A NOTE ON THE USE OF ANTICHOLINERGICS IN THE MANAGEMENT OF DUODENAL ULCERATION*

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SUMMARY

There is at present no good evidence that anticholinergic drugs, which cost the patient a lot of money, either (i) hasten the relief of the symptoms caused by a duodenal ulcer, (ii) promote the healing of the ulcer, or (iii) lessen the chances of the ulcer recurring or developing complications.

Duodenal ulceration is a common disease; and, if the patient is to adhere strictly to the treatment recommended by most doctors—a bland diet and the taking of alkalis, tranquillizers and anticholinergic drugs for periods which may vary from a few weeks to several months—an expensive one. It is, however, the experience of doctors that many patients with duodenal ulceration do not carry out their instructions to the letter, and yet the pain disappears. One of the reasons why patients default from the doctor's instructions is the cost of the drugs. Anticholinergic drugs, and alkalis which contain anticholinergics, are expensive remedies, and in this age of escalating cost-of-living, it seems necessary to review critically the continued use of a drug which may not have fulfilled its original high expectations.

It is interesting how the anticholinergic drugs achieved their present place in the treatment of duodenal ulceration: Belladonna ('a handsome woman') has been known since the early sixteenth century, and it was a favourite method of poisoning in the Middle Ages because of the obscure symptoms produced by chronic administration.[1] During the 18th and 19th centuries it was frequently used for cosmetic reasons, and sometimes as a practical joke: 'Wonderful is the power of the root, for if 1 drachm of it, roughly bruised, be macerated in wine and strained, then anyone who partakes of this on an empty stomach is totally unable to eat anything afterwards . . . It is a great joke to give this wine to some hungry sponger and then place him at a well-spread table, for owing to the dryness of his mouth and throat he is quite unable to eat anything'.[2] Atropine, so named by Linnaeus and derived from the eldest of the three Fates—'Who cut the Thread of Life' was isolated by Mein in 1831.[3] Belladonna and atropine were introduced into clinical practice about 1860 and were recommended for the treatment of peptic ulceration in the latter part of the last century and the earlier part of this century. But the use of these drugs later fell away because of the side-effects which most patients found unpleasant.

The revival in the use of anticholinergics in duodenal ulceration started in 1943 when Dragstedt and Owens[4] reported favourable results in the management of chronic duodenal ulceration by the simple procedure of dividing the vagi above the diaphragm. Soon afterwards, the drug methantheline (Banthine)—the first of a long line of synthetic anticholinergics, each with a reportedly more selective action upon the gastro-intestinal tract—became available. Grimson *et al.*[5] reported a trial in which 100 patients with peptic ulcer were given methantheline and followed up for a year. They were impressed with the drug and concluded that 'early experiences indicate that by its use most patients having serious disability from ulcer can avoid surgical operation'.[1] This original report received wide-spread recognition and support. Hall *et al.*,[6] for example, found that methantheline 100 mg given every 6 to 8 hours, reduced the average 'disappearance time' of a duodenal ulcer from 33·7 to 14·4 days, while McHardy *et al.*[7] reported that the symptoms of patients given this same anticholinergic disappeared sooner than those of patients not receiving the drug.

These initial clinical reports were augmented by many experimental observations which lead to a rationale for the use of anticholinergics in peptic ulceration: 'In a series of studies during the past 25 years, we have collected the evidence to substantiate the concept that the pathologic physiology of peptic ulcer is mediated through the dorsal vagus nuclei and nerves. The data seem to establish the following: (*i*) sham feeding (vagal phase) produces a high volume of secretion in duodenal ulcer; (*ii*) the nocturnal secretion (vagal in origin) is high in duodenal ulcer; (*iii*) insulin hypoglycaemia which stimulates the dorsal vagus nucleus is followed by high volume, acidity, and pepsin in ulcer patients as compared with normals; (*iv*) the chemical phase of gastric secretion is not increased in ulcer; (*v*) persistent free acid after gastric resection for duodenal ulcer is due to continued transfer of stimuli through the vagi; (*vi*) vagotomy added to resection increases the incidence of post-operative achlorhydria'.[8]

The evidence for the use of anticholinergics in patients with duodenal ulceration was further strengthened by the persuasive report of Sun.[9] He conducted two trials. In the first, 25 patients treated with tricyclamol were compared with 20 patients receiving a placebo, treatment in all other respects being similar. Whereas 6 of the patients receiving the placebo developed complications, only 2 of those on tricyclamol developed complications. In the second trial, 20 patients given 1 mg glycopyrrolate 3 times per day before meals, were compared with 17 patients receiving a similar but inert tablet. The two groups were similar in age, sex, length of history of symptoms, previous complications and need for hospital treatment. During a period of 18 months, 12 of the 17 (71%) patients given the placebo experienced recurrences, whereas only 3 of the 20 (15%) patients on glycopyrrolate had further symptoms. Combining the results of these two trials, Sun noted that 7% of the patients receiving the anticholinergics developed complications compared with 43% of the patients given the placebo tablets. He therefore advised the long-term use of anticholinergics by patients with duodenal ulceration.

