FURTHER EXPERIENCE WITH ANTICHOLINERGIC DRUGS:

A Clinical Appraisal in 201 Patients

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THE formation of a peptic ulcer is associated with the action of acid peptic juice. When free hydrochloric acid is absent, its formation is impossible. Conversely, increased free acid secretion is commonly present in patients with duodenal ulcer. Although the ancient Greeks and Romans used alkalies for the treatment of "acid stomach," Sippy[1] was the first to introduce an intensive program of neutralizing the gastric acidity in patients with peptic ulcer. His treatment resulted in a high percentage of healing. Various modifications of Sippy's original treatment using different neutralizing agents and a more liberal diet have appeared, but the basis for the treatment of peptic ulcer—adequate neutralization of gastric acidity—has remained the same.

The physiologic basis for the operations of vagotomy and gastroenterostomy for duodenal ulcer is the fact that patients with these ulcers have increased acidity and secretion[2,3] due to vagal stimulation which can be abolished by section of the vagal nerves to the stomach.[4,5] Since cutting the vagus nerves decreases acidity and secretion, the possibility of medically blocking the vagal impulses as treatment for duodenal ulcer arose. The Sippy program is one of neutralizing the excess acid secreted. The objective of anticholinergic drugs is to suppress and prevent the excess acid secretion.

Tetraethyl ammonium chloride is capable of decreasing gastric secretion and motility and is an effective drug for this purpose. However, it must be given intravenously, the action is relatively brief, and it causes extreme hypotension. The hexamethonium salts are blocking agents, but again have a generalized action that results in prolonged hypotension. The effect of the hexamethonium salts on gastric secretion has been sufficient to cause the British to use them in the treatment of duodenal ulcer, but the hypotension produced made the drug impractical for this purpose. Atropine and belladonna have been used for years but their effect on gastric secretion and motility is minimal even though large doses are given which cause excessive dryness and loss of accommodation.

An anticholinergic drug, Banthine, was made available to us in January 1950 for clinical trial. Longino et al.[6] reported that this drug caused prolonged depression of gastrointestinal motility and usually reduction in volume and acidity of gastric secretions. Smith et al.[7] found that Banthine produced a "marked reduction in the secretion of gastric juice in dogs" and a "marked reduction in the nocturnal gastric secretions of peptic ulcer patients."

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Banthine was given to 117 of our patients with duodenal ulcer.[8,9] Most of the patients were not given antacids or other medications in order to evaluate the effect of the drug itself. Ninety-seven of 117 patients experienced prompt relief that usually occurred within two to three days. Progress roentgen examinations of the stomach were obtained for 69 patients; the crater disappeared in 55 patients and became smaller in five. The symptomatic and roentgenologic responses of these patients suggest that anticholinergic drugs may have an extremely useful function in the treatment of duodenal ulcer.

Kirsner and Palmer,[10] studying the effect of 16 new anticholinergic drugs in producing anacidity, found that Pamine, Win 4369, and Probanthine were the most potent after intragastric administration; partially effective anti-secretory drugs included Antrenyl and Prantal. They stated, "None of the currently available anti-secretory drugs consistently produces an anacidity in man without side effects."

Sleisenger, Eisenbud, and Almy[11] compared the effectiveness of 18 antispasmodic drugs on colon motility as determined by balloon studies. Among the drugs that we have used, they found that Bentyl was variably effective, and that Probanthine, Prantal, and Antrenyl were frequently effective. They found a close correlation between side effects and effectiveness on colonic motility, and suggested that "any anticholinergic drug which clinically has no side effects, probably has no action upon the colon." There have been many other reports on the pharmacology and physiology of these new anticholinergic drugs; it is not our purpose to review these studies.

Because of the results that we obtained with Banthine in 1950, we have been interested in other anticholinergic drugs that might have fewer side reactions and a more specific action on gastric motility and secretion. The purpose of this report is to review our clinical appraisal of some of the new anticholinergic drugs in 201 patients.

