Oral Metiamide as an Effective Inhibitor of Gastric Acid Secretion in Man

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SUMMARY

A method is described for the evaluation of the effect of oral therapy on gastric acid secretion. Metiamide, a histamine H_2-receptor antagonist, produced a 51% inhibition of pentagastrin-stimulated gastric acid secretion during the third hour after a standard 200-mg oral dose in man.

S. Afr. Med. J., **48**, 2018 (1974).

Histamine H_2-receptor antagonists[1] have evoked intense interest as inhibitors of gastric acid secretion. Burimamide, and its derivative metiamide, have been shown to inhibit gastric acid secretion stimulated by histamine, pentagastrin, insulin hypoglycaemia, food and cholinergic stimuli. Studies have been performed in rats,[1,2] dogs,[3,4] cats,[5] pigs,[6] and man.[7,8] The potential of this drug as a therapeutic agent in the treatment of duodenal ulcer is presently being investigated. Metiamide is available in tablet form, and two recent studies have demonstrated its effect on overnight fasting gastric acid secretion.[9,10] In this article we have investigated the effect of oral metiamide on gastric acid secretion stimulated by maximal doses of pentagastrin in man.

PATIENTS AND METHODS

Studies were performed on 9 patients with endoscopically proved duodenal ulcers. Their mean age was 31,1 years (range 20 - 53 years). None had any complicating factors.

After an overnight fast, a nasogastric tube was positioned in the dependant part of the stomach, and its position checked fluoroscopically. Fasting gastric juice was aspirated and discarded. Basal secretions were collected for two 15-minute periods. An intravenous infusion of pentagastrin (6 μg/kg - h) was then given into a forearm vein by means of a Braun Unita 1 pump (B. Braun, Melsungen, West Germany) for 1 hour. Gastric secretions were aspirated by continuous mechanical suction for 1 hour. The tube was frequently cleared with a syringe. Samples were divided into four 15-minute collections. At the end of the hour, 0,15M NaCl was infused intravenously, instead of the pentagastrin. Nasogastric aspiration was stopped. Metiamide tablets (200 mg) were crushed, suspended in 100 ml 0,03M HCl solution and injected into the stomach via the nasogastric tube. The metiamide suspension contained a radioactive marker (^{14}C-polyethylene glycol (PEG) in 1 patient and tritiated metiamide in 8), and a 2-ml aliquot was retained for isotope counting. After 1½ hours, gastric aspiration was recommended. The first 15-minute sample was discarded and the second retained as 'basal' collection. The intravenous infusion of pentagastrin (6 μg/kg - h) was restarted and four 15-minute samples of gastric secretion collected. Each patient therefore acted as his own control, the first study without metiamide and the second after metiamide. Aliquots of gastric aspirate from all samples collected after giving metiamide were examined for radioactivity, by using a Beckman LS-250 liquid scintillation system. This enabled calculation of how much metiamide had been retained in the stomach and how much withdrawn during subsequent gastric aspiration. Acid concentration in the gastric aspirate was titrated against 0,1M NaOH using a Metrohm Automatic Titrator (Metrohm Ltd, Herisau, Switzerland). Basal volume and acid output for the first half of the study represent 30-minute collections multiplied by 2, and for the second half of the study 15-minute collections multiplied by 4. Maximal acid output (MAO) represents the total acid output during the hour of pentagastrin stimulation. Peak acid output (PAO) represents the highest stimulated acid output in a 30-minute period multiplied by 2. Results are compared by means of a paired Student's *t*-test.

RESULTS

There was a significant reduction in basal and pentagastrin-stimulated volume output and acid concentration (Table I, Figs 1 and 2). Maximal acid output and PAO were reduced by 51,8% (range 33,2 - 72,5%) and 51% (range 19,0 - 71,7%) respectively, which represents a highly significant inhibition of gastric acid secretion ($P<0,001$ and $P<0,005$ respectively) (Table I, Figs 3 and 4).