The opinion of Sun was widely accepted and anticholinergics became firmly established in the management of duodenal ulceration. Not only was it believed that these drugs brought about the rapid relief of ulcer symptoms

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and promoted the healing of duodenal ulcers, but there was also evidence proving that these drugs reduced the tendency of duodenal ulcers to relapse.

While these clinical trials were in progress, physiologists were observing the effects of anticholinergics on gastric function. There is general agreement that: (*i*) dose for dose anticholinergics are more effective when given by injection than when taken by mouth; (*ii*) there is a great variation in the response of the individual patient to a given anticholinergic: in some patients these drugs bring about a marked lowering in the amount of acid secreted in response to histamine or food, but in other patients acid secretion remains virtually unchanged; (*iii*) for any noticeable effect on gastric-acid secretion to occur, the dose of the anticholinergic should be so adjusted that the patient experiences side-effects (it was claimed that the newer anticholinergics were more selective in their action and free of side-effects, but it was concluded that 'the action of these substances is essentially similar and claims for a selective effect on the gastro-intestinal tract are unsubstantiated. Side-effects similar to those of atropine may be produced and, like atropine, these drugs do not appear to have any significant antisecretory action under the ordinary conditions of use'[10]); (*iv*) the motility of the stomach is reduced, and consequently there is a delay in gastric emptying; and (*v*) pepsinogen secretion is reduced more or less in parallel with acid secretion.

The amount of acid (mEq) secreted by the stomach is a product of the volume of the juice secreted and the concentration (mEq/litre) of acid in that juice. In a person with a normal gastric mucosa there is a close correlation between the volume of gastric juice secreted and the mEq/litre acid in the juice: the greater the volume, the greater the concentration of acid. In a patient with gastritis this relationship is disturbed and the concentration of the juice secreted is reduced much more than the volume,[11] i.e. it is the quality of the juice that suffers. The opposite happens after the administration of anticholinergics: the volume is much depressed whereas the concentration is only slightly reduced (Fig. 1), i.e. the quality is maintained, but the quantity is diminished. Pepsinogen activation can still take place. In an exceptional patient, anticholinergics may have such a profound effect on gastric-acid secretion that achlorhydria results.

There is still a tendency among doctors not to distinguish between, on the one hand, *relief* of the symptoms produced by an ulcer, and, on the other hand, the *healing* of the ulcer causing those symptoms. Most patients with uncomplicated duodenal ulcers find that their bouts of ulcer symptoms last between one and two weeks, whereas the ulcers take many weeks to heal. Because this distinction is not always made, treatment which was given for relief of ulcer symptoms is continued until such time as the ulcer has healed, i.e. an unnecessarily long period. It is at present believed that treatment aimed at obtaining relief of ulcer symptoms—alkalis, tranquillizers and dietary advice—do not influence the tendency for duodenal ulcers to heal. Bed rest may be the exception. The advantages of persisting with treatment until a duodenal ulcer has healed have been questioned.[12] Long treatment also increases the expenses of a patient with a duodenal ulcer.

In principle the management of a duodenal ulcer consists of measures aimed at (*i*) relieving the patient's symptoms as rapidly as possible, (*ii*) healing the ulcer as soon as possible, and (*iii*) preventing the ulcer from recurring after it has healed. What does the evidence at present available suggest the role of anticholinergics to be in each of these three aspects of duodenal ulceration?