RESULTS

Since the introduction of Banthine, a large number of similar and related compounds have been introduced. It has not been possible to study all of them, but we have tried to evaluate clinically a few of the most promising. Since Banthine was an entirely new type of treatment for duodenal ulcer, and since early results appeared promising, we withheld antacids and frequent feedings to evaluate the drug more accurately. Since anticholinergic therapy has already been shown by us and others to be helpful, we did not feel justified in withholding antacids and frequent feedings merely to ascertain the relative merits of different anticholinergic drugs. Because the combination of antacid therapy and frequent feedings[12] is usually an extremely effective treatment of duodenal ulcer, it becomes difficult to evaluate a drug that is added to other treatment. Therefore, realizing these shortcomings, our results are presented as clinical impressions and not as the findings from controlled experiments.

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1. **Pamine (UO-382)*** was supplied to us in 5 mg. tablets (now available in 2.5 mg. tablets). McHardy et al.[13] obtained complete symptomatic relief in 16 and partial relief in 3 of a total of 20 patients given this drug without antacid therapy. Progress x-rays showed the ulcer completely healed in ten, the crater disappeared in four, residual irritability in four, and no change in two.

This medication was given to 40 patients, 34 of whom had duodenal ulcer and 6 of whom had other gastrointestinal conditions. Five patients were given 10 mg. q.i.d. Only one patient of the five tolerated this dose, and he complained of dryness of the mouth. The dose was reduced to 1 tablet (5 mg.) q.i.d. in the four other patients, because they complained of dryness, lack of accommodation, hoarseness and urinary symptoms.

Thirty-nine patients were then given 1 tablet (5 mg.) q.i.d. or 20 mg. a day. Four patients did not tolerate this dose, all had excessive dryness, one had lack of accommodation, one urinary distress and one nausea. Nineteen had some side reactions (dryness in 16, lack of accommodation in 4, and slowness of the urinary stream in 2), but they were able to continue the full dose. Sixteen of the 40 patients had no side effects.

Sixteen patients with duodenal ulcer were given a trial on Pamine alone without any antacids or diet for one to two weeks. Fifteen of the 16 patients obtained complete and one partial relief of their ulcer symptoms. Pamine administration to 18 other patients with duodenal ulcer was supplemented with an hour ulcer schedule,[12] and all obtained complete relief. Progress roentgen examinations were obtained in 15 of the 34 patients and showed that the ulcer crater had disappeared in 11, was smaller in 3, and in 1 patient there was less deformity.

Six patients with other gastrointestinal conditions were given Pamine in the same dosage. Of two patients with ulcerative colitis, one had less diarrhea and the other noted no effect. The drug was helpful to one patient with "hyperacidity syndrome" but not to another. One patient with severe chronic pancreatitis obtained relief, but the side effects were too severe. The sixth patient also did not tolerate the drug.

Our experience suggests that Pamine in a dose of 5 mg. q.i.d. is of considerable help to the patient with a duodenal ulcer, but is of less value in other gastrointestinal conditions. Ten per cent of the patients did not tolerate this dosage, and almost half had minor side reactions but were able to continue with the medication. Five mg. q.i.d. should be an effective dose.

2. **Probanthine (SC-3171)**** was supplied to us in large white tablets of 15 mg. each. It is now on the market in smaller pink tablets of the same dose. A total of 64 patients were given Probanthine. Twenty-three were given a dose of two tablets or 30 mg. q.i.d. which was reduced in five patients because of side effects of dryness, loss of accommodation, slow urination and constipation. Six other patients had similar side reactions which were not too severe and they were able to maintain this dose. Twelve patients had no side reactions.

The remaining 41 patients and the 5 for whom a dose reduction was

Kindly supplied by Dr. Joseph P. Webb of the Upjohn Company.

**We are indebted to Dr. Irwin C. Winter of G. D. Searle and Co. for supplying the Probanthine.*

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necessary were given 15 mg. q.i.d. The medication was stopped for three patients, one because of urinary difficulty and two because of increased stomach distress. Of the remaining 43 patients, 38 had no appreciable side reaction, while 5 complained of some dryness and urinary difficulty, but were able to continue with the full dose.

