Gastric acid secretion in patients with duodenal ulcer treated for one year with anticholinergic drugs

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SUMMARY Ninety patients with duodenal ulcer, divided randomly into three groups, were treated continuously for one year with either glycopyrronium, 1-hyoscyamine (as a sustained-release preparation) or inert tablets. Dosage with active tablets was so adjusted that the patient experienced definite but tolerable side-effects. Basal and maximal gastric acid secretion were measured immediately before and one week after cessation of treatment. There was no significant change in the means of these measurements in patients who received placebo or 1-hyoscyamine. In those given glycopyrronium, mean basal output was significantly increased. Mean maximal acid output in this group fell, but not significantly.

Individual measurements of maximal acid output showed quite marked fluctuations in all groups. It is concluded that spontaneous changes in parietal cell mass may occur in patients with duodenal ulcer, and that prolonged anticholinergic therapy does not reduce parietal cell mass.

Although it is established that gastric acid secretion is reduced for several hours after the administration of a variety of anticholinergic compounds, there is little information on the effect on gastric secretion of prolonged administration of these drugs. It was reported (Kowaleski, 1964 and 1967) that in the rat administration of propantheline bromide for several months led to a marked reduction of acid secretion, as measured 48 hours after the last dose of the drug. However, a recent study (Kaye, Jacobs, Ireson, and Trevett, 1968a) failed to confirm these findings. Posey, Elliott, Aldridge, Turner, and Franklin (1966), who gave glycopyrronium to dogs four times daily for 11 weeks, found that the secretion of Heidenhain pouches, and the histamine-stimulated secretion of the intact stomach, did not rise to normal until four weeks after drug withdrawal. However, more recent observations by this group (Posey, Elliott, Shewmake, and Posey, 1968) indicate that maximal acid output and parietal cell mass remain constant in dogs during prolonged treatment with glycopyrronium. In 16 patients with peptic ulcer (14 duodenal, two gastric) treated for a mean period of three years with poldine methylsulphate, Douthwaite, Hills, and Hunt (1961) found a 50% reduction in acid secretion measured by the distension test meal. This reduction persisted, with some individual fluctuations, throughout the period of drug administration. In a follow-up report on those patients (Hunt and Wales, 1966) it

was stated that reduced levels of acid secretion persisted for up to 30 months after the drug had been stopped. This maintained reduction was thought to reflect the course of the underlying disorder rather than a direct effect of the anticholinergic drug.

In this report, we describe our findings in a group of 90 patients with duodenal ulcer who were treated continuously for one year with anticholinergic drugs.

PATIENTS AND METHODS

All patients were male, had a duodenal ulcer recently demonstrated by radiograph, and had had symptoms within six months of the first examination. They were taking part in a trial of long-term anticholinergic therapy, full details of which will be published shortly, and were allocated randomly to one of three groups.

Twenty-eight patients (group A) received glycopyrronium.¹ The dosage was adjusted so that mild side-effects were experienced throughout the trial period.

Thirty patients (group B) received a sustained-release preparation of 1-hyoscyamine,² dosage being controlled in the same way as in group A.

Thirty-two patients (group C) received placebo tablets, identical in appearance to either group A or group B tablets.

In all groups, treatment was given as three daily divided doses, and was continued for one year.

Gastric acid secretion was measured immediately

¹Robinul, A. H. Robins Co.

²Egacen durules, Astra Ltd, Sweden.

before the patients were admitted to the trial, and again after one year. Treatment was stopped seven days before the second test.

MEASUREMENT OF GASTRIC ACID SECRETION Patients fasted for at least 12 hours before the test. After aspiration of resting juice, basal secretion was collected for 30 minutes. A constant-rate intravenous infusion of pentagastrin (Peptavlon, ICI), 6 µg/kg body weight/hour, was then begun, and continued for 75 minutes with continuous aspiration of gastric juice in five 15-minute samples. The maximal hourly output was determined from either the last three or four samples, depending upon when the plateau was reached.

RESULTS

Basal acid output and maximal acid output before treatment are shown in Tables I and II respectively. There is no significant difference between the three groups in maximal acid output, or basal acid output after the exclusion of one atypical subject (see footnote to Table I).

TABLE I

BASAL ACID OUTPUT BEFORE TREATMENT

Treatment	Group	No. of Patients	Basal Acid Output (mean, m-equiv/hr)	Variance	SD
Glycopyrronium	A	28	5.0	19.6	4.4
L-hyoscyamine	B	30	6.7	33.7	5.8
Placebo	C	32	6.9	72.6	8.5
		(31) ¹	(5.7) ¹	(28.9) ¹	(5.4) ¹

¹The figures in brackets are those obtained after exclusion of one extreme value (43.5) which was more than 7 SD above the mean of the group (when SD is calculated using only the 31 other members of the group). Inclusion of this subject inflates the variance from 28.9 to 72.6. Comparison of this latter value with those for groups B and C shows significant differences in variance, whereas differences are well within expected limits if this patient is excluded.

