The Effect of an H_2-Receptor Antagonist on Food-Stimulated Acid Secretion, Serum Gastrin, and Gastric Emptying in Patients with Duodenal Ulcers

COMPARISON WITH AN ANTICHOLINERGIC DRUG

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ABSTRACT The purpose of the present series of experiments was to measure and compare the effects of an anticholinergic drug (isopropamide) and an antagonist of the histamine H_2 receptor (metiamide) on food-stimulated acid secretion. Patients with duodenal ulcers were stimulated by a steak meal, and acid secretion was measured by in vivo intragastric titration. The largest dose of isopropamide that can be taken clinically without producing intolerable side effects (maximum tolerated dose) suppressed food-stimulated acid secretion by 35%. By contrast, metiamide in a 400-mg dose produced no side effects and almost completely abolished food-stimulated acid secretion. A dose-response curve revealed that a 50-mg dose of metiamide was required to suppress food-stimulated acid secretion by 50%. Further studies showed that metiamide and isopropamide are additive in suppressing food-stimulated acid secretion, and that metiamide has no effect on serum gastrin concentration or on gastric emptying.

INTRODUCTION

Histamine exerts physiologic and pharmacologic effects by interaction with at least two different receptors. The H_1 receptors mediate the action of histamine on smooth muscle of the gut and bronchi, and this action is blocked by classic antihistamines (1). In contrast the effects of histamine on the gastric parietal cell, on the guinea pig atria, and on the rat uterus are not blocked by the classic antihistamines. The histamine receptors in the stomach, guinea pig atria, and rat uterus that are not inhibited by the classic antihistamine drugs have been labeled H_2 receptors by Black, Duncan, Durant, Ganellin, and Parsons (2). These workers have synthesized two analogues of histamine, burimamide and metiamide, that competitively inhibit the action of histamine on the H_2 receptors.

In animal studies H_2-receptor antagonists have been shown to inhibit gastric acid secretion in response to histamine, pentagastrin, 2-deoxyglucose, and food (2, 3). In man these drugs suppress basal and nocturnal acid secretion and acid secretion stimulated by pentagastrin and histamine (2, 4, 5). The purpose of the present study was to measure the inhibitory effect of an H_2-receptor antagonist on food-stimulated acid secretion in patients with duodenal ulcers. This is thought to be of special importance since food is the normal physiological stimulant of acid secretion, since patients with duodenal ulcers have an exaggerated secretory response to food (6), and since food-stimulated acid secretion is poorly inhibited by currently available antisecretory drugs. Because anticholinergic drugs are a standard by which the effects of a new antisecretory agent can be measured, we have compared the effect of metiamide with that of isopropamide (Darbid, Smith Kline & French Laboratories, Philadelphia, Pa.) on gastric acid secretion, gastric emptying, and the serum gastrin concentration after the ingestion of food. Since metiamide and isopropamide may suppress food-stimulated acid secretion by blocking

Received for publication 6 August 1974 and in revised form 29 October 1974.

TABLE I

Age, Sex, Basal Acid Output, and Peak Acid Output (Histamine) in Patients with Duodenal Ulcers

Patient	Age	Sex	Basal*	Peak*
	yr		*meq/h*	*meq/h*
T. K.	45	M	8.6	80.3
M. C.	28	M	34.9	72.8
F. M.	48	M	3.0	41.3
J. M.	46	M	14.1	47.1
L. P.	27	M	9.4	34.5
R. T.	45	F	7.1	28.5
V. S.	53	F	9.6	32.3
Mean ±SE	41.7±3.8		12.4±3.9	48.1±7.7

* The mean basal and peak for the six patients shown in Fig. 1 is 8.6±1.5 and 44.0±7.6 meq/h.

two different parietal cell receptors, the H_2 receptor and cholinergic receptor, we also studied the inhibitory effect of a combination of these drugs.

METHODS

Subjects. Seven duodenal ulcer patients with a mean age of 41.7 yr (range: 27–53 yr) were studied; two were women and five were men (Table I). They were being treated with noncalcium antacids but were taking no other medications. All had X-ray evidence of duodenal ulcer, but none had clinical or radiographic evidence of impaired gastric emptying or a recent history of gastrointestinal bleeding. The study was approved by a Human Research Committee, and informed consent was obtained from each patient.