Of the 64 patients given Probanthine, 40 were patients with duodenal ulcer. Eight patients were given Probanthine alone without antacids and interval feedings for a short time, and seven obtained relief on Probanthine alone. Thirty-two patients were given this drug in addition to the regular ulcer schedule;[12] 30 of these improved symptomatically, while 2 thought the medication made their gastric symptoms worse. Progress roentgen examination in 21 patients showed the ulcer crater had disappeared in 16, was smaller in 2, had persisted in 2, and in 1 patient there was less deformity.

Probanthine was used in 24 patients with other conditions. It relieved eight of ten patients with "hyperacidity syndrome" but without a demonstrable ulcer. It was helpful to one patient with hypermotility and decreased the ileal discharges in one patient with an ileostomy. One patient with regional enteritis noted less diarrhea, but two patients with chronic ulcerative colitis and one with extensive lymphosarcoma of the small intestine noted no change. Four patients with irritable colon, one with dysmenorrhea, one with chronic pancreatitis, and two with dumping syndrome, thought the drug was helpful. It was of questionable value to one patient with gastric crises.

The preceding results suggest that Probanthine may be a useful adjunct in the treatment of duodenal ulcer and some other gastrointestinal conditions. Eighteen of 23 patients tolerated 30 mg. q.i.d., and only minimal side reactions were noted with 1 tablet or 15 mg. q.i.d. Six to eight tablets daily should be an effective dose with minimal side reactions for most patients.

3. Prantal* was originally supplied in 50 mg. tablets. A dose of 50 mg. q.i.d. proved ineffectual, and the size of the tablets was increased to 100 mg. Sixty patients were given Prantal. Five patients tolerated two tablets or 200 mg. q.i.d. without serious side effects. The remaining 55 patients tolerated 100 mg. q.i.d. with minimal reactions. The drug had to be stopped in only four patients because of excessive dryness in two, slowness of urination in two, and increased gas and bloating and "choking" in one each. Six other patients complained of minimal side reactions consisting of the same symptoms, but were able to continue with the medication.

Of the 60 patients given Prantal, 50 had duodenal ulcers. Only 3 of these 50 were given the drug alone without antacids, but they all obtained relief. Three patients obtained no relief on both Prantal and an hour ulcer schedule, and all required surgery; the duodenal ulcer perforated in one of the three patients while he was on Prantal. Four patients obtained only partial relief on both Prantal and routine ulcer management, and all believed Banthine was

Kindly supplied by Dr. Edward Henderson, the Schering Corp. Most of the patients given Prantal were treated by E. N. Collins, M.D., J. A. Ecker, M.D. and H. S. Bennett, M.D. of the Department of Gastroenterology. We are grateful to them for permission to include these patients in this report.

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more effective. The remaining 40 patients obtained relief on both Prantal and the intensive ulcer schedule.[12] Progress roentgen examinations were obtained in 37 patients, and showed the ulcer crater had healed in 23, was smaller in 4, and had persisted in 7. In three patients there was less deformity. The crater had not healed in two months in 11 of the 37 patients in whom we were able to obtain progress x-rays.

Prantal was given to ten patients with other gastrointestinal conditions, and was helpful in four of five patients with "hyperacidity syndrome," one with hypersalivation, and in one patient with ulcerative colitis. It was of no aid to one patient with an irritable colon, one with hypersalivation, and one with a severe gastric neurosis.

Only three patients were given Prantal alone without antacids or other treatment, so that evaluation of the drug is difficult. The drug caused few side reactions and was well tolerated in a dose of 100 mg. q.i.d. We did not feel it was as effective in the dosage used as were Pamine or Probanthine. Three patients required surgery despite Prantal, and the ulcer persisted in 11 of 37 patients who had progress roentgenograms. Possibly a greater dose (i.e. 200 mg. q.i.d.) would be more effective.

4. Antrenyl* was supplied in 5 mg. tablets. Eight patients (seven with duodenal ulcer) were given this drug. Seven patients tolerated 4 tablets q.i.d. while one patient tolerated 2 tablets q.i.d.

