THE EFFECT OF GLYCOPYRROLATE AND A COMBINED OXYPHENCYCLIMINE-HYDROXIZINE PREPARATION ON GASTRIC ACID SECRETION

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In the medical management of peptic ulcer, great emphasis is placed on the neutralization or inhibition of gastric acid secretion. Antacid preparations are of unquestionable value in the transient reduction of gastric acidity, but it is generally agreed that anticholinergic drugs are required to achieve a more uniform suppression of the acidity of the gastric contents. The present study was undertaken to investigate the antisecretory effect of two recently available anticholinergic preparations on gastric secretion.

METHOD

Twenty-seven patients were used for the present study. Twenty-four of these had duodenal ulcers, 1 a gastric ulcer and 2 a functional dyspepsia. Their ages ranged between 17 and 55 years.

Each patient underwent 2 - 5 augmented histamine tests, which included a control test and tests carried out during a course of treatment with one or more of the following anticholinergic agents: Glycopyrrolate (Robinul) in a 1, 2 or 3 mg. *b.d.* dosage level, a combination preparation of 5 mg. oxyphencyclimine and 10 mg. hydroxizine (Enarax) in a 1, 2 or 3 tabs. *b.d.* dosage level and propantheline (Pro-banthine P.A.) in a 30 mg. *b.d.* dosage level. A total of 81 tests were carried out in the 30 patients.

The augmented histamine test was carried out as previously described.[1] After an overnight fast, a tube was introduced through the nose and passed into the stomach. Under fluoroscopic control, the tip of the tube was adjusted to lie in the most dependent part of the stomach. The fasting contents were aspirated and the patient allowed to lie comfortably on his back or on his left side. Throughout the test a vacuum of 30 - 50 mm.Hg was applied to the tube, in order to maintain continuous aspiration, interrupted only by occasional manual aspiration of gastric contents with a syringe to ensure complete collections. The patient was urged to expectorate any saliva accumulating in the mouth. Gastric contents were aspirated for 1 hour before and 1 hour following the administration of histamine acid phosphate (0·04 mg./kg. bodyweight, given subcutaneously). Fifty mg. of mepyramine maleate (Anthisan) was given by intramuscular injection, 30 minutes before the injection of histamine. Aliquots of the basal and post-histamine collections were titrated with N/10 NaOH using Töpfers reagent and phenolphthalein as indicators for 'free' and 'total' acid, respectively. The basal acid output was calculated from the output of 'total' acid during the hour preceding the injection of histamine and the maximal acid output (MAO) from the output of 'total' acid during the hour following the injection of histamine. Only these measures of acid secretion were employed in the present paper.

Subsequent augmented histamine tests were carried out after the administration of a given dosage of one of the anticholinergic preparations for a period of 3 days. The preparation was given orally at 8 a.m. and 8 p.m., except on the morning of the test when it was given 3 hours before the test was due to start. Ten of the 30 patients were tested with 2 or 3 anticholinergic preparations and a further 2 were tested on 2 occasions with the same preparation. The remaining 18 patients were tested on only one occasion with either Robinul or Enarax.

RESULTS

Glycopyrrolate (*Robinul*)

Robinul was tested in 15 patients, six of whom were investigated on more than one occasion. The dose of Robinul employed in these patients ranged from 1 to 3 mg. *b.d.* The results of the 22 tests carried out in the 16 patients are illustrated in Fig. 1 and the mean reduction in basal secretion and the MAO with the different dosage levels of Robinul presented in Table I.

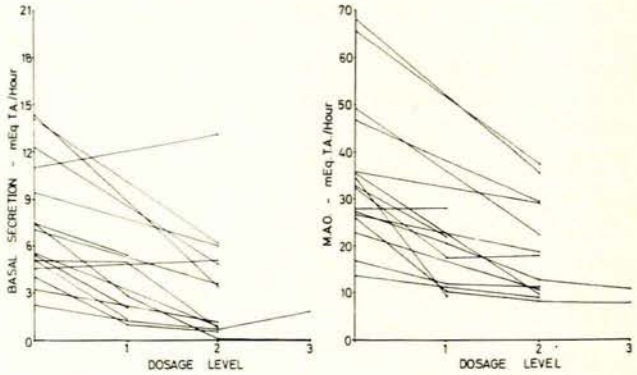

Fig. 1. Effect of varying doses of glycopyrrolate (Robinul) on basal secretion and the MAO. The dose was administered twice daily (1 dose = 1·0 mg.).

