Aspects of the effect of metiamide on pentagastrin-stimulated and basal gastric secretion of acid and pepsin in man

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SUMMARY This study has examined the inhibition produced by metiamide on the gastric secretion of acid and pepsin in 13 patients with duodenal and three with gastric ulcer. The effect of metiamide on the response to a range of doses of pentagastrin in three normal individuals was determined, as was the interaction of metiamide and atropine on prolonged basal secretion. Metiamide inhibited the secretion of acid more than pepsin and the gastric secretion of patients with gastric ulcer more than duodenal ulcer. Metiamide inhibited both the maximal secretory response attainable with pentagastrin and decreased the sensitivity to pentagastrin. Atropine augmented and prolonged the action of metiamide.

Metiamide, an H₂-receptor antagonist (Black, Duncan, Durant, Ganellin, and Parsons, 1972), has been shown to inhibit the basal (Konturek, Biernat, and Oleksy, 1974; Mainardi, Maxwell, Sturdevant, and Isenberg, 1974), nocturnal (Milton-Thompson, Jenkins, Williams, and Misiewicz, 1974; Thjodleifsson and Wormsley, 1974), and pentagastrin-stimulated (Konturek *et al*, 1974; Thjodleifsson and Wormsley, 1974) secretion of acid and pepsin from the human stomach. The present study has sought to examine different aspects of the pharmacological basis of the gastric secretory inhibition produced by metiamide and has also attempted to provide a basis for assessing the dose requirements of metiamide in the treatment of peptic ulcer.

Methods and Patients

Thirteen patients with duodenal ulcer and three patients with gastric ulcer, in all of whom the diagnosis had been confirmed endoscopically, were invited to take part in the study. All gave informed consent. After an overnight fast, gastric contents were aspirated for 20 minutes through a modified nasogastric (Ryle's) tube. Pentagastrin was then given by constant-rate intravenous infusion at a

rate of 2 µg/kg body weight-hour for 165 minutes. Gastric contents were aspirated continuously in 11 batches of 15 minutes each. During the period from 60 to 120 minutes (periods 4 to 8) after starting the pentagastrin infusion, 200 mg metiamide (tritiated at the 2 position of the imidazole ring and dissolved in 0.15 M sodium chloride) was given in a separate infusion into the same arm as the pentagastrin infusion. Blood for measurement of the metiamide concentration was taken from the opposite arm before the start of the metiamide infusion and then at 15-minute intervals until the end of the test.

In order to assess the relevance of the blood concentrations of metiamide attained by intravenous infusion of the drug, blood concentrations were measured at 30, 60, 120, 240, and 360 minutes after oral administration of 200 mg tritiated metiamide, given immediately after breakfast. In eight of the patients with duodenal ulcer who were undergoing treatment with the drug, blood concentrations were again measured after the same oral dose of tritiated metiamide, following treatment for one to three weeks.

In three normal subjects (medical students) the relationship between gastric secretion and dose of pentagastrin was determined by giving 0.05, 0.2, 1.0, and 4.0 µg/kg-hour pentagastrin for 60 minutes on separate days and aspirating gastric contents in 15-minute batches. The same dose schedule was then repeated twice for each subject in order to study the

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effect of two dose levels of metiamide, except that the lowest dose of pentagastrin was not given during administration of the higher dose of metiamide because secretory inhibition was almost complete with the second lowest dose of pentagastrin. The metiamide was given intravenously 10 minutes before the start and during the course of the pentagastrin infusion in two dose schedules: (I) an intravenous bolus dose of 75 mg followed by continuous infusion of 30 mg during 60 minutes; and (II) an intravenous bolus dose of 20 mg, followed by continuous infusion of 30 mg during 60 minutes.

The two dose schedules had been calculated to give approximately steady blood concentrations of metiamide of 6 to 8 and 1 to 3 μM respectively. The calculations were confirmed by direct monitoring of the blood levels during the test.

In two patients with duodenal ulcer an attempt was made to establish a possible therapeutic basis for augmenting the gastric inhibitory action of metiamide by the use of anticholinergic drugs.