TABLE II

MAXIMAL ACID OUTPUT (INTRAVENOUS PENTAGASTRIN 6 µg/kg/hr) BEFORE TREATMENT

Treatment	Group	No. of Patients	Maximal Acid Output (mean, m-equiv/hr)	Variance	SD
Glycopyrronium	A	28	39.6	100.1	10.0
L-hyoscyamine	B	30	41.6	144.0	12.0
Placebo	C	32	39.1	105.7	10.3

Changes in basal acid output are shown in Table III. After one year's treatment with glycopyrronium, basal acid output had increased significantly from a mean of 4.98 m-equiv/hour to 8.19 m-equiv/hour ($P < 0.01$). Basal acid output did not change significantly in groups B and C.

TABLE III

CHANGES IN BASAL ACID OUTPUT

Treatment	Group	No. of Patients	Mean Difference in Basal Acid Output ¹	SE of Mean Difference	P
Glycopyrronium	A	28	+ 3.2	1.1	$P < 0.01$
L-hyoscyamine	B	30	+ 1.6	1.0	$0.1 < P < 0.2$
Placebo	C	32	+ 0.2	0.9	$0.8 < P < 0.9$

¹Two tests in each patient: the first immediately before, and the second one week after one year's treatment. Positive figures indicate a higher secretion at the end of the trial.

TABLE IV

CHANGES IN MAXIMAL ACID OUTPUT

Treatment	Group	No. of Patients	Mean Difference in Maximal Acid Output ¹	SE of Mean Difference	P
Glycopyrronium	A	28	- 3.3	2.1	$0.1 < P < 0.2$
L-hyoscyamine	B	30	- 0.6	1.1	$0.6 < P < 0.7$
Placebo	C	32	+ 0.2	1.3	$0.9 < P$

¹Two tests in each patient: the first immediately before, and the second one week after one year's treatment. Positive figures indicate a higher secretion at the end of the trial period.

There was no significant change in the mean maximal acid output in any group (Table IV). Figure 1 illustrates individual changes in maximal acid output in the three groups. The variation in these changes of maximal acid output, whether considered as simple numerical differences or as percentages of the

FIG. 1. Individual changes in maximal acid output. 1 and 2 refer to first and second tests.

initial output, is significantly ($P < 0.01$) greater in group A than in groups B or C. There is, however, no significant difference in the mean change of output between the three groups.

There was no correlation, either direct or inverse, between individual changes in basal acid output and changes in maximal acid output (Table V).

TABLE V

CORRELATIONS BETWEEN CHANGES IN BASAL AND MAXIMAL ACID OUTPUT¹

Treatment	Group	No. of Patients	Correlation Coefficient <i>r</i>	P
Glycopyrronium	A	28	- 0.02	0.9 < P
L-hyoscyamine	B	30	+ 0.24	0.2 < P < 0.3
Placebo	C	32	+ 0.04	0.8 < P < 0.9

¹Changes taken as straight numerical differences.

DISCUSSION

Both drugs used in this study cause transient reduction in gastric acid secretion in man. In the case of glycopyrronium, this has been shown for basal (Moeller, 1962; Posey, 1962; Abbott, Sourial, Krieger, and Levey, 1962; Sun, 1962), nocturnal (Barman and Larson, 1963), and histamine-stimulated (Abbott *et al*, 1962; Dotevall, Schroder and Walan, 1965; Kaye, Rhodes, and Sweetman, 1968b) secretion. Similar observations have been made with L-hyoscyamine for basal and histamine-stimulated secretion (Dotevall *et al*, 1965; Christianson and Rodbro, 1967; Kaye *et al*, 1968b), and there have been numerous other studies of belladonna, of which L-hyoscyamine is a constituent alkaloid. As judged by salivary flow measurements (Kaye *et al*, 1968b), both these drugs are relatively long acting. L-hyoscyamine, in Egacen durules, is released slowly from a plastic matrix, and glycopyrronium is a slowly absorbed quaternary ammonium compound. With very few exceptions, patients in this study said that they took their tablets regularly, and in a dose which produced side-effects. If their statements were true it would be reasonable to conclude that the majority underwent maximum tolerable cholinergic suppression continuously for one year. However, the degree of suppression of gastric acid secretion may not have been commensurate with that of other end organs. Furthermore, anticholinergic drugs may have relatively little effect on food-stimulated secretion (Nicol, 1939; Lennard-Jones, 1961; Soergel and Hogan, 1964).

