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Effect of Histamine H_2-Receptor Blockade on Vagally Induced Gastric Secretion in Man

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Summary

Metiamide, an antagonist of histamine H_2 receptors, was administered intravenously to normal subjects and to patients with a peptic ulcer during vagal stimulation with a constant infusion of insulin. In normal and peptic-ulcer subjects there were reductions of 70% and 71% respectively in gastric-acid output compared with control tests on the same subjects. The decreased acid output resulted from a reduction in both volume of secretion and acid concentration. Metiamide is therefore a potent inhibitor of vagally-induced gastric acid secretion.

Introduction

Certain actions of histamine in the body, such as the stimulation of smooth muscle in the gut and bronchi, are antagonized by mepyramine. Ash and Schild (1966) termed such mepyramine-sensitive receptors H_1 receptors and suggested that those actions of histamine which were unaffected by mepyramine, including the stimulation of gastric secretion, were mediated by a second type of receptor. This second group, now known as H_2 receptors, was defined by Black *et al.* (1972) when they described the properties of burimamide, the first selective H_2 receptor antagonist.

The H_2 receptor antagonists, burimamide and its more potent analogue metiamide (fig. 1), antagonize the stimulation of gastric secretion in man both by histamine and pentagastrin (Wyllie and Hesselbo, 1973). These findings have rekindled controversy as to the physiological role of histamine in gastric secretion and have suggested that H_2 receptor antagonists might have therapeutic value in the treatment of peptic ulcer.

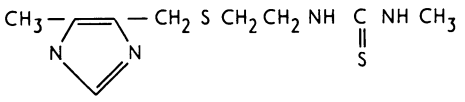

FIG. 1—Chemical structure of metiamide.

The present experiments were undertaken to assess the effect of metiamide on vagally-induced gastric secretion in man using the insulin infusion test as a constant vagal stimulus (Carter *et al.*, 1972).

Patients and Methods

HEALTHY VOLUNTEERS

Paired insulin infusion tests were carried out in six healthy male volunteers with no previous dyspeptic history and ranging in age from 27 to 34 years.

After a 12-hour overnight fast the subject was intubated as described by Hassan and Hobsley (1970). The tests began with collection of two 15-minute samples of basal gastric secretion after which insulin (0·03 U/kg/hr) were infused intravenously for 150 minutes while gastric juice was collected every 15 minutes. All samples were assessed in terms of volume (ml), pH, acid concentration (mmol/l.), and acid output (mmol). All titrations were carried out to end-point pH 7 using 0·1 N NaOH solution, a glass pH electrode, and an automatic titrator (Radiometer, Copenhagen).

After 60 minutes of insulin infusion a second intravenous infusion was begun in the opposite arm. In tests using metiamide 250 mg of the drug diluted to 13·2 ml with normal saline was delivered at a constant rate of 200 mg/hr for 75 minutes. In the control tests the technique was identical but for the omission of metiamide from the saline vehicle. The order of the paired tests was randomized and unknown to the subject. The interval between the two tests was less than two weeks in all but one of the subjects in whom the tests were six weeks apart.

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Venous blood was taken once during the basal period and every 30 minutes during insulin infusion for blood glucose estimation by a glucose oxidase method and autoanalyser.

PEPTIC ULCER PATIENTS

Paired insulin infusion tests were carried out in five men with chronic peptic ulceration (four duodenal ulcer, one gastric ulcer) whose ages ranged from 34 to 63 years.

The techniques of the paired tests were identical to those used in healthy volunteers but for the fact that an insulin dose of 0·04 U/kg/hr was used. The order of the paired tests was again randomized and unknown to the subject. In every case, the interval between the paired tests was less than two weeks.

In four further patients (three men, one woman; age range 34-52) with chronic duodenal ulceration single extended insulin infusion tests were carried out. In each case insulin 0·04 U/kg/hr was infused for '80 minutes. After 105 minutes of insulin infusion a second intravenous infusion was begun in the opposite arm and 200 mg metiamide diluted to 10·6 ml with normal saline, was infused at a constant rate for 75 minutes.

PLASMA METIAMIDE LEVELS

In five subjects (two volunteers and three peptic ulcer subjects) tritium-labelled metiamide was infused. In these cases serial blood samples were withdrawn and the estimation of plasma metiamide levels was undertaken as described by Hesselbo (1973).