Cayer[13] reinvestigated the original claim by Sun that the continuous administration of anticholinergics reduces the recurrence rate of duodenal ulceration. He divided a group of 116 patients into 4 sub-groups, giving them each day either 400 mg methantheline, 120 mg propantheline, 1·6 mg atropine, or a placebo. The study was done on a blind basis and the drugs did not cost the patient any money. Cayer noted that the tendency to recurrence and the development of such complications as haemorrhage, perforation or obstruction was the same in the 4 groups. Similar conclusions were reported by Trevino *et al.*[14] They repeated Sun's observation with glycopyrrolate. A group of 151 patients with duodenal ulceration was given either

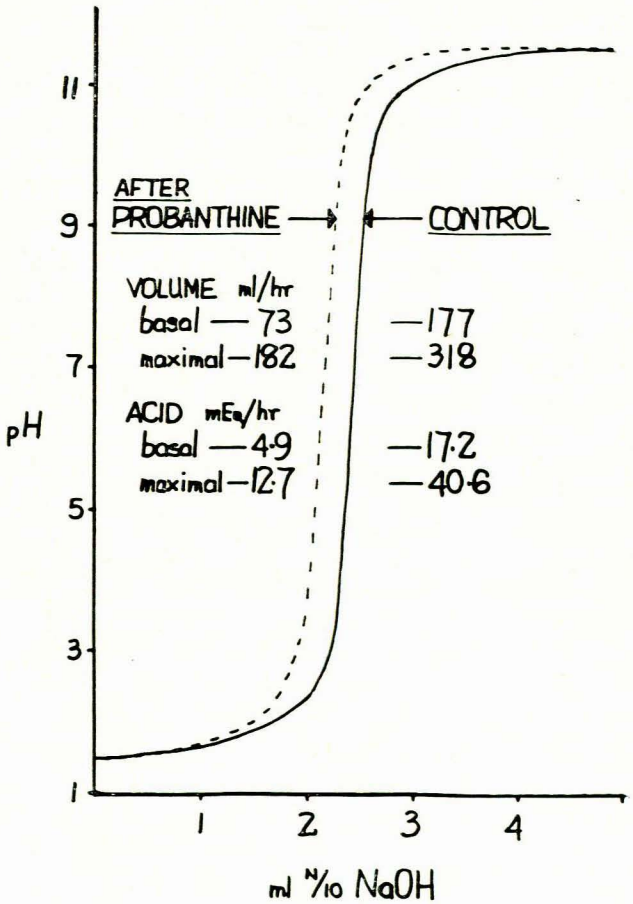

Fig. 1. The titration curves of two specimens of 2 ml gastric juice obtained from a 25-year-old Coloured man with a duodenal ulcer. The control specimen was obtained on 15 July 1969 and the other the next day. Probanthine 30 mg was injected intramuscularly 30 minutes before the start of the second augmented histamine test. In each case the specimen titrated was an aliquot of the juice collected between 30 and 45 minutes after the injection of 2 mg histamine.

2 mg three times a day, or as much as caused minimal side-effects. Glycopyrrolate was compared with a placebo. The patients were observed for periods between 18 and 27 months, when they were evaluated by 2 clinicians who decided that there had been 'no change' in the patients' symptoms during the period of treatment or that they had 'improved' or were 'worse'. They concluded that there was no significant difference attributable to the drug.

More recently Kaye *et al.*[15] did a controlled single blind trial on 106 male patients with duodenal ulceration. They compared 1 natural-occurring anticholinergic—l-hyoscyamine in a sustained-release form—with a synthetic anticholinergic—glycopyrronium—and an inert tablet. The 3 groups of patients were followed up for 1 year and were compared for frequency of symptoms, severity of symptoms, antacid consumption, monthly assessments by the individual patients themselves and the radiological appearances of the duodenum. Symptomatic improvement, judged subjectively and objectively, occurred in about 80% of all patients and there was no significant difference between the 3 groups, and they concluded that 'by all criteria, glycopyrronium and l-hyoscyamine were not significantly superior to placebo.'

Similarly the belief that anticholinergics may hasten the healing of a duodenal ulceration has not thus far been substantiated, but it should be noted that studies in this regard are hampered by the fact that the distortion of the duodenal bulb, which results when a duodenal ulcer heals, often precludes a definite opinion as to whether or not an ulcer is still present.

As far as the relief of ulcer symptoms is concerned, many clinicians are of the opinion that anticholinergics help to bring ulcer symptoms under control more quickly than might be expected if the drug were not used. However, this brings to mind a remark made by Ewald[16] in the 1890s: 'Gentleman, bismuth has been recommended by so many leading practitioners with such good results in cases of gastralgia that all possibility of a mistake would seem to be excluded, but in spite of this the question remains to be decided whether it possesses any specific efficacy, or whether it might not be replaced by another preparation of an alkaline sparingly salt such as bicarbonate of lime'. Kaye *et al.*[15] found no evidence that anticholinergics shortened the period that patients with duodenal ulcers were troubled by pain.

