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24-hour intragastric acidity and nocturnal acid secretion in patients with duodenal ulcer during oral administration of cimetidine and atropine

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SUMMARY Cimetidine markedly inhibits gastric acid secretion, but from the therapeutic point of view it is important to know whether concurrent treatment with an anticholinergic increases its effect. This possibility has been investigated by measuring the 24 h intragastric acidity and nocturnal output of acid in four duodenal ulcer patients, each receiving on separate occasions cimetidine 1 g/day and placebo, atropine 2·4 mg/day and placebo, cimetidine and atropine, or two placebos. Cimetidine alone decreased mean hourly hydrogen ion activity by 63% of control values, decreased mean hourly hydrogen ion concentration (total acid) by 41%, inhibited nocturnal acid secretion by 83% and resulted in half the nocturnal samples being anacidic. Atropine alone had no effect when compared with control and combined treatment with both drugs was not superior to cimetidine alone. Atropine did not affect the absorption or urinary excretion of cimetidine. Fasting serum gastrin concentrations were not changed by any of the treatments.

At the doses studied, the combination of cimetidine with an anticholinergic appears to offer no advantages over treatment with the H_2-antagonist alone. Cimetidine is the only potent anti-secretory drug that does not cause acute side-effects and this important advantage would be lost if it were given with a maximal dose of an anticholinergic.

There is experimental and clinical evidence to suggest that the actions of a histamine H_2-receptor antagonist and an anticholinergic might be additive or even synergistic (Thjodleifsson and Wormsley, 1974; Richardson *et al.*, 1975; Thompson *et al.*, 1975; Richardson and Walsh, 1976).

The object of the present study was to determine whether combined treatment with cimetidine and an anticholinergic is likely to be more effective than either drug alone.

Methods

Four male patients, weighing 62·3, 85·5, 85·9 and 85·9 kg and aged 33, 19, 21 and 24 years respectively, were studied for 24 h periods on the same days of four successive weeks. All the patients had a duodenal ulcer in symptomatic remission, the diagnosis having been established at endoscopy. They had received no anti-secretory drugs for at least one month before the series of experiments. All gave their informed consent before starting the study, which was approved by the appropriate ethical committees.

The experimental design is shown in Fig. 1. Medication was given before and after breakfast, lunch and dinner, and at bedtime. Atropine 0·6 mg, or a placebo capsule of identical appearance, was given before meals and cimetidine 200 mg, or a placebo tablet, was given after meals. At bedtime the dose of atropine was unchanged but the dose of cimetidine was increased to 400 mg (two tablets).

The 0·6 mg dose of atropine was chosen to produce minimal symptoms of cholinergic blockade. Independently of the main study, the patients were tested in a randomised blind trial of pre-prandial

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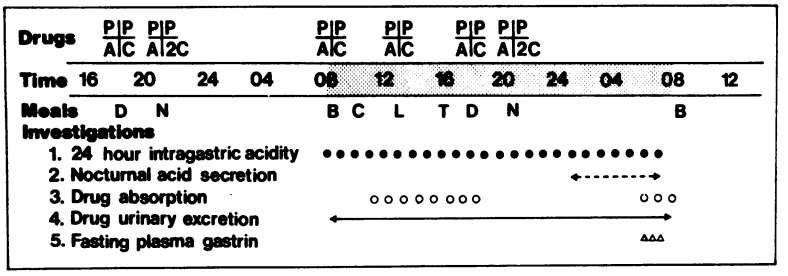

Fig. 1 *Experimental design. Drugs: P = placebo, A = atropine, C = cimetidine 200 mg, 2C = cimetidine 400 mg. Meals: B = breakfast, C = coffee, L = lunch, T = tea, D = dinner, N = nightcap.*

doses of atropine (0·0, 0·4, 0·6, 0·8 and 1·0 mg). Side-effects were dose-related and at a dose of atropine 0·6 mg two of the four patients had a dry mouth.

Four different regimens were tested on each patient: placebo/placebo, placebo/cimetidine, atropine/placebo and atropine/cimetidine. The regimens were allocated according to a predetermined four by four Latin square pattern and the patients were not informed of changes in the nature of their medication, which was started at 17.30 h on the evening before the study. Later that evening three of the patients were intubated with a double-lumen nasogastric tube, but for administrative reasons one patient was always intubated at 07.00 h next morning.