The tests started in the morning after an overnight fast. Each patient was intubated with a modified nasogastric (Ryle's) tube. Resting gastric contents were discarded. The following experimental schedules were employed:

1 The control tests involved collection of 30-minute batches of basal (unstimulated) gastric contents for at least four hours.

2 After control collection for at least 30 minutes, tritiated metiamide was given intravenously in a dose of 75 mg and followed by continuous infusion of metiamide at a rate of 40 or 80 mg per hour (for subjects SP and AM, respectively) for one hour. Blood was taken for measurement of concentrations of metiamide at five, 30, 60, 90, 120, and 240 minutes after starting the infusion. Gastric aspiration was continued throughout and for 2½ and 3½ hours, respectively, after the infusion.

3 After the control collection, metiamide was infused in doses as in (2). At the same time, atropine was given intravenously in a single injection of 0.6 mg. Gastric aspiration was continued as in (2).

4 Subject SP had one further test. After controlled collection, atropine was given intravenously in a single injection of 0.6 mg. Gastric aspiration was continued as in (2).

The concentration of acid in all samples of gastric juice was determined by automatic titration with 0.1 M sodium hydroxide to pH 7.0. The activity of pepsin was measured by the method of Hunt (1948). (In the remainder of the text, 'peptic activity' will be referred to as 'pepsin'.) The concentration of metiamide was measured by scintillation counting of an octanol extract of the blood.

The statistical analyses were carried out according

to Snedecor and Cochran (1967) as appropriate, using the two-tailed paired 't' test; comparison of means of unequal samples with unequal variances; and linear regression using the method of least squares.

CALCULATIONS

Intravenous infusion of metiamide

The mean output of acid and pepsin during the two 15-minute periods preceding the metiamide infusion (periods 3 and 4) has been taken as control and is referred to as 100%. The proportional (percentage) inhibition in all subsequent periods was calculated as follows:

$100 - (S_x \cdot 100)/([S_3 + S_4]/2)$ —where S_x = output of acid (or pepsin) in period x and $[S_3 + S_4]/2$ = mean output of acid (or pepsin) during control periods. Blood concentrations of metiamide during each period were assumed to be the arithmetic mean of the levels at the beginning and the end of the respective period. The blood concentration of metiamide required to achieve 50% inhibition (IC_{50}) was calculated for each patient by least squares regression analysis of $\log[(\% \text{ inhibition})/(100 - \% \text{ inhibition})]$ on $\log$ blood concentration of metiamide for periods 7 to 11. Logit 0 (intercept of regression line with x -axis) gave $\log \text{IC}_{50}$. The value of IC_{50} for acid secretion could not be calculated for three patients. In one individual, the gastric aspirate remained alkaline during metiamide infusion and IC_{50} was considered to be less than 1 μM . In the other two subjects, the inhibition remained constant at 76 to 80% and 95 to 98% respectively for all concentrations of metiamide and extrapolation to 50% inhibition was therefore impossible. The value of IC_{50} for pepsin secretion could not be calculated for five patients because linear regression was not significant, due to the pattern of the time course of the interaction between metiamide and pepsin secretion.

Effect of metiamide on dose response to pentagastrin

The results from the three subjects were pooled. For each dose, the outputs during the last 30 minutes of each test were compared. For the purpose of comparison, gastric acid secretion in response to different doses of pentagastrin has been analysed in terms of Michaelis-Menten kinetics. In order to obtain the most accurate kinetic constants, the transformation of the Michaelis-Menten equation suggested by Dowd and Riggs (1965) was used to calculate ED_{50} (dose of pentagastrin required for 50% of maximal secretion) and CMR (calculated maximal response) according to the equation: $\text{response} = \text{CMR} - \text{ED}_{50} (\text{response/dose})$.

Least squares linear regression of response/dose (abscissa) against response (ordinate) gave estimates of CMR ($y - \text{intercept}$) and ED_{50} (negative slope).

Inhibition of basal secretion

The inhibition of basal secretion was calculated for each period from the corresponding period in the control test, according to the formula: percentage inhibition = $100 - [(S_x \cdot 100) / S_c]$ where S_x is the secretion in the test period and S_c in the corresponding control period.