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There were marked variations in the magnitude of the reduction of basal secretion and the MAO with all dosage levels employed, but the data in Table I indicate that the larger dosage levels suppressed both basal secretion and the MAO more effectively than did the smaller doses. The mean reduction in basal secretion ranged from 49% with the 1 mg. dose to 61% with the 3 mg. dose and the mean reduction in MAO varied between 38% with the smaller and 64% with the larger dose.

TABLE I. EFFECT OF VARIOUS ANTICHOLINERGIC PREPARATIONS ON GASTRIC SECRETION EXPRESSED IN TERMS OF MEAN PERCENTAGE REDUCTION OF BASAL SECRETION AND MAO

Preparation	*Dose*	*Number of patients*	*Mean % reduction and range*	
			Basal	*MAO*
Robinul	1 *b.d.*	7	49 (0–75)	38 (0–71)
	2 *b.d.*	13	59 (0–85)	45 (19–73)
	3 *b.d.*	2	61 (22–100)	64 (60–67)
Enarax	1 *b.d.*	5	42 (7–75)	40 (0–79)
	2 *b.d.*	13	46 (0–76)	38 (0–66)
	3 *b.d.*	4	66 (46–91)	47 (39–54)
Pro-banthine P.A. (30 mg.)	1 *b.d.*	7	51 (0–80)	31 (1–76)

Side-effects were experienced in patients during 4 of the 22 tests. One of the 7 patients on a 1 mg. *b.d.* dosage level, 2 of the 13 patients on a 2 mg. *b.d.* dosage level and 1 of the 2 on a 3 mg. *b.d.* dosage level had slight dryness of the mouth. More serious side-effects were not encountered.

Oxyphencyclimine-Hydroxizine (Enarax)

Twenty-two tests with Enarax were carried out in 19 patients. The dose of Enarax employed ranged from 1 to 3 tablets *b.d.* The data on these and the respective control tests are illustrated in Fig. 2 and the mean reduction in

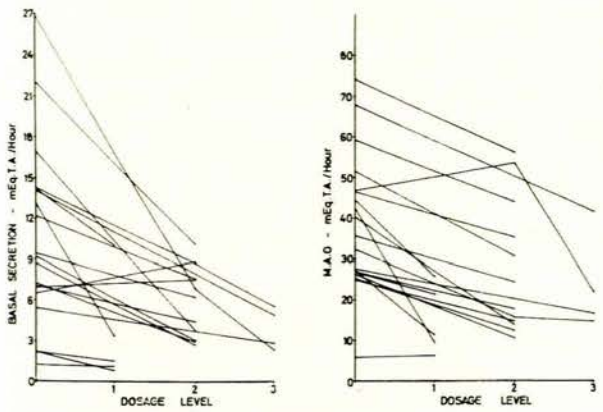

Fig. 2. Effect of varying doses of oxyphencyclimine-hydroxizine (Enarax) on basal secretion and the MAO. The dose was administered twice daily (1 dose = 5 mg. oxyphencyclimine + 10 mg. hydroxizine).

basal secretion and the MAO with the different dosage levels of Enarax are presented in Table I.

Marked variations in the percentage reduction in basal secretion and MAO were again noted for each of the 3 dosage levels, the larger doses tending to suppress basal secretion and MAO more effectively than the smaller ones. The mean reduction in basal secretion ranged from 43% with the tabs. 1 *b.d.* dose to 66% with the tabs. 3 *b.d.* dose and the mean reduction in MAO ranged from about 40% with the smaller dose to 47% with the larger dose.

Dryness of the mouth was troublesome in 1 of the 4 patients on the tabs. 3 *b.d.* dose but in none of the patients on the smaller doses and was present to a lesser degree in 2 of the remaining 18 patients. The tranquillizing effect of the hydroxizine (Aterax) was difficult to assess because of the shortness of the trial periods but none of the patients complained of undue lassitude or tiredness.

Comparison of Robinul, Enarax and Pro-banthine P.A.