The general conditions of the study resembled closely those previously described (Pounder *et al.*, 1975, 1976) and were designed to ensure normal dietary and physical conditions. The diet in this study was slightly lighter than that used in the earlier studies: the last meal of the day was at 18.00 h and the nightcap at 21.00 h consisted of only a cup of tea without food.

Intragastric acidity was measured at hourly intervals from 08.00 to 08.00 h on the following day. To measure hydrogen ion activity, the pH of 5 ml gastric aspirates was measured immediately and the samples were then stored at +4 °C. Within 72 h, the hydrogen ion concentration (total acid) of each sample was determined by automatic titration (Radiometer, Copenhagen) to pH 7·0 using sodium hydroxide (100 mmol/l). From 01.00 to 07.00 h nocturnal gastric acid secretion was measured in hourly samples collected by continuous nasogastric aspiration at −50 mmHg, supplemented by manual suction every 20 min. Aliquots of these gastric aspirates were titrated to pH 7·0. The last dose of cimetidine was given at 21.30 h and continuous gastric aspiration was started at 01.00 h; this long interval was to allow time for cimetidine to leave the stomach, in case atropine delayed gastric emptying.

The absorption of cimetidine was measured in venous blood samples collected at hourly intervals from 11.30 to 18.30 h and at 06.00, 07.00 and 08.00 h on the second morning. The concentration of cimetidine in the blood samples, in the nocturnal gastric aspirates and in 24 h urine outputs collected from 08.00 to 08.00 h, was measured by high pressure liquid chromatography.

On the second morning of each study venous blood was collected at 06.00, 06.30 and 07.00 h for the radioimmunoassay of fasting plasma gastrin. Biochemical and haematological safety studies were performed at the start of the study and after each 36 h treatment period with cimetidine.

Results

Administration of cimetidine 1 g/day did not produce unwanted effects, or abnormalities in the haematological or biochemical safety studies. Some of the patients reported a dry mouth when given atropine, but in none was this effect severe.

24 h intragastric acidity

The results of the four regimens are shown in Fig. 2 and the mean values for hourly intragastric acidity are shown in Table 1. Atropine 2·4 mg/day had little effect on intragastric acidity but cimetidine 1·0 g/day resulted in a 63% decrease of mean hourly hydrogen ion activity and a 41% decrease of mean hourly total acid. Cimetidine decreased acidity in every patient. The concurrent administration of cimetidine and atropine did not decrease acidity more than cimetidine and placebo.

Nocturnal acid secretion

The mean nocturnal gastric secretion per hour from 01.00 to 07.00 h is shown in Fig. 3. Medication with atropine resulted in a small, but non-significant, rise of acid secretion. Cimetidine alone resulted in a 83% decrease of nocturnal secretion ($P < 0.01$), which was not significantly altered by the addition of atropine.

Periods of intragastric anacidity were observed in three of the four patients when they received cimetidine alone, but only for two hours in one patient when cimetidine was given with atropine