Results

In the expression of results the following terms are used: (*a*) plateau acid output is the sum of the four highest consecutive 15-minute acid outputs during insulin infusion, expressed in mmol/hr; (*b*) peak acid output is the sum of the two highest consecutive 15-minute acid outputs during insulin infusion multiplied by two and expressed in mmol/hr; (*c*) plateau blood glucose is the mean of all blood glucose values recorded after insulin infusion had been in progress 60 minutes expressed in mg/100 ml.

Healthy Volunteers.—The results of a typical pair of tests in one volunteer are shown in fig. 2. In the control test a sustained secretory response was obtained after an hour of insulin infusion. When metiamide was infused concurrently the acid output dropped markedly. The results in the six pairs of tests are summarized in the table. In all cases the plateau acid output was reduced by metiamide, the mean reduction being 70·3% compared with the controls. This reduction resulted from a fall in both the volume of secretion and the acid concentration and was statistically significant (paired *t* test, $P < 0.01$).

Peptic-Ulcer Patients.—The results of the five pairs of tests in peptic ulcer patients are summarized in the table, the mean reduction in plateau acid output being 71·2% compared with the controls ($P < 0.01$). The results of the four single extended insulin infusion tests in duodenal ulcer patients are shown in fig. 3. In every case the established

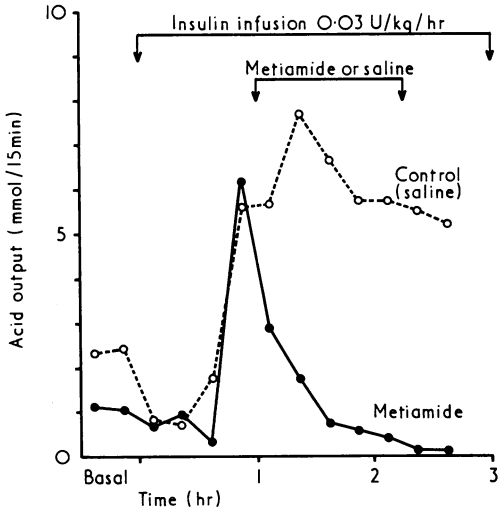

FIG. 2—Effect of metiamide infusion on acid output induced by insulin infusion in healthy volunteer.

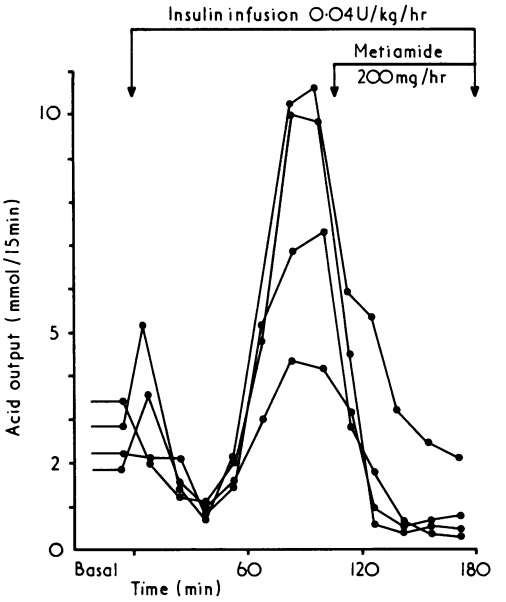

FIG. 3—Effect of metiamide on acid output induced by insulin infusion in four patients with peptic ulceration.

secretory response to insulin infusion was reduced on beginning concurrent metiamide infusion. When the peak acid output in the test before metiamide was compared to the peak acid output in the final hour of the three-hour test there was a mean reduction in peak acid output of 76·9% This reduction was statistically significant (*t* test on paired data, $P < 0.01$).

Blood Glucose Changes.—When all 11 paired tests were considered there was no significant difference between control and metiamide tests in terms of either the mean fasting or mean plateau blood glucose. No adverse side effects were

Effect of Metiamide on Gastric Acid Secretion in Paired Tests. Results are expressed as Means ± S.D.