Only 4,1% of the radioactive marker introduced into the stomach with the metiamide was recovered during the second half of the study, the remainder having presumably passed into the duodenum. The one patient who received PEG as a marker had 18,7% of the ingested dose aspirated from his stomach, while the remainder, who received tritiated metiamide, had a mean recovery of 2,3%. The test was repeated in this patient by using tritiated metiamide, and the label recovered from the stomach 1½ hours later was again high (16,2%). This patient, therefore, had slow gastric emptying.

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Date received: 25 June 1974.

TABLE I. GASTRIC SECRETION BEFORE AND AFTER METIAMIDE

	Before metiamide (mean ± SEM)	After metiamide (mean ± SEM)	Mean % reduction	*P*
Volume (ml/h)				
Basal	156 ± 17,2	91 ± 20,7	41,7	<0,02
MAO	343 ± 30,4	206 ± 19,2	39,9	<0,001
Acid concentration (mEq/litre)				
Basal	45,4 ± 5,8	24,1 ± 10,7	46,9	<0,025
MAO	100,3 ± 5,6	76,9 ± 6,7	23,3	<0,005
Acid output (mEq/h)				
Basal	6,9 ± 1,1	3,3 ± 2,2	52,2	NS
MAO	35,5 ± 4,4	17,1 ± 2,9	51,8	<0,001
PAO	44,1 ± 5,9	21,6 ± 3,1	51,0	<0,005

MAO = maximal (stimulated) acid output; PAO = peak acid output; *P* = probability value; NS = not significant.

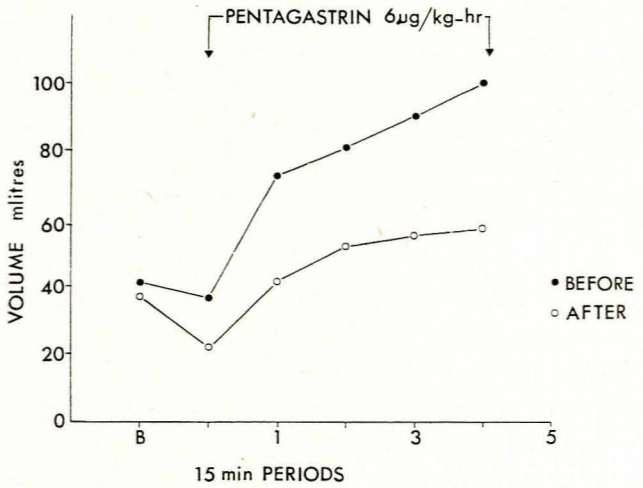

Fig. 1. Volume output before and after metiamide.

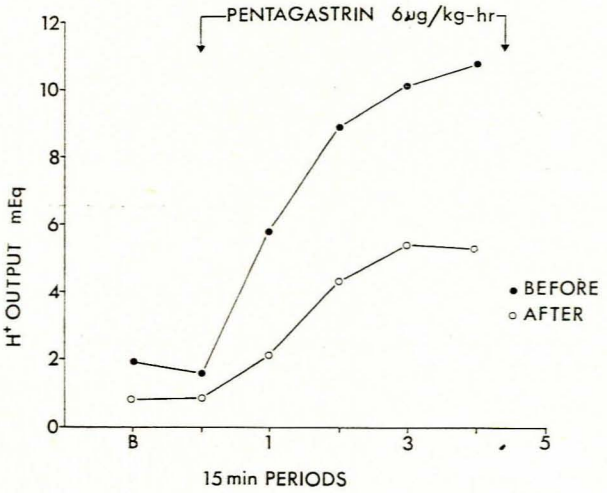

Fig. 3. Acid output before and after metiamide.