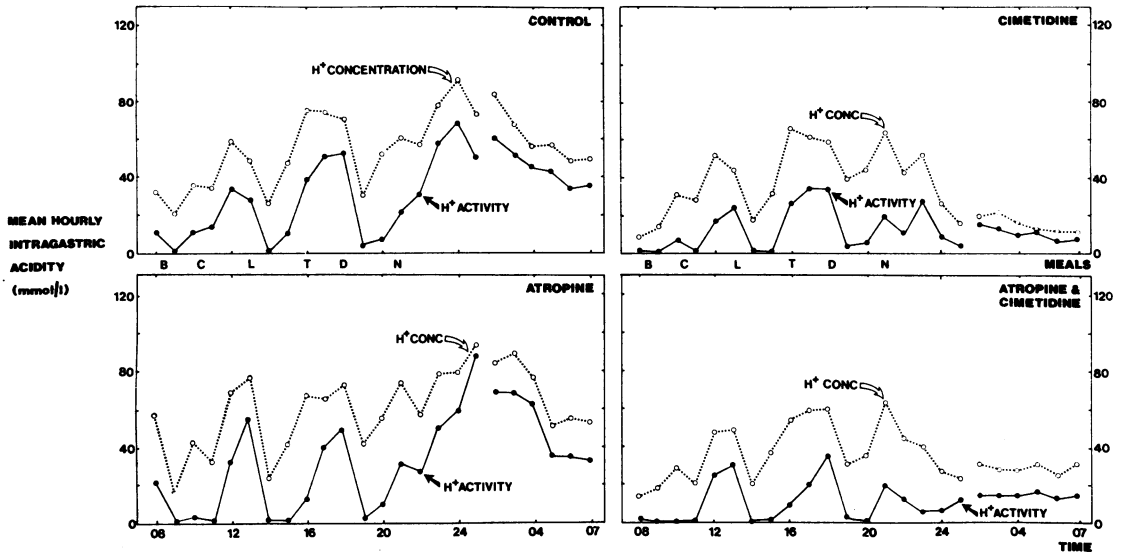

Fig. 2 *Mean hourly intragastric acidity during the four treatment regimens. (Control = placebo/placebo). Break in lines marks start of continuous gastric aspiration. H^+ activity derived from pH measurements using glass electrode. H^+ concentration equals total acid, measured by titration to pH 7·0.*

Table 1 *Mean 24 h intragastric acidity ± SEM (± percentage change from placebo/placebo)*

	H^+ activity		Total acid
	mmol/l	*pH*	*mmol/l*
Placebo/placebo	32·1 ± 2·7	1·50	55·3 ± 2·8
Atropine/placebo	33·4 ± 3·2 (+4%)	1·48	60·6 ± 2·9 (+10%)
Placebo/cimetidine	11·8 ± 1·7 (−63%)	1·93	32·7 ± 2·7 (−41%)
Atropine/cimetidine	11·5 ± 1·6 (−64%)	1·94	35·7 ± 2·5 (−35%)

(Table 2). The number of anacidic samples aspirated during treatment with cimetidine alone was significantly higher than the number of anacidic samples obtained during treatment with atropine and cimetidine (χ^2 = 8·17; P < 0·01, Table 2).

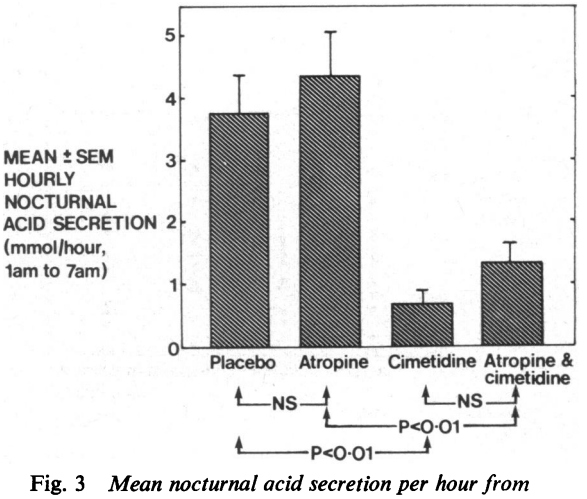

Fig. 3 *Mean nocturnal acid secretion per hour from 01.00 to 07.00 h.*

ABSORPTION AND EXCRETION OF CIMETIDINE

Small amounts of cimetidine were detected in the gastric aspirates at 01.00 h: 1·4 ± 1·2 (0·5-8·9) mg (mean ± SEM, range) but the amount of cimetidine recovered was unaffected by treatment with atropine. Concurrent administration of atropine did not affect the absorption of cimetidine as shown by the mean whole blood cimetidine concentrations from 11.30 to 18.30 h and from 06.00 to 08.00 h (Fig. 4). The mean 24 h urinary excretion of cimetidine was 353 ± 35 (284-449) mg when the drug was taken with placebo and 419 ± 78 (259-599) mg when taken with atropine; this difference is not significant (P > 0·05, Student's *t* test for paired data).

FASTING PLASMA GASTRIN

The fasting plasma gastrin concentrations (three samples from each patient collected at 06.00, 06.30

Table 2 *Incidence of anacidity in hourly gastric aspirates, 01.00 to 07.00 h. Six samples from each of four patients.*

	Below pH 7·0	*pH 7·0 and above*
Placebo/placebo	24	0
Atropine/placebo	24	0
Placebo/cimetidine	12	12
Atropine/cimetidine	22	2

