# Gastric Response to Metiamide

B. THJODLEIFSSON, K. G. WORMSLEY

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## Summary

**Metiamide greatly reduced pentagastrin-stimulated and overnight secretion of acid and pepsin in 11 patients with duodenal ulcer and virtually abolished gastric secretion in three patients with gastric ulcer. The drug was equally effective when infused intravenously or intraduodenally. A therapeutic trial of Metiamide is warranted in diseases caused or aggravated by excess gastric secretion of acid and pepsin.**


## Introduction

Acid and pepsin have long been assumed to be implicated in the pathogenesis of duodenal and gastric ulceration, so currently the most popular treatments for these diseases are surgical procedures to reduce the secretory capacity of the stomach. We report here the results of a study of a pharmacological means of suppressing gastric secretion by the intravenous or intraduodenal infusion of Metiamide.

## Patients and Methods

Thirteen patients with duodenal ulceration and three with gastric ulceration, in whom the diagnosis had been confirmed endoscopically, were invited to take part in the study. The intended procedures were explained to them in detail and their enthusiastic consent obtained. All patients underwent at least one pair of secretory tests.

The first pair of tests was as follows. Firstly, after an overnight fast gastric secretions were aspirated for 20 minutes through a modified Ryle's tube. Pentagastrin (2 $\mu$g/kg/hr) was then given in 0·15 mol NaCl/l. for two hours by continuous intravenous infusion and the gastric contents were then aspirated at intervals of 15 minutes. Secondly, after an interval of not less than two days, a similar infusion of pentagastrin was given but for 2¾ hours—45 minutes longer than in the first test. One hour after the start of the pentagastrin infusion an additional infusion of Metiamide (N-methyl-N′ (2((5-Methylimidazol-4 yl) methio)ethyl)-thiourea) (200 mg in 0·15 mol NaCl/l.) was given for one hour, after which the pentagastrin infusion was continued alone for a further 45 minutes. Gastric contents were aspirated at 15-minute intervals.

A second pair of tests were done on six patients with duodenal ulcer. In the first test they were fasted from 13·00 hours. A triple-lumen tube was passed at 16·00 hours so that the tip was in the fourth part of the duodenum and the gastric aspiration holes sited in the antrum. Metiamide 200 mg was given in tablet form at 16·00 hours and 200 mg Metiamide in the form of crushed tablets was injected directly into the duodenum through the duodenal tube at 22·00 and 04·00 hours. Gastric contents were continuously aspirated from 20·00 hours until 08·00 hours the next morning. In the second test the same procedure was followed except that no Metiamide was given by either route.

In one patient with severe nocturnal hypersecretion of acid three further overnight studies were made. In the first the patient was given 400 mg Metiamide (double the standard dose) at 17·00, 22·00, and 04·00 hours. In the second atropine 0·6 mg was given subcutaneously at 16·00, 22·00, and 04·00 hours. In the third the patient was given 200 mg Metiamide as in the standard test plus atropine 200 mg subcutaneously at 16·00, 22·00, and 04·00 hours.

In a third set of tests, done on two patients with duodenal ulcer, the effect of Metiamide by intravenous infusion was compared with its effect by continuous infusion into the duodenum. Both patients underwent three tests. In a control test 0·15 mol NaCl/l. was infused into the fourth part of the duodenum during the administration of pentagastrin (2 $\mu$g/kg/hr). In the other two tests Metiamide 200 mg in 150 ml 0·15 mol NaCl/l. was infused either intravenously or into the fourth part of the duodenum. The concentration of acid in all samples of gastric juice was determined by automatic titration with sodium hydroxide to pH 7·0. The concentration of pepsin was measured by the method of Hunt (1948).

## Results

No side effects were encountered.