	Volume (ml/hr)		Acid Concentration (mmol/l.)		Plateau Acid Output (mmol/hr)	
	Control	Metiamide	Control	Metiamide	Control	Metiamide
Normal volunteers (n = 6)	180·5 ± 32·5	88·3 ± 22·3	116 ± 16	71 ± 25	20·9 ± 6·4	6·2 ± 3·7
Peptic-ulcer patients (n = 5)	248·5 ± 80·4	116·9 ± 43·7	106·2 ± 17·7	64·7 ± 31·4	26·4 ± 11·4	7·6 ± 7·0

recorded during any of the tests apart from occasional mild hypoglycaemic symptoms attributable to insulin.

Plasma Metiamide Concentrations.—In the five subjects studied with tritium-labelled metiamide the mean plasma concentration 60 minutes after the start of the infusion was 7·09 μmol/l. (range 6·18-8·65 μmol/l.).

Discussion

Though histamine H_2 receptor antagonists clearly inhibit both histamine-induced and pentagastrin-induced gastric secretion there has been some uncertainty concerning their effects on vagally-induced secretion. In their description of the properties of the first H_2 receptor blocking agent, burimamide, Black *et al.* (1972) observed no inhibition of carbachol-stimulated gastric secretion in the rat. In the fistula dog, however, metiamide has been shown to inhibit vagally induced gastric secretion when 2-deoxy-D-glucose was used as the stimulant (Grossman and Konturek, 1973). Our own results now show conclusively that metiamide also inhibits vagally-stimulated acid secretion in man, with reduction of both the volume and acid concentration of the gastric juice.

Metiamide thus inhibits acid secretion evoked in man by the three major agonists—histamine, gastrin, and acetylcholine. At first sight this lends support to the theory of MacIntosh (1938) that histamine serves as the "final common pathway" in the mediation of the gastric secretion since specific blockade of the histamine receptor would be expected to inhibit the effect of gastric secretory stimuli acting through histamine but not those independent of it. Grossman and Konturek (1973) have suggested, however, that the three major agonists each bind to a specific receptor site on the parietal cell and that blockade of one receptor may modify the response of one or both the other receptors to their respective agonists. Consistent with this hypothesis is the observation that cholinergic blockade by atropine inhibits secretion induced by histamine or pentagastrin (Konturek *et al.*, 1968), and histamine H_2 receptor blockade by metiamide may thus inhibit vagally mediated gastric secretion by a similar mechanism of receptor interaction. The effect of metiamide on vagally induced secretion would seem, however, to be more substantial than that of atropine on histamine-induced secretion, suggesting that functional integrity of the histamine receptor may have a particular importance. Thus the role of histamine in the physiology of gastric secretion is still controversial though it seems likely that further work with H_2 receptor antagonists will enhance our understanding of the problem.

Regardless of the physiological implications of H_2 receptor blockade the efficacy of metiamide as an inhibitor of acid secretion raises the question of its therapeutic potential. In the present studies the inhibition of acid secretion has been achieved at plasma metiamide concentrations comparable with those which follow a 300-mg oral dose of the drug (unpublished observations). One possible limitation to the value of metiamide in the treatment of peptic ulceration, however, relates to its effect on pepsin secretion. Our own preliminary studies in man and those of Hirschowitz and Gibson (1973) in the fistula dog suggest that pepsin secretion in response to cholinergic stimuli may be unaffected or even increased by metiamide. Nevertheless, on satisfactory conclusion of current toxicity trials formal therapeutic trials will be indicated to assess the value of metiamide in peptic ulcer therapy.

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Oral Contraceptives and Increased Formation of Soluble Fibrin

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Summary

Soluble fibrin was measured weekly for two months in 12 normal women and in 12 women on combined oestrogen-progestogen therapy (Ortho-Novin, Norinyl, Enavid, Ovral, Ovulen, Demulen). Plasma soluble fibrin concentration in women on oral contraceptives showed an increase of 97·2% ($P < 0·001$) above that of normal women. In three cases, where each woman on the oral contraceptive served as her own control, stopping medication led to a return to normal of the plasma content of soluble fibrin.

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Introduction

A similarity between the magnitude and the direction of changes in blood clotting and thrombolytic factors in patients with thrombosis and in women using oestrogen- and progestogen-based oral contraceptives was reported 10 years ago (Pilgeram, 1964; Pilgeram and Amundson, 1964; Pilgeram *et al.*, 1964).