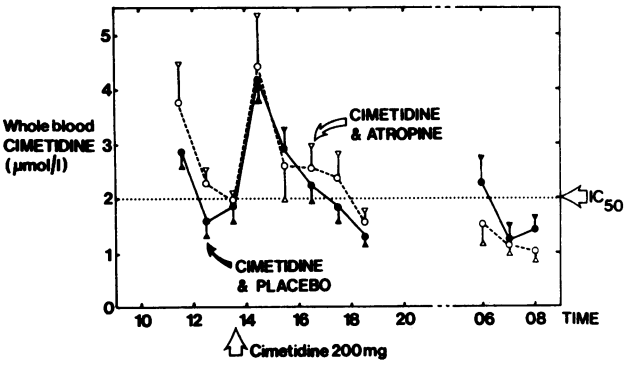

Fig. 4 *Whole blood cimetidine concentrations (mean ± SEM). IC_{50} = blood concentration of cimetidine inhibiting maximally stimulated acid secretion by 50% (Burland* et al., *1975).*

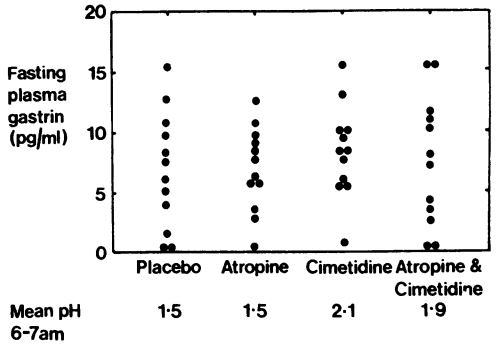

Fig. 5 *Fasting plasma gastrin concentrations. Three samples from each of the four patients on each study day.*

and 07.00 h) for each morning of the study are shown in Fig. 5. Despite the rise of intragastric pH after treatment with cimetidine, there was no significant change of the fasting plasma gastrin ($P > 0.05$, Student's *t* test for paired data).

Discussion

In a study of 24 h intragastric acidity, we demonstrated that doubling the dose of cimetidine resulted in a doubling of the peak blood concentration of the drug, but this had only a small additional effect on intragastric acidity, mostly in the latter part of the night (Pounder *et al.*, 1975). It is likely that anacidity will be achieved in the stimulated stomach only by very high blood concentrations of cimetidine. We therefore investigated whether the effects of cimetidine can be improved by the addition of atropine. We had been encouraged by earlier reports which suggested that the actions of an H_2-antagonist and an anticholinergic were additive or even synergistic (Thjodleifsson and Wormsley, 1974; Richardson *et al.*, 1975; Thompson *et al.*, 1975; Richardson and Walsh, 1976).

Atropine was chosen for the present study because it is the only anticholinergic drug with a well-defined bioavailability after oral administration and because it is completely absorbed from the gut (Beerman *et al.*, 1971, 1972a). Unlike other anticholinergics, atropine is not degraded in the lumen of the small intestine (Beerman *et al.*, 1972a, b). In a critical review of anticholinergic drugs Ivey (1975) recommended that the tertiary compounds (atropine, oxyphencyclamine, dicyclamine, belladonna, or l-hyoscyamine) should be used in clinical practice for oral medication rather than the quarternary compounds (propantheline, poldine etc.). He suggested that the relative absence of side-effects with the latter group of compounds was due to their poor absorption from the gut.

Most human subjects experience symptoms of parasympathetic blockade after an oral dose of atropine 0·5 to 1·0 mg (Innes and Nickerson, 1975). In sufficiently large doses atropine is a potent inhibitor of gastric acid secretion: Konturek *et al.* (1974) reported that a mean dose of 1·8 mg/hour given intravenously resulted in a 70% decrease of peptone-stimulated gastric acid secretion and a 30% decrease of pentagastrin-stimulated secretion, but the toxic effects were unacceptable for anything but short experiments. The dose of atropine that was used in the present study was chosen for three reasons: firstly, as an acceptable dose that did not cause severe side-effects in order to ensure the return of the patients for repeated studies; secondly, to avoid severe symptoms of parasympathetic blockade so that the single blind control of the study was not broken; and thirdly, to observe the effects, alone and in combination, of submaximal doses of the two antisecretory drugs.

Atropine 2·4 mg/day produced a small increase of mean hourly intragastric hydrogen ion activity and

concentration (Table 1) which is within the experimental error of this technique (Pounder *et al.*, 1976) and a non-significant change of nocturnal acid secretion (Fig. 3). These results confirm Nicol's (1939) observation that oral atropine 0·6 mg every four hours does not decrease intragastric acidity and they are compatible with those of Kirsner and Palmer (1940) who found no effect on intragastric acidity when they gave atropine 1·0 mg four times during the day. The results of this study do not support the report of Mitchell *et al.* (1962) that a mean single oral dose of atropine 0·8 mg can decrease postprandial intragastric acidity by approximately 40%.