*Response to Pentagastrin.*—In patients with duodenal ulcer Metiamide reduced the output of acid in response to pentagastrin by about 75% (fig. 1), decreasing the volume and the

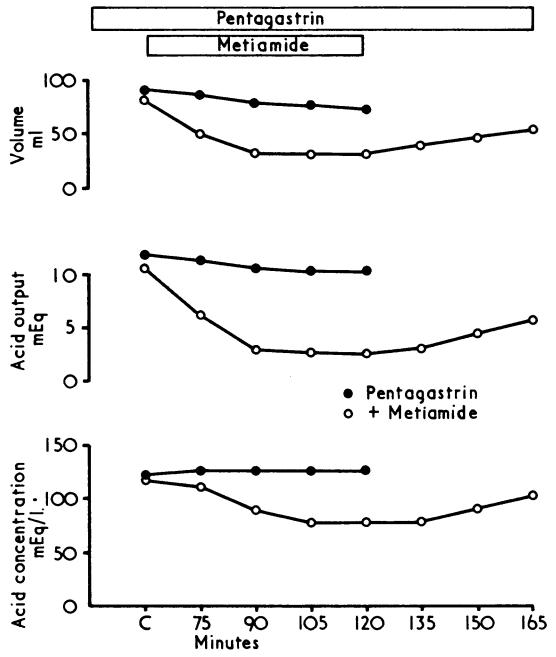


FIG. 1—Effect of Metiamide on pentagastrin-stimulated secretion of acid. Each point represents mean of responses from 11 patients with duodenal ulcer. Pentagastrin was given throughout 165 minutes of study; Metiamide was infused intravenously from 60 to 120 minutes after start of pentagastrin infusion. C represents mean values of volume, acid concentration, and acid output of two 15-minute periods before the start of Metiamide infusion. Closed symbols represent responses during infusion of pentagastrin alone; open symbols represent responses during Metiamide study.

**Department of Therapeutics, University of Dundee, Dundee DD1 4HN**

B. THJODLEIFSSON, CAND. MED., M.R.C.P., Research Fellow
K. G. WORMSLEY, M.D., F.R.C.P., Consultant Physician

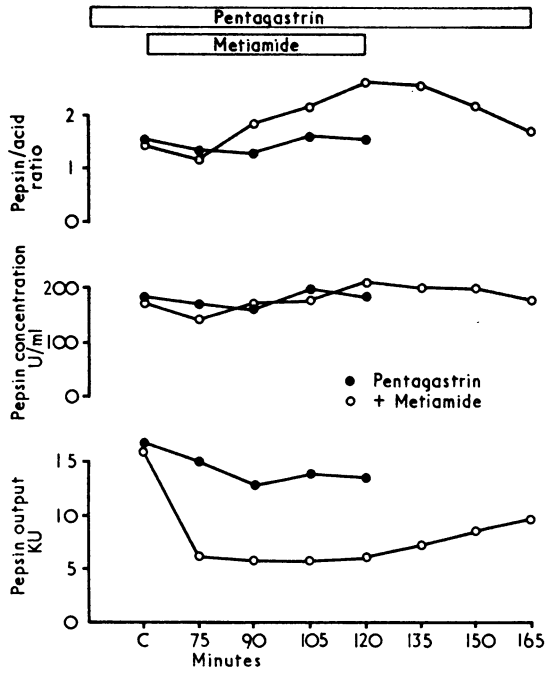


FIG. 2—Effect of Metiamide on pentagastrin-stimulated secretion of pepsin. Significance of symbols as in fig. 1. Pepsin/acid ratio indicates relationship between concentration of pepsin and acid in 11 patients with duodenal ulcer.

concentration of acid of the gastric secretions. The output of pepsin in response to pentagastrin was also reduced significantly during the infusion of Metiamide (fig. 2) though the concentration of pepsin was not significantly altered (fig. 2). In patients with gastric ulcer Metiamide almost abolished the outputs of acid and pepsin in response to pentagastrin (fig. 3).

*Overnight Secretion.*—In patients with duodenal ulcer the overnight secretion of acid was reduced by an average of 50% during the administration of 600 mg Metiamide (fig. 4). Doubling the dose of Metiamide in one patient did not significantly increase inhibition of the overnight secretion. Simultaneous administration of atropine, however, potentiated the inhibitory effect of Metiamide, resulting in considerable lowering of the overnight secretion of acid (see table).

*Intraduodenal Metiamide.*—Intraduodenal and intravenous infusions of Metiamide reduced pentagastrin-stimulated gastric secretion comparably (fig. 5). In one patient the inhibition of gastric secretion was delayed 30 minutes in response to duodenal administration of Metiamide but it persisted longer after the infusion was stopped (fig. 5).

