Management of Peptic Ulcer with Glycopyrrolate

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The therapeutic approach to active peptic ulceration of the upper gastrointestinal tract has altered little in the past generation. The combination of a bland diet with intermeal feedings, antacids given at frequent intervals, appropriate sedation, effective anticholinergic medication coupled with proscription of acid secretagogic substances such as tobacco and alcohol, and adherence to a sensible living pattern, constitutes the usual regimen for an uncomplicated situation.

In recent years, however, critical studies of the various components of this program have given rise to speculation about their relative importance. Some observers have questioned the necessity for a strict diet. Others have reported wide variations in the effectiveness of acid neutralization by the popularly employed antacids. Further, the inherent tendency for the average duodenal ulcer to undergo spontaneous remission complicates the thoughtful clinician's problem of accurately assessing the true therapeutic value of newly released products.

There is little doubt that cholinergic mediation is essential for the genesis of peptic ulcer. Acid production (nonhormonal) as well as gastrointestinal motility, and possibly, parietal cell population are subservient to vagal innervation. Gastrin production by the antrum is at least partly under vagal control, although antral stasis and/or gastric pH above 1.7 assume primacy in this regard.

Renewed interest in the vagal mechanism has been fostered by the demonstration that vagectomy alone is insufficient to control peptic ulcer. The gastric atony and antral stasis resulting from motor inhibition when the vagus is severed leads to stimulation of the antral mechanism, with subsequent gastrin elaboration and further acid production. When resection of the vagus is combined with an adequate drainage procedure, however, antral stasis is minimized and further stimulation of the antral mechanism is avoided. This procedure has proved highly effective.

The development of increasingly potent anticholinergic drugs has nourished the vision of a "medical vagotomy" by which complete control
of the ulcer may be accomplished. This ideal has not yet been achieved. Troublesome, occasionally disabling side effects (mydriasis, xerostomia, urinary retention) and profound inhibition of gastric motility, with resultant antral stasis, have attended use of these agents. It is doubtful that the ileus that would result if anticholinergics were 100 per cent effective would be either beneficial or desirable. Response to a given amount of anticholinergic, also, varies widely from individual to individual as well as from time to time in the same patient. Long-term follow-up studies have failed to demonstrate that anticholinergics reduce the likelihood of complications or recurrences in a significant percentage of patients with ulcer.

Anticholinergic medications, accordingly, are currently held to be a useful, although adjunctive, element in the management of peptic ulcer disease. The ideal agent is one which exerts the maximal acid inhibition with a minimal motor inhibition and does not induce intolerable side effects.

During the investigation of a series of recently synthesized anticholinergic agents, the effectiveness of one drug in particular, glycopyrrolate,* was impressive.

Glycopyrrolate is a synthetic quaternary ammonium compound with marked gastric antisecretory properties and selective action on motor activity of the gastrointestinal tract (Fig. 1).

![Fig. 1. 1 methyl-3-pyrrolyldyl-phenylcyclopentaneglycolate methobromide.](image)

It was chosen for clinical study from among 30 related compounds because of its superior antisecretory action in the Shay rat and its high therapeautic index (the difference between the effective dose and the lethal dose). In these studies, reported by Franko and Lunsford,11 glycopyrrolate was effective when administered by either the oral or parenteral route.

In subsequent studies using the isolated guinea pig ileum and the charcoal meal progression tests, glycopyrrolate was observed to reduce intestinal tone without appreciably affecting the propulsive action of peristalsis.

Experimental and clinical studies with this agent in the management of patients with peptic ulcer are reported below.