Six of the seven patients with duodenal ulcers obtained relief, four on Antrenyl alone and two on Antrenyl plus antacid therapy. The seventh patient who had a penetrating ulcer did not obtain relief and required surgical intervention. The ulcer crater disappeared in two months in the six patients who continued medical treatment. One patient with a hiatus hernia and short esophagus, who also required surgery, discontinued Antrenyl because of increased nausea.

This is a very small series, but suggests that Antrenyl may be a useful anticholinergic drug. It partially corroborates the report of Rogers and Gray[14] who found a favorable response to Antrenyl alone in 24 patients with duodenal ulcer.

5. Win 4369** was supplied in tablets of 5 mg. Of nine patients given the drug, three tolerated 6 tablets a day, while six tolerated 4 tablets a day. Three patients with duodenal ulcer obtained relief, two on Win 4369 alone. The crater disappeared in two patients for whom progress roentgenograms were obtained. Two patients with irritable colon, one with regional enteritis and one with ulcerative colitis noted some improvement on the drug. One patient with unexplained diarrhea and one with ulcerative colitis had no decrease in diarrhea. There are suggestions in the few patients studied that Win 4369 may be a useful anticholinergic drug.

6. Bentyl†, 10 mg. capsules, was used in 20 patients. We could observe

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no effect in eight patients with duodenal ulcer who were given this drug for short periods, so we discontinued its use in these patients. Seven patients with irritable colon syndrome obtained some relief on the medication, and felt it was better than tincture of belladonna. Chamberlin[15] and Collins[16] have believed it to be helpful in some patients with irritable colon. It appeared to us that this drug was relatively impotent in patients with duodenal ulcer, but may be of some value in patients with irritable colon syndrome. We believe, however, that more potent antispasmodic drugs are available.

DISCUSSION

A number of new anticholinergic drugs have been used clinically and appear to be effective and important adjuncts in the treatment of duodenal ulcer. Pamine seemed to be the most effective in a dose of 5 mg. q.i.d., but was associated with minimal side reactions in more than half of the patients. Results with Probanthine were almost as satisfactory, and patients on this drug had fewer side reactions than those on Pamine. Fifteen of 16 patients with duodenal ulcer on Pamine alone and seven of eight patients on Probanthine alone obtained symptomatic relief. Although fewer side reactions were obtained with Prantal in a dose of 100 mg. q.i.d., the results were less favorable than those obtained with Pamine and Probanthine for the ulcer crater persisted in 11 of 37 patients treated with Prantal. Antrenyl and Win 4369 showed promise, but they were used in only eight and nine patients, respectively. We could see no particular benefit from Bentyl.

The newer anticholinergic drugs studied seemed to cause fewer side reactions than Banthine, and they did not have the bitter taste of Banthine. No serious reactions were observed. The side reactions noted were similar to those caused by Banthine, and consisted of excessive dryness of the mouth, lack of accommodation, hoarseness, difficulty in urination with slowness of the urinary stream, and constipation. Occasionally a patient complained of some decrease in libido. The drugs rarely caused an increase in the patient's symptoms with more gas and bloating.

Dose. The dose of the anticholinergic drug that is effective in decreasing gastric acid secretion and motility may be the same dose that causes minimal side effects. We believe, therefore, that the proper dosage for each patient must be individualized. Only by causing minimal side effects can one be sure the patient is getting a dose adequate to decrease acid secretion and motility. We believe adequate dosage is most important, and our poorer results with Prantal may have been due to an inadequate dose of the drug. Suggested doses that one should strive for with these drugs are: Pamine—5 mg. or two tablets q.i.d., Probanthine—30 mg. or two tablets q.i.d., Prantal—200 mg. or two tablets q.i.d. All patients will not tolerate these doses, and the number of tablets taken daily may have to be decreased. It must be remembered also that some patients can tolerate a greater dose after they have received the medication for one to two weeks, than they can at the onset of treatment.