In this study cimetidine 1·0 g/day decreased the mean 24 h intragastric hydrogen ion activity by 63% —a result similar to those of our earlier studies (Pounder *et al.*, 1975, 1976)—and it decreased the mean intragastric total acid by 41% (Table 1). As in the earlier studies, all the patients responded to the administration of cimetidine by a decrease of intragastric acidity.

H_2-receptor blockade with cimetidine significantly inhibited the nocturnal secretion of acid: the mean hourly acid output from 01.00 to 07.00 h was decreased by 83% (Fig. 3) and half the nocturnal samples of gastric secretion contained no acid (Table 2). This observation is similar to that of Milton-Thompson *et al.* (1974) and Longstreth *et al.* (1976) who measured the effects of single doses of metiamide or cimetidine on the resting nocturnal acid secretion of patients with duodenal ulcer. It is unlike the results in our earlier studies of 24 h intragastric acidity when cimetidine did not produce nocturnal anacidity (Pounder *et al.*, 1975, 1976), but in those studies the subjects were given food late in the evening and were not subjected to continuous nocturnal gastric aspiration. In order completely to inhibit the nocturnal secretion of acid by H_2-receptor blockade it may be necessary to avoid food late in the evening.

Administration of atropine 2·4 mg/day and cimetidine 1·0 g/day did not result in a greater decrease of either 24 h intragastric acidity or nocturnal acid secretion than that produced by cimetidine alone (Table 1, Figs. 2 and 3). Indeed, during the night the addition of atropine to cimetidine significantly diminished the number of anacidic hourly aspirates. This finding contrasts with the reports that anticholinergic and H_2-receptor blocking drugs interact to produce a greater decrease of intragastric acidity: Thompson *et al.* (1975) found that the antisecretory effects of metiamide and atropine were additive in the cat, Richardson *et al.* (1975) reported additional inhibition of food stimulated gastric secretion when isopropamide was given with metiamide, Thjodleifsson and Wormsley (1974) implied a synergistic potentiation of inhibition of nocturnal acid secretion when atropine was given with metiamide and Richardson and Walsh (1976) suggested that glycopyrrolate prolonged the action of a single dose of metiamide in the Zollinger-Ellison syndrome.

Anticholinergics can alter the rate of absorption of other drugs. For example, oral atropine and intravenous propantheline decrease the rate of alcohol absorption (Gibbons and Lant, 1975) and intravenous propantheline delays the absorption of paracetamol, alcohol, and sodium (Groisser and Farrar, 1962; Nimmo *et al.*, 1973; Finch *et al.*, 1974). In the present study atropine had no effect on the rate of absorption of cimetidine (Fig. 4). The results of the authors quoted above were all obtained in fasting subjects, and it is possible that anticholinergics have little effect on the emptying of a normal meal. Atropine 2·0 to 4·0 mg delayed the emptying of a liquid test meal in only four of eight experiments (Brömster *et al.*, 1969).

Simultaneous administration of an anticholinergic may increase the absorption of another drug (Levy *et al.*, 1972; Manninen *et al.*, 1973; Jaffe, 1975); delayed gastric emptying and intestinal transit could result in a more complete absorption of some drugs in the small intestine. Although in the present study atropine had no effect on the blood concentrations of cimetidine, it was associated with an increase of the mean 24 h urinary excretion of cimetidine from 353 to 419 mg/day, a change that was not statistically significant.

On the mornings after the 36 h of treatment with cimetidine, despite a raised intragastric pH, there was no associated rise of fasting plasma gastrin (Fig. 5). After a similar change of acidity in previous 24 h experiments with cimetidine, there was a rise of fasting plasma gastrin in healthy subjects (Pounder *et al.*, 1976) but no response in six duodenal ulcer patients (Pounder *et al.*, 1975). This apparent difference between the two groups requires further investigation.

The results of this study show that in terms of the 24 h intragastric acidity and nocturnal acid secretion of patients with duodenal ulcer there is little to be gained by the simultaneous use of submaximal doses of an H_2-receptor antagonist and an anticholinergic. Larger doses of an anticholinergic could add to the anti-secretory effect of an H_2-receptor antagonist, or alter its rate of absorption, but it is probable that they would produce unpleasant side effects due to systemic parasympathetic blockade.

Cimetidine is the only potent anti-secretory drug that does not appear to cause acute side-effects, and this important advantage would be lost if it were given with a maximal dose of an anticholinergic.

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