Results

INTRAVENOUS METIAMIDE

Results from the 13 patients with duodenal ulcer (DU) were analysed separately from the pooled results of the three patients with gastric ulcer (GU). Gastric secretion of acid and pepsin in the patients with GU was inhibited more than in patients with DU by all concentrations of metiamide (fig 1). The

Fig 1 Relationship between concentration of metiamide in blood and inhibition of secretion of acid and pepsin. Each point represents mean values ($\pm$ SEM) derived as described in the text. The closed circles indicate results from patients with duodenal ulcer; the open circles, from patients with gastric ulcer. The lines joining the points have been fitted by visual inspection

Patient No.	Acid		Pepsin	
	IC_{50}^1	r	IC_{50}	r
1	5.93	0.79	7.55	0.74
2	4.13	0.95	7.18	0.95
3 (GU)	1.53	0.87	2.14	0.67
4	4.95	0.89	4.86	0.95
5	5.55	0.91	5.46	0.73
6	5.80	0.70	—	—
7 (GU)	1.0	—	1.70	0.98
8	3.50	0.93	5.90	0.83
9	6.40	0.62	—	—
10 (GU)	2.65	0.93	4.95	0.70
11	2.12	0.81	7.54	0.35
12	2.50	0.87	—	—
13	—	—	—	—
14	5.60	0.85	11.30	0.87
15	—	—	—	—
16	3.80	0.99	3.33	0.53
Overall mean	3.96	—	5.63	—
SD	1.79	—	2.75	—
GU mean	1.73	—	2.93	—
SD	0.84	—	1.76	—
DU mean	4.57	—	6.64	—
SD	1.45	—	2.38	—

Table Kinetic analysis of inhibitory effects of plasma levels of metiamide on pentagastrin-stimulated secretion of acid and pepsin by the stomach

¹ IC_{50} = dose of metiamide ($\mu\text{mol/l}$) necessary to elicit 50% inhibition of pentagastrin-stimulated secretion of acid or pepsin.

maximal inhibition of the secretion of acid and pepsin was significantly greater in the patients with GU than DU ($P < 0.05$). The inhibition of pepsin secretion was less than acid secretion at all concentrations of metiamide and the maximal degree of inhibition of pepsin secretion was significantly less than acid secretion in both groups of patients (DU— $P < 0.01$; GU— $P < 0.05$).

The IC_{50} of metiamide was significantly higher for pepsin secretion than for acid secretion in all individuals considered together (table) ($P < 0.025$) and in the group of DU patients alone ($P < 0.05$). The group of GU patients had a significantly lower IC_{50} for acid secretion than the patients with DU ($P < 0.05$) but the IC_{50} for pepsin secretion was not significantly different in the two groups.

The IC_{50} for inhibition of acid secretion by metiamide showed positive correlation with the acid-secretory response to pentagastrin when the results from all patients (DU and GU) were considered together (fig 2) ($r = 0.72$; $P < 0.01$) but the correlation was not significant for the DU group alone. The correlation between pepsin-secretory response and IC_{50} for pepsin secretion was not significant.

ORAL DOSE OF METIAMIDE

Since the results were homogeneous, for clarity of presentation only the results from the eight patients

Fig 2 Relationship between IC_{50} for inhibition of acid secretion by metiamide and acid-secretory response to pentagastrin.

Closed circles denote results from patients with duodenal ulcer; open circles from patients with gastric ulcer

who had tests before and during treatment with metiamide are shown (fig 3). The blood concentrations of metiamide rose more rapidly and remained higher after the second dose of metiamide (given during the course of treatment) than after the first dose. The difference between the two sets of blood concentrations was greatest at 30 minutes but did not reach levels of significance.

EFFECT OF METIAMIDE ON DOSE RESPONSE TO PENTAGASTRIN

Acid secretion

The mean CMR to pentagastrin was progressively depressed from the control value of 16.2 to 8.9 mmol/30 minutes with schedule II dosage of metiamide and further reduced to 6.1 mmol/30 minutes with schedule I dosage (fig 4). The ED_{50} of pentagastrin increased from the control value of 0.15 to 0.32 $\mu\text{g/kg-hour}$ (schedule II) and to 0.90 $\mu\text{g/kg-hour}$ for schedule I.