Contraindications. The contraindications to other anticholinergic drugs

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are the same as those to Banthine, namely: (1) Bladder neck obstruction. We have seen several patients develop acute urinary retention with these medicines. Due to a decrease of bladder motility and tone, these drugs can convert a partial bladder neck obstruction into a complete acute obstruction. (2) Coronary insufficiency and cardiac decompensation. These drugs increase the heart rate, and so may increase the frequency of anginal attacks in patients with coronary insufficiency. A physician-patient of mine noted a definite increase in the frequency of his anginal attacks whenever he attempted to take any of these medications for a penetrating ulcer. Under proper supervision, many cardiac patients may tolerate the medication. (3) Glaucoma. These medications cause changes in accommodation. (4) Achalasia and (5) Pyloric obstruction. These drugs decrease gastrointestinal motility and should not be used in such cases until the obstruction is relieved by other measures.

Indications

Ulcer. The chief indication for anticholinergic drugs is duodenal ulcer. While withholding antacids and using these drugs alone is helpful in evaluating the medicine, we do not advise such a practice in the routine treatment of patients. The antacid therapy of peptic ulcer is well founded and is effective. We believe that the best treatment for an active ulcer is a combination of an intensive hour ulcer schedule as outlined elsewhere[12] and anticholinergic drugs. Anticholinergic therapy will not eliminate the necessity for surgery in patients with complicated duodenal ulcer, such as organic obstruction, perforation and repeated hemorrhage, but their use with conventional treatment has in our hands considerably decreased the number of patients referred to the surgeons. Anticholinergic drugs do not replace adequate medical treatment for duodenal ulcer, but are useful supplements and adjuncts.

Other Gastrointestinal Conditions. Other gastrointestinal conditions have responded less satisfactorily to anticholinergic treatment, but have shown some response. Some patients with irritable colon have reacted favorably. Some patients with regional enteritis and ulcerative colitis have had less diarrhea and cramps on the drug, while others have noted no improvement. Two patients with chronic pancreatitis have been helped considerably, one patient returning to work for the first time in 12 months. Patients with a "hyperacidity syndrome" (i.e. a typical ulcer story but with no demonstrable ulcer) have responded well. The use of the drugs in severe biliary dyskinesia, biliary colic, and severe dumping syndrome should be considered. The drugs are of little value in patients with a "gastric neurosis" or bowel fixation.

Urology and Anesthesia. There are a few conditions outside of the gastrointestinal tract in which these drugs may be helpful. Engel[17] has found them helpful in patients with irritable bladders and certain types of cystitis. He has found that frequently they will relieve the pain of ureteral colic caused by ureteral calculus, and may relax the ureters sufficiently to allow the stone to pass without causing any further pain. O'Malley and Owens[18] have reported

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a beneficial effect of Banthine in patients with enuresis. Wasmuth and Hale[19] have reported Banthine given intravenously decreased the nausea and vomiting and increased the pulse rate in bradycardia associated with spinal anesthesias. Patients with hyperhydrosis or hypersalivation can expect some relief from these drugs.

As Kirsner and Palmer[10] have pointed out, the ideal gastric anti-secretory drug is not available at the present time. Nonetheless, we have at hand now drugs that are capable of affecting gastric acid secretion and profoundly affecting gastrointestinal motility. The relatively inert compounds previously available cannot be compared with the group of new anticholinergic drugs. These medicines still have a rather wide range of action. If drugs can be devised that are more selective in action (i.e. that affect the stomach, but cause no dryness, or changes in the eye or colonic and bladder motility, or that affect acid secretion of the stomach but not the motility and vice versa) many clinical problems will be solved. The anticholinergic drugs available at the present time, however, are more selective in action, have a much greater effect on the gastrointestinal tract, and have a wider clinical application than any previously available medicine.

SUMMARY

Clinical experience with six new, anticholinergic, antispasmodic drugs in a total of 201 patients has been reviewed. In the doses used, Pamine and Probanthine were the most effective in patients with duodenal ulcer. These drugs are regarded not as substitutes to routine ulcer therapy, but as extremely useful adjuncts. With the use of these drugs the number of patients requiring surgery has decreased. Suggested dosage, indications, and contraindications of the anticholinergic drugs are discussed. It is hoped that in the future similar compounds with even more specificity of action will be available.

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