firm

conclusions on the clinical usefulness of anticholinergic drugs from experimental studies—no matter how they are devised. This underlines the necessity for more, carefully controlled, long-term clinical studies of large homogeneous patient groups before the role of anticholinergic agents in the therapy of duodenal ulcer can be assessed conclusively.

SUMMARY

There is no standard dose of anticholinergic agents which can be relied upon to affect gastrointestinal function. The optimal effective dose must be established for each patient individually and there is no anticholinergic capable of selective action on the stomach.

Anticholinergic drugs suppress basal gastric secretion and, in many cases, nocturnal acid secretion. Alleviation of ulcer pain by anticholinergics is not consistently related to inhibition of gastric secretion. Under conditions of actual clinical use, they do not decrease gastric acidity but their possible effect on total acid and pepsinogen output remains unknown.

There is no convincing evidence that anticholinergic medication favorably influences the course of duodenal ulcer disease.

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