The standard meal. The meal consisted of 5 ounces of ground sirloin steak, one piece of toast, one teaspoon of butter, and 12 g polyethylene glycol (PEG).[1] This was homogenized in a Waring Blendor (Waring Products Div., New Hartford, Conn.), adjusted to exactly pH 5.0 by the addition of 10–20 ml of 0.3 N HCl, and then brought to a final volume of 600 ml by the addition of water. The meal was infused into the stomach over a 5-min period through a 16-FR Levin tube. Unpublished data from our laboratory have shown that infusion of this homogenized meal into the stomach elicits the same secretory response as when the unhomogenized meal is eaten normally.

Drug therapy. 100-mg tablets metiamide, 5-mg tablets isopropamide, and placebo tablets were furnished by Smith Kline & French Laboratories). The drugs were given alone or in combination as described in the Results. The onset of action of isopropamide occurs between 1½ and 2 h after ingestion, and the duration of action is 6–8 h (7). Because we wanted to study the drug during the period of its maximum effectiveness, we elected to give isopropamide 2 h before the test meal.

In each patient a maximum tolerated dose (8) of isopropamide was established by giving 5-mg tablets before each meal for 1–2 wk before the experiments. If side effects were not noted after 2 days on 5 mg, the dose was increased to 10 mg 2 h before meals. The dose was increased by 5-mg increments until blurring of vision occurred. When this occurred, the dose was decreased 5 mg, and this was defined as the maximum tolerated dose. With this dose all patients had mild dryness of the mouth. The maximum tolerated dose varied from 20 to 40 mg/dose in the six patients studied with this drug.

Food-stimulated acid secretion. Acid secretion rate was measured for 3 h after the meal by continuous intragastric titration, as described in a recent publication from our laboratory (6). Meal samples were obtained every 2 min through a Levin tube, the pH was measured, and the sample was returned to the stomach. 0.3 N sodium bicarbonate was infused through a small polyvinyl tube at a rate required to maintain the pH at 5.0. The number of milliequivalents of bicarbonate required to prevent a fall of gastric pH below 5 is equal to the number of milliequivalents of acid secreted in response to food.

Basal and peak histamine response. Basal acid secretion and the peak secretion rate after 0.04 mg/kg histamine acid phosphate were measured by standard methods (9). The results for each of our patients are shown in Table I. Note that the mean basal acid output was 12.4 meq/h and the mean peak acid output was 48.1 meq/h in this group of patients.

Hydrogen ion concentration was measured by the method of Moore and Scarlata (10). The peak histamine response was calculated as the sum of the two highest consecutive 15-min secretion rates multiplied by 2 to express the results in milliequivalents per hour.

Gastric emptying. The amount of PEG (originally ingested with the meal) remaining in the stomach at 30, 60, and 180 min after the meal was calculated from the PEG concentration of the gastric contents multiplied by the estimated gastric volume. Gastric volume at 30 and 60 min was measured by a nonabsorbable marker dilution method similar to that reported by George (11). The markers were 2 μCi [^{3}H]mannitol and 1 μCi [^{14}C]PEG. Gastric volume at 180 min was determined by quantitative removal of the gastric contents.

The results are expressed as the percent of the original 12 g of PEG ingested with the meal remaining in the stomach at 30, 60, and 180 min.

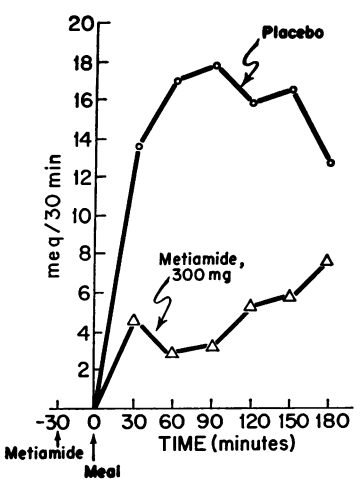

FIGURE 1 Effect of 300 mg metiamide orally on food-stimulated acid secretion in six patients with duodenal ulcers. Metiamide or placebo was given 30 min before the meal.

[1] *Abbreviation used in this paper:* PEG, polyethylene glycol.