In this study, basal secretion was collected for 30 minutes. While a longer collection period provides a more accurate estimate of basal acid output,

we believe that comparisons between first and second tests, and between the three groups, are nevertheless valid, since a standard method was used for all tests, and since the initial measurements in the three groups were similar. In patients who received L-hyoscyamine there was no significant change in mean basal acid output or maximal acid output after one year's treatment. With regard to individual differences in the two tests, the changes observed were very similar to those which occurred in the placebo group. Treatment with glycopyrronium, however, resulted in a significant increase in the mean basal acid output. Moreover, while the fall in the mean maximal output in this group, from 39.56 to 36.28 m-equiv/hour, was not significant ($0.1 < P < 0.2$), the variation in changes of maximal acid output was significantly greater in this than in the other two groups. Two questions therefore arise. First, why are the effects of prolonged therapy with glycopyrronium different from those with L-hyoscyamine; and secondly, what is the explanation for the increase in basal acid output and the greater variation in changes of maximal acid output observed in patients given glycopyrronium.

On the first point, it may be relevant that the duration of action of glycopyrronium, as assessed by measurement of salivary flow after single doses of drugs, is greater than that of L-hyoscyamine (Kaye *et al*, 1968b). It is also possible, though unproven, that the end-organ specificity of the two drugs may differ, so that glycopyrronium may have a relatively greater effect on the stomach. In addition, glycopyrronium induces changes in parietal cell ultrastructure in the dog and rat, an effect which is not produced by atropine, propantheline, or vagotomy (Elliott and Posey, 1967; Posey *et al*, 1968). Furthermore, the reduction in histamine-stimulated acid secretion after vagotomy in dogs is further augmented by glycopyrronium (Posey *et al*, 1968). These observations suggest that this drug acts not only by competition with acetylcholine at neuroreceptor sites, but possibly also at a more peripheral level. They also indicate a difference between the mode of action of glycopyrronium and that of some, at least, of the other available anticholinergic compounds.

The effects of glycopyrronium upon acid secretion, as observed in this study, are difficult to explain. The increase in basal acid output in patients who received this drug may be a 'rebound' phenomenon, due perhaps to vagal overactivity following removal of the inhibitory effect. We do not know whether this increase is sustained, since further measurements of basal acid secretion have not been performed on these patients. There was also an increase in mean basal acid output in patients who received L-hyoscyamine, from 6.70 to 8.28, though this change

does not reach statistical significance ($0.1 < P < 0.2$).

Quite marked fluctuations in maximal acid output occurred in patients from all three groups. The data of Kay (1953), Sircus (1960), and Marks (1961) indicate that changes of up to $\pm 10\%$ in maximal acid output may result from errors in the method itself. Table VI shows the numbers of patients from each group in whom changes exceeded these arbitrary limits, and illustrates the greater variability of changes in group A. Approximately equal numbers from each group showed an increase greater than 10% . A decrease occurred in rather more patients from group A (glycopyrronium) though this difference between the groups may be due to chance.

TABLE VI

CHANGES IN MAXIMAL ACID OUTPUT¹

Treatment	Group	No. of Patients	No. of Patients with Increase > 10%	No. of Patients with Change < 10%	No. of Patients with Decrease > 10%
Glycopyrronium	A	28	8	6	14
L-hyoscyamine	B	30	7	15	8
Placebo	C	32	9	14	9

¹Expressed as percentage differences between first and second measurements. χ^2 (4 DF) = 6.42; $0.1 < P < 0.2$.

Little is known about the possibility that spontaneous fluctuations of parietal cell mass may occur as part of the natural history of duodenal ulcer. These results strongly support this possibility since parietal cell mass correlates closely with histamine-stimulated maximal acid output (Card and Marks, 1960) and this with pentagastrin-stimulated maximal acid output (Multicentre pilot study, 1967).

Finally, while the parietal cell mass can be artificially increased by such methods as repeated histamine injection (Marks, 1957; Ritchie, Delaney, Barzilai, Lande, and Wangenstein, 1966) or partial duodenal obstruction (Crean, 1967) there is as yet no reliable means whereby the parietal cell mass may be experimentally reduced, with the possible exception of immunological techniques (Walder, 1968). It would appear from this study that the prolonged and continuous suppression of function which results from long-term administration of potent anticholinergic drugs does not cause a reduction in parietal cell mass.

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