It is perhaps not surprising that the value of the anticholinergics in the management of duodenal ulceration has not stood the test of time. Although it is undisputed that duodenal ulceration does not occur in the presence of achlorhydria, and that duodenal ulcer patients as a *group* have higher acid secretions than normal individuals, it is surprising how often a patient who has a lot of trouble from his duodenal ulcer has an acid secretion in the normal, or even low normal, range. Furthermore, there is no evidence that the severity of the patient's symptoms, or the natural history of his ulcer (i.e. the tendency towards relapses and remissions and the development of complications such as perforation, haemorrhage or stenosis), can be related to the amount of acid that the patient's stomach can secrete in response to a meal or an agent exciting maximal acid secretion (the amount of acid secreted in response to a meal is the same as that elicited by maximal doses of histamine).[17] In other words, the fact that one patient with a duodenal ulcer has a maximal acid output after pentagastrin (or histamine) stimulation of 15 mEq/hr, and another patient of similar age, sex, social standing and ulcer history has an acid output of 45 mEq/hr, does not mean that the latter patient is more likely to develop complications in the future than the first-mentioned patient. That is, the amount of acid secreted by the stomach is not the whole answer to the duodenal ulcer problem. This may explain why our present therapeutic measures are so unsuccessful, since it is virtually impossible to produce prolonged achlorhydria in a patient with a duodenal ulcer by means of the drugs at present available. The ulcer is likely to recur as long as the gastric juice contains some acid, even if this is a small amount.

But if, despite the present evidence, there are those who feel that anticholinergics may still have a place in managing the symptoms of duodenal ulceration, then it should be remembered that the drug must be given before meals—in order to suppress the acid secretion provoked by the food— and that the dose must be so adjusted that the patient has a dry mouth. But care should be taken that the patient has not got actual or incipient pyloric stenosis, glaucoma, or an enlarged prostate. The drug should also be given at bedtime—to suppress nocturnal acid secretion —and the dose should be such that the patient wakes up with a dry mouth in the morning. Because the response of individual patients to a standard dose of anticholinergic varies so greatly, many advocates of the drug feel that tincture of belladonna is possibly the best as the dose can be adjusted more readily. The use of alkalis containing anticholinergics is compatible with adding fine Napoleon brandy to a well-known soft drink—the coke tastes the same and the good brandy can no longer be appreciated!

REFERENCES

1. Sollmann, T. (1957): *A Manual of Pharmacology and its Application to Therapeutics and Toxicology,* 8th ed., p. 381. Philadelphia: W. B. Saunders.
2. Marthiolus, quoted by Cullumbine, H. *in* Drill, V. A., ed. (1958): *Pharmacology in Medicine,* 2nd ed., p. 408. New York: McGraw-Hill.
3. Mein (1831), quoted by Lewis, J. J. (1962): *An Introduction to Pharmacology,* 2nd ed., p. 66. Edinburgh: E. & S. Livingstone.
4. Dragstedt, L. R. and Owens, E. M. (1943): Proc. Soc. Exp. Biol. (N.Y.), **53**, 152.
5. Grimson, K. S., Lyons, C. K., and Reeves, R. J. (1950): J. Amer. Med. Assoc., **143**, 873.
6. Hall, A. A., Hornisher, C. J., and Weeks, R. E. (1951): Gastroenterology, **18**, 197.
7. McHardy, G. G., Browne, D. C., Marek, F. H., McHardy, R., and Ward, S. (1951): J. Amer. Med. Assoc., **147**, 1620.
8. Winkelstein, A. (1952): Gastroenterology, **20**, 464.
9. Sun, D. C. H. (1964): Amer. J. Dig. Dis., **9**, 706.
10. Leading Article (1963): Brit. Med. J., **2**, 1387.
11. Bock, O. A. A. (1962): 'Some tests of gastric function and their application in thyrotoxicosis and diabetes mellitus', D.M. thesis, Oxford University.
12. *Idem* (1970): S. Afr. Med. J., **44**, 552.
13. Cayer, D. (1956): Amer. J. Dig. Dis., **1**, 301.
14. Trevino, H., Anderson, J., Davey, P. G. and Henley, K. S. (1967): *Ibid.*, **12**, 983.
15. Kaye, M. D., Rhodes, J., Beck, P., Sweetham, P. M., Davies, G. T., and Evans, K. T. (1970): Gut, **11**, 559.
16. Ewald, C. A. (1892): *Lectures on Diseases of the Digestive Organs,* vol. II, p. 434. London: New Sydenham Society.
17. Rune, S. J. (1967): Clin. Sci., **32**, 443.