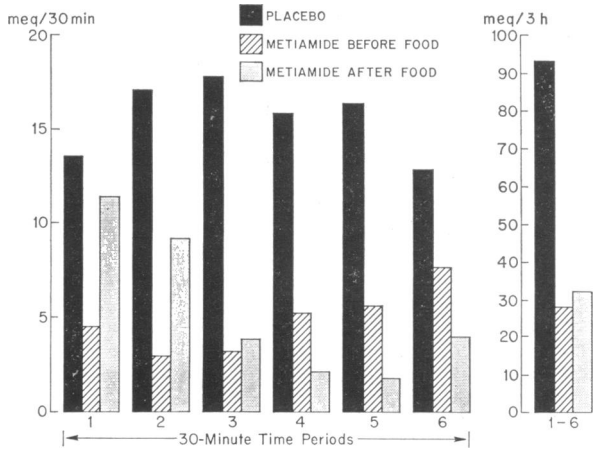

FIGURE 2 Effect of 300 mg metiamide given either 30 min before or 15 min after food on gastric acid secretion in six duodenal ulcer patients. Results are given for each of the six 30-min periods after the meal and for the total 3-h period.

Serum gastrin. Venous blood was collected through an indwelling catheter (Medicut i.v. cannula, A. S. Aloe Co., St. Louis, Mo.) that was kept open by a slow saline infusion. Blood samples were obtained immediately before medication, immediately before the infusion of the meal, and at 30, 60, 90, 120, and 180 min after the meal. The blood was allowed to clot, and serum was obtained by centrifugation and stored at −20°C until assayed.

Serum gastrin concentrations were measured by radioimmunoassay (12). All samples were tested in duplicate in the same assay. Antibody 1296, rabbit antigastrin prepared by immunization with gastrin conjugated to bovine serum albumin, was used at a final dilution of 1:300,000 (13). Prior testing established that heptadecapeptide gastrin (G-17) and 34 amino acid "big gastrin" (G-34) were measured on an equimolar basis in this system. Cross reactivity with cholecystokinin is less than 0.5% for antibody 1296 (12). Results were expressed as picograms per milliliter with natural human G-17-I used as standard.

Patient evalution. Before, immediately after, and 1 wk after each of the studies a complete blood count, urinalysis, blood urea nitrogen, creatinine, fasting blood sugar, serum glutamic oxalotransaminase, alkaline phosphatase, and bilirubin were obtained. An electrocardiogram was obtained before, during, and after each of the studies, and blood pressure and pulse rate were measured every 30 min during each 3-h test period. The patients were carefully observed for subjective symptoms.

RESULTS

Onset of action, peak effect, and duration of action with 300 mg metiamide. Fig. 1 shows the pattern of food-stimulated acid secretion when six duodenal ulcer patients were given either 300 mg of metiamide or placebo tablets 30 min before the meal. Acid secretion rate is plotted for every 30 min. With the placebo, acid secretion increased to 17 meq/30 min at 60 min after the meal and remained relatively steady at this level for the next 1½ h. The placebo meal response in this group of patients is equivalent to 77% of their peak acid output (Table I). Metiamide markedly inhibited acid secretion throughout the 3-h test period. The onset of action was noted during the first 30 min after the meal or within the first 60 min after the drug was ingested. At 60 min after the meal, metiamide reached its peak effectiveness and suppressed acid secretion from 17 to 3 meq/30 min.

When metiamide was given 15 min after rather than 30 min before the meal, its onset of action occurred during the second 30-min test period (i.e., from 15 to 45 min after dosage), its peak effect was delayed to the fifth 30-min test period, and suppression of acid secretion during the fourth, fifth, and sixth test periods was enhanced (Fig. 2). Although the pattern of secretory inhibition can, therefore, be altered by timing of the dose in relation to the meal, the total inhibition of acid secretion during the 3-h study was the same with both regimens (Fig. 2, final bars).

Effect of varying doses of metiamide on food-stimulated acid secretion. Fig. 3 shows the effect on food-stimulated acid secretion of 50, 100, 200, 300, and 400 mg of metiamide given orally 30 min before the meal in five duodenal ulcer patients as compared to a placebo. Milliequivalents of acid secreted for the total 3-h period is shown. With the 50-mg dose, acid secretion was reduced by 34 meq, from 107 to 73 meq ($P < 0.05$). When the patients were given 100 mg, acid secretion was suppressed by 63 meq, from 107 to 44 meq ($P < 0.05$). With the 200- and 300-mg dose, acid secretion was not inhibited to a greater extent than with the 100-mg dose. However, when 400 mg was given, acid secretion was reduced by 91 meq, from 107 to 16 meq, which is significantly greater than the inhibition with the 100-mg dose ($P < 0.025$).