Pepsin secretion

The mean peak output for the three students in the control tests was achieved with 1.0 $\mu\text{g/kg-hour}$ pentagastrin. The highest dose of pentagastrin

Fig 3 Concentrations of metiamide in blood after oral dosage, before, and during treatment.

Each point represents mean values ($\pm$ SEM) of concentrations in blood of eight subjects. The pretreatment test is denoted by the symbol I and the test during treatment with metiamide by II.

The horizontal line depicts, for patients with duodenal ulcer, the mean IC_{50} for inhibition of pentagastrin-stimulated acid secretion by metiamide.

Fig 4 Acid secretion in response to increasing doses of pentagastrin, without and with metiamide.

Each point represents the mean values from three subjects. The closed circles indicate the control dose-response relationship between acid secretion and dose of pentagastrin; the closed squares indicate the dose-response pattern with the smaller dose of metiamide and the open squares indicate the dose response relationship during administration of the larger dose of metiamide.

The log dosage of pentagastrin is depicted along the abscissa; the arithmetic values of the doses are shown in parentheses

Fig 5 Pepsin secretion in response to increasing doses of pentagastrin, without and with metiamide. Significance of symbols as in figure 4

resulted in lower pepsin outputs (fig 5). Kinetic analysis was therefore not possible. The lower dose of metiamide (schedule II) resulted in mean inhibition of 35 and 42% for the two lowest doses of pentagastrin and 58 and 53% respectively for the two highest doses. For dose schedule I, the mean inhibition was 59, 68, and 68% respectively.

EFFECTS OF METIAMIDE AND ATROPINE ON BASAL GASTRIC SECRETION

During the course of prolonged aspiration of basal gastric secretion in subject SP, there was a greater degree of inhibition of acid than pepsin secretion both by metiamide (mean inhibition of acid = 83.2% and of pepsin = 27.5%) and by atropine (mean inhibition 74.0% and 39.8% respectively). Basal gastric secretion was abolished for 2½ hours by the combination of the two drugs (fig 6).

In subject AM, the higher dose of metiamide alone had a greater inhibitory effect than in patient SP, but secretion of acid and pepsin had similarly returned to control levels within 90 minutes after discounting the infusion of metiamide. The addition of atropine abolished the rebound secretion (fig 7).

Fig 6 Time course of basal secretion of gastric juice in patient SP.

Each set of four columns represents values for volume (dots), acid concentration (cross hatch), acid output (solid bars) and pepsin output (open bars) during a 30-minute collection period, the timing of which is depicted along the abscissa.

Atropine, metiamide, or the combination of drugs was given, as described in the text, at the time indicated by the arrow.

The closed circles indicate the concentration of metiamide in blood

Fig 7 Time course of basal secretion of gastric juice in patient AM.

Significance of symbols as in figure 6

Discussion

GASTRIC INHIBITORY EFFECT OF METIAMIDE IN PATIENTS WITH DUODENAL OR GASTRIC ULCER

The dose of metiamide used in the present study had previously been shown to inhibit acid secretion in normal subjects by 87%, a value intermediate between our patients with duodenal ulcer (80%) and gastric ulcer (97%). The degree of inhibition of gastric acid secretion has previously been shown to be inversely related to the intensity of stimulation of the stomach (Code and Watkinson, 1955) and since patients with duodenal ulcer tend to be more sensitive to stimulants than normal (Isenberg, Grossman, Maxwell, and Walsh, 1975), it seems possible that the dose of pentagastrin (2 µg/kg-hour) used in the present study may have provided a relatively greater degree of stimulation for patients with duodenal ulcer, resulting in the lesser inhibitory effect of metiamide in the patients with duodenal ulcer compared with those with gastric ulcer. An alternative explanation is provided by the lower values of IC_{50} (concentration of metiamide required to achieve 50% inhibition) in our patients with

gastric ulcer compared with duodenal ulcer, a finding which is compatible with greater 'sensitivity' of gastric ulcer patients to the gastric inhibitory action of metiamide, or greater relative 'resistance' to metiamide of patients with duodenal ulcer.