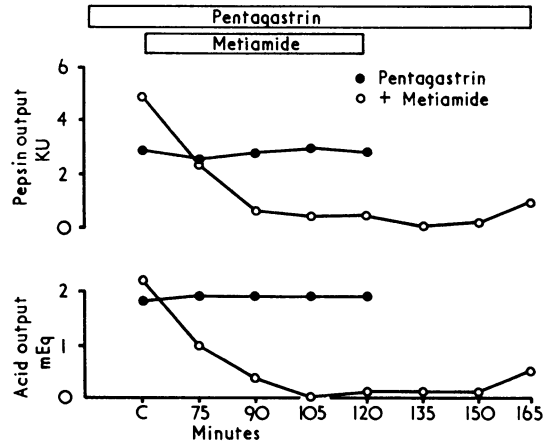


FIG. 3—Effect of Metiamide on pentagastrin-stimulated secretion of acid and pepsin in three patients with gastric ulcer. Significance of symbols as in fig. 1.

*Serial Studies of 12-hour Overnight Gastric Aspirate of One Patient*

| | Volume (ml) | Acid Concentration (mEq/l.) | Acid Output (mEq) |
|---|---|---|---|
| Untreated | 1,450 | 88 | 127·6 |
| Metiamide 200 mg × 3 | 1,220 | 65 | 79·3 |
| Metiamide 200 mg × 3 | 1,160 | 64 | 74·2 |
| Atropine 0·6 mg × 3 | 780 | 86 | 67·1 |
| Metiamide 200 mg × 3 plus Atropine 0·6 mg × 3 | 460 | 22 | 10·1 |

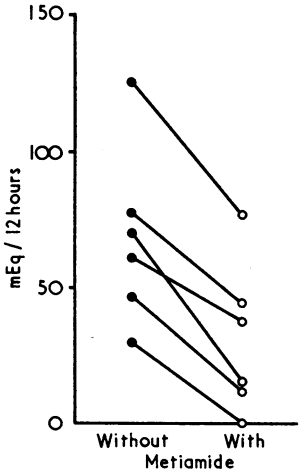


FIG. 4—Effect of Metiamide on overnight acid secretion in six patients with duodenal ulcer. Each pair of symbols indicates results from one patient. Closed circles denote overnight output of acid during control study; open circles indicate values during administration of Metiamide.

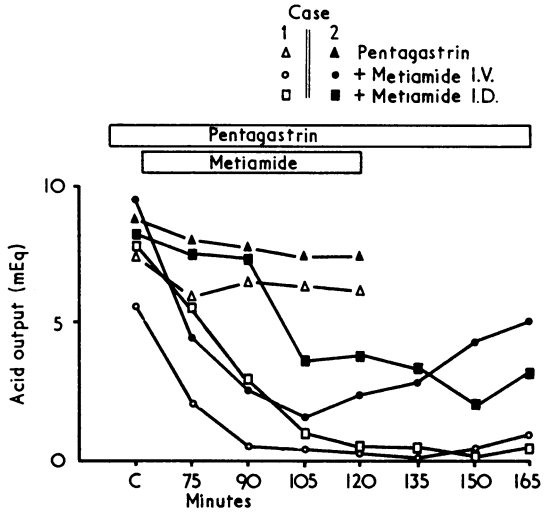


FIG. 5—Comparison of effect of Metiamide infused intravenously and intraduodenally on pentagastrin-stimulated acid output. Each set of like symbols represents results from one study. Closed symbols represent three studies in case 1; open symbols represent three studies in case 2. Triangles denote response to infusion of pentagastrin alone; circles indicate response to Metiamide given intravenously (I.V.); and squares represent effect of Metiamide given intraduodenally (I.D.).