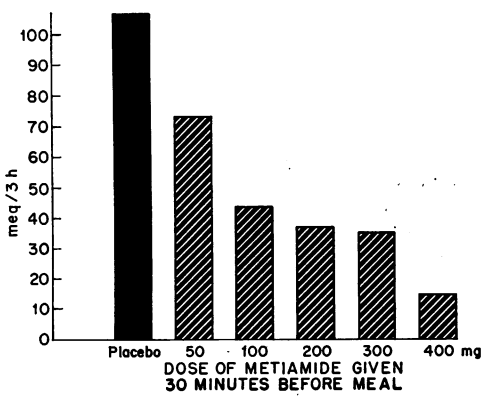

FIGURE 3 Effect of increasing doses of metiamide on meal-stimulated acid secretion in five patients with duodenal ulcers. Acid secretion is shown for the total 3-h period after the meal.

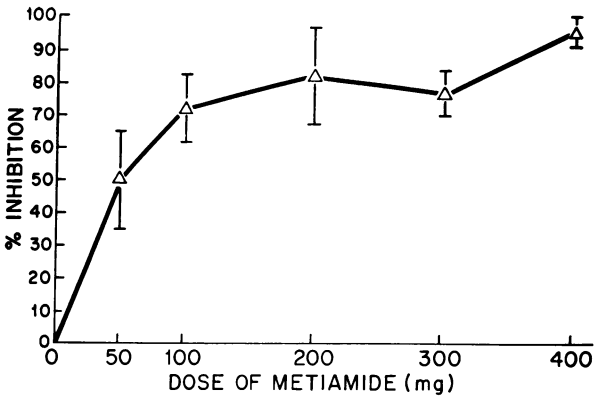

FIGURE 4 Maximal percent inhibition of food-stimulated acid secretion with each dose of metiamide in five duodenal ulcer patients (±1 SE).

The maximal inhibition of acid secretion with each dose of metiamide was also calculated. For example, with the 300-mg dose of metiamide, acid secretion was maximally inhibited by 82% (from 17 to 3 meq/30 min) during the second 30-min test period (Fig. 1). The maximum inhibition with the other doses was calculated in a similar fashion, and the results are shown in Fig. 4. The 50-mg dose maximally inhibited acid secretion by 50%. The 100-, 200-, and 300-mg dose inhibited secretion from 70 to 80%; these values are significantly greater than the inhibition with the 50-mg dose ($P < 0.05$), but the inhibition with the 200- and 300-mg dose was not significantly different from the 100-mg dose. On the other hand the 400-mg dose inhibited secretion by 96%, and this is significantly greater than the inhibition with the 100-mg dose ($P < 0.05$).

TABLE II

Meal-Stimulated Acid Secretion (meq/3 h) after Placebo, Isopropamide, 300 mg Metiamide, 400 mg Metiamide, and Isopropamide plus 300 mg Metiamide

Patient	Placebo	Isopropamide	Metiamide 300 mg	Metiamide 400 mg	Isopropamide + metiamide, 300 mg
T. K.	128	100	45		7
M. C.	152	133	47	29	19
F. M.	130	72	37	17	11
J. M.	73	55	47	15	5
R. T.	66	53	27	10	6
V. S.	68	59	15	8	7
Mean ±SE*	97.8±18	74.4±15	34.6±6.1	15.8±3.7	9.6±2.6

* Mean omitting T. K.

Comparison of the effect of metiamide and isopropamide on food-stimulated gastric acid secretion. Fig. 5 compares the effect of 300 mg metiamide, a maximum tolerated dose of isopropamide, and a placebo on food-stimulated gastric acid secretion in six duodenal ulcer patients. Metiamide was given orally 30 min before the meal, and isopropamide was given 2 h before the meal. Isopropamide did not suppress acid secretion during the first 30 min but inhibited secretion by 25–35% during the remainder of the study. Metiamide, on the other hand, suppressed secretion by 49% during the first 30 min and by 60–85% for the remainder of the study. The difference in total 3-h acid secretion was statistically significant by paired t test between placebo and isopropamide and between isopropamide and metiamide

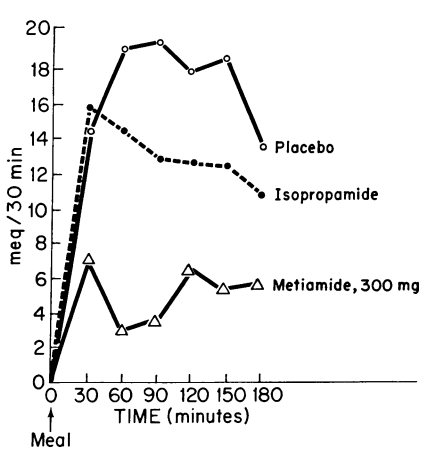

FIGURE 5 Effect of a maximum tolerated dose of isopropamide and 300 mg metiamide on food-stimulated acid secretion in six patients with duodenal ulcers. The difference in total 3-h acid secretion between isopropamide and placebo and between metiamide and isopropamide was statistically significant by paired t test ($P < 0.025$).