INHIBITORY EFFECT OF METIAMIDE ON SECRETION OF ACID AND PEPSIN

The present study has confirmed our previous observation (Thjodleifsson and Wormsley, 1974) that metiamide inhibits gastric secretion of acid more than secretion of pepsin in man. The relatively greater inhibitory effect of metiamide on acid, compared with pepsin, secretion results mainly from change in the pattern of secretion of the two components of gastric juice, since the concentration of acid, but not of pepsin, decreases during inhibition by metiamide (Thjodleifsson and Wormsley, 1974).

More detailed examination of the inhibitory effect of metiamide involved the use of doses of the drug which gave blood concentrations respectively greater and less than the IC_{50} . We used a linear transformation of the Michaelis-Menten equation for estimation of the 'kinetic constants' V_{max} , which in gastric secretory terms is the CMR (calculated maximal response) and K_m , which in terms of interaction between stimulant and gastric response is the ED_{50} (dose of pentagastrin required to stimulate secretion at half the maximal rate), since description in terms derived from kinetic analysis of enzymically controlled biochemical reactions has been found useful for describing and comparing pharmacological reactions such as the gastric secretory responses to stimulants and inhibitors (Makhlouf, McManus, and Card, 1966; Grossman, 1970). If a gastric secretory inhibitor increases the ED_{50} but leaves the CMR unchanged, then the interaction between inhibitor and stimulant is considered to be competitive, while reduction in the CMR is considered to show non-competitive antagonism between the drugs.

In the present study, metiamide affected the acid-secretory response to increasing doses of pentagastrin in three normal subjects both by decreasing the calculated maximal response and by increasing the dose of pentagastrin required to elicit the half-maximal secretory rate. The higher of the two blood levels had a greater effect on both aspects of the gastric secretory response (higher ED_{50} , lower CMR) than the lower blood level. The antagonism on acid secretion between metiamide and pentagastrin is therefore 'mixed type'. Metiamide also decreased the calculated maximal pepsin response to pentagastrin, although an approximate estimate of the ED_{50} for pepsin showed little change. In dogs, the inhibitory effect of metiamide has similarly been

interpreted as 'uncompetitive', both with histamine and pentagastrin as stimulant, since ED_{50} was markedly increased and CMR reduced by metiamide (Gibson, Hirschowitz, and Hutchison, 1974). In man and dog metiamide, therefore, both decreases the total capacity of the stomach to respond to pentagastrin and decreases the sensitivity of the acid-secreting cells to pentagastrin.

The implications of the mixed competitive and non-competitive pattern of the effect of metiamide on pentagastrin- and histamine-stimulated gastric secretion have complicated the hypothesis that metiamide acts only by blocking the action of drugs on the H_2 -receptors of the parietal cells. Black (1973) proposed the presence of both excitatory and inhibitory receptors to pentagastrin on the parietal cells and showed how a pattern suggestive of non-competitive interaction might result if the inhibitory action of pentagastrin were more difficult to activate than the excitatory effect. We have recently suggested that if the effects of metiamide cannot be explained by blockade of the H_2 -receptors alone, then our recent confirmation in man (Shepherd, Thjodleifsson, Turnbull, and Wormsley, 1974) of the finding *in vitro* that metiamide stimulates histamine methyl transferase (Barth, Niemeyer, and Lorenz, 1973) may indicate a further possible mechanism for the complex action of metiamide on gastric secretion.

DOSAGE OF METIAMIDE REQUIRED FOR GASTRIC INHIBITION

The blood concentration of metiamide required to obtain 50% inhibition of pentagastrin-stimulated secretion of acid has been found to range from less than 1 to 6.4 $\mu\text{mol/l}$, so that dose requirements for inhibition may differ appreciably between individuals. The present study has shown that there is a correlation between a wide range of acid-secretory capacity and IC_{50} (dose of metiamide required to produce 50% inhibition) in our combined population of patients with gastric or duodenal ulcers. If the correlation represents the pattern in the population as a whole (and is not fortuitously caused by the selection and combination of a 'sensitive' (GU) and 'resistant' (DU) population) then measurement of acid secretory capacity may serve as a guide to dose requirement of metiamide.