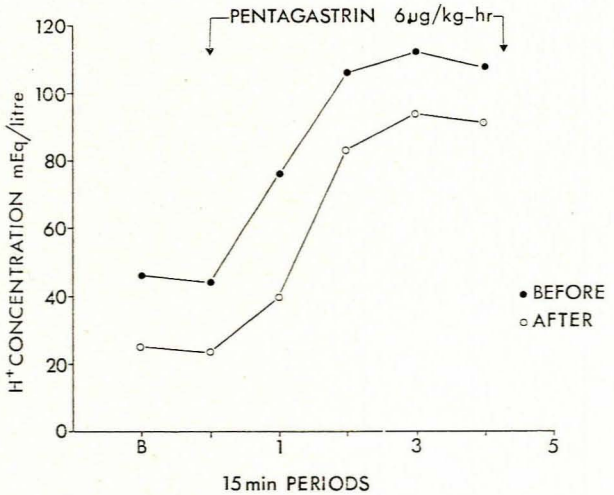

Fig. 2. Acid concentration before and after metiamide.

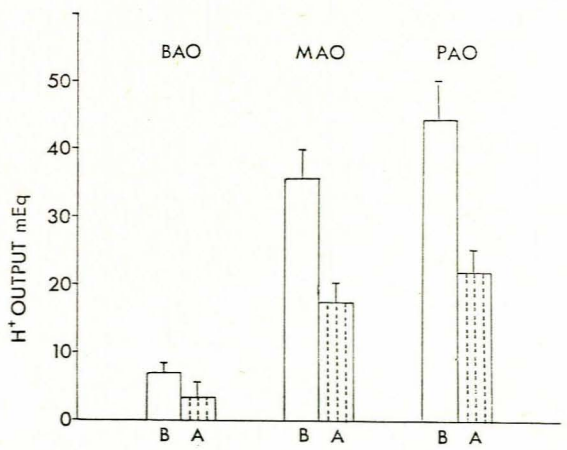

Fig. 4. Mean basal, stimulated and peak acid output before and after metiamide.

DISCUSSION

The results of the present study show that metiamide is highly effective in reducing pentagastrin-stimulated gastric acid secretion when taken orally. A standard 200 - mg dose produced a 51% reduction in acid output, both volume output and acid concentration being inhibited. This reduction represents the effect of the drug 2 - 3 hours after entering the stomach. The dose of pentagastrin given by intravenous infusion in this study (6 μg/kg - h) is somewhat supramaximal, since most patients reach their maximal output with doses of 2 μg/kg - h. This is therefore a more strenuous test of drug efficacy. The relatively small drop in mean basal acid secretion in the second test was probably due to one patient who increased his basal acid output after metiamide. Excluding this patient resulted in a highly significant inhibition of basal acid secretion with metiamide ($P<0,005$), as has been found in previous studies.[9,10] It is unlikely that this was a legacy of the previous pentagastrin infusion.

Metiamide is well absorbed from the gastro-intestinal tract. A study in 2 patients has shown that it produces similar inhibition when perfused into the duodenum as when given intravenously.[10] A 51% reduction in acid output is only slightly less than that achieved with vagotomy, a procedure associated with a high incidence of healing duodenal ulcers.[11-13] Anticholinergics may also produce significant inhibition of gastric acid secretion,[12] but doses required to achieve this are often associated with unpleasant side-effects. In contrast, there have been no subjective side-effects with the 200 - mg dose of metiamide. The safety of long-term administration of this drug is presently being evaluated. Initial impressions in an open pilot study on 10 patients are that it affords rapid symptomatic relief of duodenal ulcer pain. Seven of the patients showed complete and 3 partial endoscopic healing of their ulcers in 4 - 6 weeks.[14] A randomised double-blind trial of metiamide in the treatment of duodenal ulcer is needed to assess its value as a therapeutic agent.

We wish to thank Mrs S. Bridger and Mrs M. Daniel for technical help; Dr B. Shepstone for providing facilities for the isotope counting; and Smith, Kline & French Laboratories Ltd for the metiamide.

Financial support was provided by the South African Medical Research Council and the University of Cape Town Staff Research Fund.

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