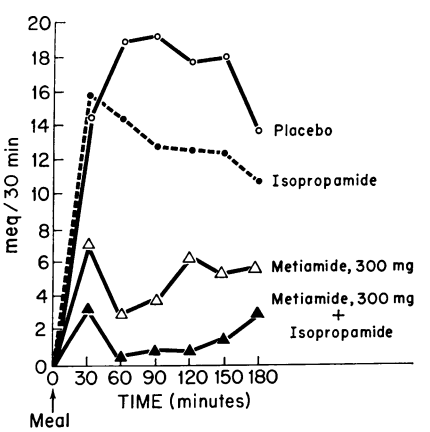

FIGURE 6 Effect of a maximum tolerated dose of isopropamide, of 300 mg metiamide, and of 300 mg metiamide plus isopropamide on meal-stimulated acid secretion in six patients with duodenal ulcers. The difference in total 3-h acid secretion between 300 mg metiamide plus isopropamide and 300 mg metiamide given alone is statistically significant by paired t test ($P < 0.025$).

($P < 0.025$). 3-h acid secretion was suppressed to a greater extent by metiamide than by isopropamide in each of our six duodenal ulcer patients (See Table II).

The effect of the combination of metiamide and isopropamide on food-stimulated acid secretion. Fig. 6 shows the effect of a combination of 300 mg metiamide plus a maximum tolerated dose of isopropamide on food-stimulated acid secretion in six duodenal ulcer patients as compared to a placebo, isopropamide alone, and 300 mg metiamide alone. The drug combination was more effective in suppressing food-stimulated acid secretion than was either of the drugs given alone. At 60, 90, and 120 min after the meal, acid secretion with the combination was less than 1 meq/30 min, and even at 180 min acid secretion was only 2.4 meq/30 min. All of the differences in total 3-h acid secretion were statistically significant by paired t test ($P < 0.025$). It is concluded, therefore, that the inhibitory effects of metiamide and isopropamide were additive and that the combination of these drugs suppressed acid secretion to a greater extent than either of the drugs alone. As shown in Table II, 300 mg of metiamide combined with isopropamide was also more effective than a 400-mg dose of metiamide in suppressing food-stimulated acid secretion in each of our five duodenal ulcer patients.

Effect of metiamide, isopropamide, and their combination on serum gastrin concentration. Serum gastrin concentration in response to a meal after 300 mg metiamide or placebo is shown in seven patients (Fig. 7A). The rise in serum gastrin after the meal was similar with the placebo and with metiamide, and none of the differences are statistically significant by paired t test. Fig. 7B shows the serum gastrin response to a meal in five patients after isopropamide as compared to a placebo. Isopropamide had no effect on serum gastrin. As shown in Fig. 7C there was a slight increase in serum gastrin concentration after the drug combination as compared to the placebo, but this increase was not statistically significant.

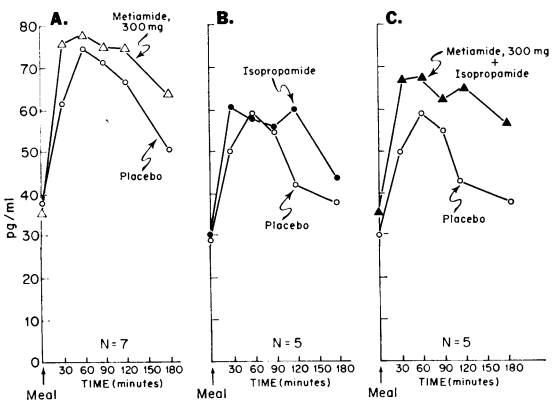

FIGURE 7 Serum gastrin concentration in response to a meal after 300 mg metiamide in seven patients (A), isopropamide in five patients (B), or 300 mg metiamide plus isopropamide in five patients (C). Serum gastrin concentration at 0 time was obtained before the meal. None of the differences were statistically significant.