INHIBITORY INTERACTION OF METIAMIDE AND ATROPINE

In accordance with the requirements of the Clinical Trials Certificate, higher doses of metiamide were not used in the present study, so that we have no information about the limits, if any, of the inhibitory action of metiamide on acid secretion. However, our findings show that atropine augments and

prolongs the gastric inhibition produced by metiamide, so that very satisfactory long-continued suppression of basal gastric secretion is provided by the combination of the two drugs.

ORAL ADMINISTRATION OF METIAMIDE

The present study has shown that the blood concentrations of metiamide, attained by intravenous infusion of the drug and shown to effect gastric inhibition, are also achieved after oral administration of the drug. The transintestinal passage of metiamide does not appear to affect significantly the chemical nature or gastric inhibitory action of metiamide. Thus, similar values for concentrations were obtained by measurement of the levels of the tritiated drug in the present study compared with direct chemical analysis by high pressure liquid chromatography in two subjects (unpublished results). The similar pharmacological (gastric inhibitory) efficacy of the two modes of administration of metiamide had been demonstrated previously (Thjodleifsson and Wormsley, 1974) when it was shown that a similar degree of gastric inhibition was achieved by intravenous and intraintestinal administration of the drug.

Pharmacological analysis based on the response to intravenously administered metiamide is therefore relevant to the utilization of the drug in tablet form.

During treatment with metiamide, the blood concentration after an oral load of 200 mg remained above the mean IC_{50} for duodenal ulcer for 2½ hours. A dose of 200 mg given after the three main meals would therefore probably achieve more than 50% secretory inhibition during the interdigestive periods of the day in patients with average acid-secretory capacities (30 to 40 mM/hour). Given after meals, blood concentrations of metiamide would be greatest at a time when the buffering effect of the meal itself was diminishing. These theoretical results have been borne out by the recent study of Richardson, Baily, Walsh, and Fordtran (1975) who investigated the inhibition by metiamide of meal-stimulated gastric secretion directly.

A previous study had shown that adequate inhibition of nocturnal gastric secretion was achieved, in most patients suffering from duodenal ulcer, with 400 mg metiamide, given as a single dose (Milton-Thompson *et al*, 1974), or in divided doses during the night (Thjodleifsson and Wormsley, 1974). The findings of the present study that atropine augments and prolongs the gastric inhibitory effect of metiamide extends our previous observation that when nocturnal gastric secretion is not satisfactorily controlled with this dose of metiamide, the degree of gastric inhibition can be increased by atropine (Thjodleifsson and Wormsley, 1974).

Conclusion

The powerful inhibitory action of metiamide on gastric secretion suggests that the drug may be valuable in the treatment of diseases in which secretion of acid and pepsin is thought to play an aetiological role. The degree of reduction of secretion of acid and pepsin which has to be achieved in order to permit healing of the mucosal lesions has not been defined. However, the majority of duodenal and gastric ulcers heal after vagotomy, which reduces acid-secretory capacity by 50% (Jepson, Lari, Humphrey, Smith, Wilkinson, and Johnston, 1973). That the healing of ulcers after vagotomy is indeed due to the reduction in the secretion of acid and pepsin, rather than to some other effect of the operation, seems likely in view of the healing which has been observed after treatment with metiamide in doses which have produced similar degrees of reduction of gastric secretion (Thjodleifsson and Wormsley, 1975).

KGW is in receipt of a grant from the Scottish Hospital Endowments Research Trust. The metiamide was kindly supplied by Dr M. Bloch of Smith, Kline and French Laboratories, Ltd, Welwyn Garden City. The authors wish to thank Miss W. Ealding for estimation of tritiated metiamide, and Mrs F. Deer and Miss S. Drummond for technical assistance.

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