## Discussion

Both duodenal and gastric ulcers heal when the gastric capacity to secrete acid and pepsin is reduced by resection of the fundus or by complete interruption of the vagal innervation of the gastric secretory cells. Complete vagotomy of the parietal cells reduces acid-secretory capacity by about 60% (John-

ston *et al.* 1973) so that if it is reduction in gastric secretion which permits healing of mucosal ulcers a therapeutically satisfactory pharmacological agent would presumably have to reduce acid secretion by an equal amount, particularly during the interdigestive periods of the day and during the night. The results of the present study confirm the findings of Wyllie *et al.* (1973) in healthy volunteers and indicate that in patients with duodenal ulcer Metiamide is capable of reducing gastric secretion to levels seen after vagotomy. A therapeutic trial of Metiamide in the treatment of duodenal and gastric ulceration (and related conditions such as hiatus hernia) is therefore warranted.

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Requests for reprints should be sent to Dr. K. G. Wormsley, Ninewells Hospital, Dundee DD2 1UB.

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# Delayed Postpartum Sterilization

J. MOWAT

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## Summary

**A series of 75 women who requested immediate postpartum sterilization were told this would not be carried out till three months postpartum, and only 64 women subsequently underwent sterilization. While some may regard this as a failure of a family limitation programme, the mental well-being of the woman is better served by allowing time for reflection before undergoing what is virtually an irreversible procedure.**

**Though depot medroxyprogesterone acetate was associated with irregular and unpredictable bleeding in almost 25% of the patients its acceptability and value as a temporary postpartum contraceptive was confirmed.**

## Introduction

Limitation of family size by immediate postpartum sterilization is now common practice. Some gynaecologists, however, have reservations about whether pregnancy and the very early puerperium is the correct time to consider seriously or perform such an irreversible and permanent procedure, particularly when these operations are today being carried out in younger patients with a lower parity then ever before.

In the present investigation all patients who during pregnancy requested sterilization were informed that this would be carried out 12 weeks postpartum, if they still wished it, and not immediately after delivery. Since there was a possibility of a pregnancy occurring before sterilization was performed the patients were offered an injection of medroxyprogesterone acetate (Depo-Provera) for contraceptive purposes. The questions considered in this study were, firstly, the number of patients subsequently reconsidering their original request for sterilization and, secondly, the acceptability of medroxyprogesterone as a temporary postpartum contraceptive.

## Patients and Methods

All patients attending the antenatal clinics of one unit in the Glasgow Royal Maternity Hospital who requested sterilization were included in the present series. Over a period of twelve months during which there were 1,267 deliveries in the unit, 75 patients in their antenatal period asked for sterilization. The patients were told that sterilization would be carried out between eight and 12 weeks postpartum and not in the period immediately after delivery. After delivery they were offered an injection of 150 mg intramuscular medroxyprogesterone acetate as a contraceptive, and all accepted. The medroxyprogesterone was given on the fifth or sixth day after delivery. An appointment was made for postnatal examination at six weeks, when a convenient time for admission for sterilization was arranged. Four patients were sterilized by Pomeroy tubal ligation and the remainder at laparoscopy. Laparoscopy was undertaken as described by Steptoe (1967) and sterilization performed by tubal coagulation, without division of the tubes (Mowat, 1974). The patients stayed in hospital for two nights after laparoscopy. They were asked to return for review at three months and thereafter as necessary. At these follow up appointments a careful note was made of any bleeding irregularities, vaginal discharge, or any other side effects which the patient may have noticed.

## Results

The average age of the patients was 32 years and the average parity was five (tables I and II).

TABLE I—*Age Groups of 75 Patients who requested Postpartum Sterilization*

| Age | 20-24 | 25-29 | 30-34 | 35-39 | 40 |
|---|---|---|---|---|---|
| No. of patients | 1 | 22 | 26 | 19 | 8 |

TABLE II—*Parity of 75 Patients who requested Postpartum Sterilization*

| Parity | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|---|---|---|---|---|---|---|---|---|---|---|
| No. of patients | 1 | 17 | 19 | 11 | 11 | 7 | 4 | 3 | 1 | 1 |

Seventy-five patients requested sterilization while still pregnant, of whom three did not return for postnatal examination, and attempts to trace them by the health visitor were unsuccessful. Eight patients said they no longer wanted sterilization because they considered that it was too drastic a form of contraception. All were on the pill. Whether any of these patients will become pregnant in the future remains to be seen

Victoria Infirmary, Glasgow G42 9TY
J. MOWAT, M.R.C.O.G., F.R.C.S., Consultant Obstetrician and Gynaecologist