The antisecretory effect of different doses of Robinul and Enarax was compared with the effect of propantheline (Pro-banthine P.A., 30 mg.) in 7 patients and a further 3 patients were investigated with both Robinul and Enarax. Table II shows that the antisecretory effect of the single

TABLE II. COMPARISON OF PERCENTAGE REDUCTION IN BASAL SECRETION AND MAO IN GROUP OF PATIENTS GIVEN MORE THAN 1 ANTICHOLINERGIC PREPARATION

	% reduction in basal secretion							*% reduction in MAO*						
	Pro-banthine P.A.	*Robinul*			*Enarax*			*Pro-banthine P.A.*	*Robinul*			*Enarax*		
No. of tablets given b.d.	*1*	*1*	*2*	*3*	*1*	*2*	*3*	*1*	*1*	*2*	*3*	*1*	*2*	*3*
	74	0	78					10	30	34				
	48	25	85					1	49	47				
	91	62	100	100				76	61	67	67			
	80	75						16	0					
	36					74	91	20					52	54
	0	43	74	22	65			58	24	53	60	58		
	25		60			40		34		27			34	
			57				66			48				39
			0			50				38			25	
			36			32				19			32	

dose levels of Robinul and Enarax was comparable with that of the Pro-banthine P.A. and that the larger doses tended to be more effective than the 30 mg. Pro-banthine preparation. This was supported by the data in Table I regarding the mean reduction in acid secretion on the 7 patients tested with Pro-banthine P.A. The mean reduction in basal secretion in this small group was 51% and the mean reduction in MAO, 31%. Two of these 7 patients admitted to dryness of the mouth while on Pro-banthine.

The data in Table II show, in addition, that the antisecretory effect of Robinul and Enarax was comparable on a tablet-for-tablet basis. However, the number of patients in this sub-group was too small to permit of a definite conclusion.

DISCUSSION

The present study confirmed the efficacy of glycopyrrolate (Robinul) and a combined oxyphencyclimine-hydroxizine preparation (Enarax) in the reduction of gastric acid secretion.[2-7] It showed, in addition, that both basal secretion and the response to maximal histamine stimulation were affected. Basal secretion was reduced to a greater extent than was the MAO in the majority of patients and the antisecretory effect of even the lower dosage levels of these preparations was comparable to that found following the administration of a 30 mg. dose of a prolonged-action preparation of propantheline. Side-effects were minimal or absent with effective antisecretory dosages of glycopyrrolate or Enarax, but it should be noted that no elderly males were included in the series.

The antisecretory effect of Robinul was perhaps slightly greater than that of Enarax on a tablet-for-tablet basis. Enarax, however, has the advantage of having a long duration of action[5,8] and in addition, of containing a 10 mg. dose of Aterax. The latter, with its central sedative, antisecretory and antispasmodic action has been claimed to be a useful adjunct to anticholinergic therapy in the treatment of peptic ulceration and functional bowel disorder.[9,10]

It should be stressed that the dosage schedule of one or more tablets administered twice daily was an arbitrary one, employed only for purposes of the present trial, and that the data regarding suppression of gastric secretion were derived from tests commenced exactly 3 hours following a given dose of one of the preparations. The present paper does not provide information on the number of doses required to produce adequate suppression of acid secretion over a 24-hour period, but available data suggest that this may be achieved with Enarax administered every 8 or 12 hours or with Robinul given at 6 to 8-hourly intervals.

The marked variations in the effect of a given dose of an anticholinergic preparation observed in different patients lends support to the concept, championed by Sun and Shay,[11] regarding the importance of the optimum effective dose (OED) in the management of peptic ulceration. They suggest that the OED be determined for each patient by gradually increasing the dose of drug to a level of one increment below that which produces uncomfortable symptoms of parasympathetic inhibition. The relative absence of these side-effects in the majority of patients in the present study suggested that the dosages employed were generally below the OED and that at least some of the patients would have tolerated a larger dose of the anticholinergic preparation than that employed. Since the degree of inhibition in acid secretion increased with an increase in the dose of drug, this would have allowed the patients to have been given an even more effective dose of anticholinergic preparation.

SUMMARY

Glycopyrrolate (Robinul) and oxyphencyclimine HCl-hydroxizine (Enarax), 2 recently available anticholinergic preparations, have been shown to result in an appreciable reduction in basal and histamine-induced acid secretion, with dose levels producing little or no side-effects.

This study was supported by the South African Council for Scientific and Industrial Research and by the Ben May Gastroenterology Research Fund. We wish to thank Dr. J. G. Burger, Medical Superintendent of Groote Schuur Hospital, for permission to publish. Glycopyrrolate (Robinul) was supplied by A. H. Robins Co., Inc., Richmond, Va., and oxyphencyclimine-hydroxizine (Enarax) by U.C.B., Brussels.

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