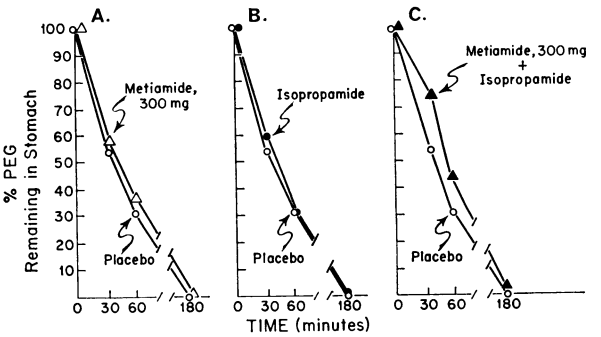

FIGURE 8 Effect of 300 mg metiamide (A), isopropamide (B), and their combination (C) on the percent PEG remaining in the stomach at 30, 60, and 180 min after the meal in six patients. None of the differences were statistically significant except the difference at 30 min after the meal with the combination of metiamide and isopropamide.

Effect of metiamide, isopropamide, and their combination on gastric emptying. Gastric emptying as estimated by the percent PEG remaining in the stomach at 30, 60, and 180 min after the meal is shown in Fig. 8. Metiamide and isopropamide had no effect on gastric emptying of PEG (Fig. 8A and 8B). The drug combination delayed emptying of PEG slightly but to a statistically significant degree only at 30 min after the meal ($P < 0.05$, Fig. 8C).

Side effects of metiamide. There were no subjective side effects noted by any of our patients. Blood pressure, pulse, and respiration remained stable throughout each of the 3-h studies. One patient developed a slightly elevated serum glutamic oxalotransaminase that subsequently returned to normal. All other laboratory studies remained normal.

DISCUSSION

Ingestion of a protein-rich meal elicits a maximal or near maximal secretion of acid by the human stomach. The mechanism of this secretion is complex and is believed to involve the action and interaction of acetylcholine, gastrin, histamine, and inhibitory hormones such as secretin. Although the relative importance of these different substances in mediating the secretory response to a meal is unknown, reduction of food-stimulated acid secretion could theoretically result from appropriate manipulation of these stimulants and inhibitors. In the present series of experiments we have examined and compared the effects of an anticholinergic drug and a histamine H_2-receptor antagonist on acid secretion

stimulated by a steak meal in patients with duodenal ulcers. Acid secretion was measured by in vivo intragastric titration (6).

When patients with duodenal ulcers were pretreated with a maximum tolerated oral dose of isopropamide, food-stimulated acid secretion was inhibited by a maximum of 35%. This dose of anticholinergic drug is usually assumed to only or mainly inhibit the muscarinic actions of acetylcholine (14), and these results suggest, therefore, that the muscarinic effects of acetylcholine play at least some role in mediating the gastric acid secretory response to food in duodenal ulcer patients. It is clear, however, that anticholinergic drugs in maximum tolerated doses can reduce food-stimulated secretion to only a modest extent. This is in contrast to basal (unstimulated) secretion, which is reduced from 50 to 80% by a maximum tolerated dose of various anticholinergic drugs (15, 16).

Metiamide is a recently synthesized drug that is believed to antagonize the effect of histamine on the gastric parietal cell (17). In hopes of defining the role of histamine and its antagonism on food-stimulated acid secretion in patients with duodenal ulcers, we studied the effect of 50, 100, 200, 300, and 400 mg of metiamide given orally 30 min before the food stimulus. It was found that a dose of 50 mg of metiamide inhibited food-stimulated acid secretion by an average maximum of 50%. Assuming an average weight of 70 kg for our patients, the D_{50} of metiamide for inhibiting food-stimulated acid secretion is therefore, 0.8 mg/kg. Metiamide D_{50} values for other stimulants of acid secretion (histamine, pentagastrin, etc.) have not been reported in man.

Doses of 100–300 mg inhibited food-stimulated secretion in our patients by 70–80%, and a 400-mg dose of metiamide inhibited secretion by 96% (Fig. 4). If metiamide in oral doses of up to 400 mg is a specific inhibitor of the H_2 receptor, as is generally assumed (17), these results indicate that histamine plays a dominant role in mediating food-stimulated acid secretion and that when the histamine receptor is sufficiently antagonized (i.e., with a 400-mg dose), food-stimulated acid secretion is nearly abolished. Although there is no unequivocal proof that metiamide inhibits acid secretion solely by virtue of antagonizing the histamine receptor, to our knowledge there is no evidence for any other mode of action of this drug.

Since a maximum tolerated dose of anticholinergic drug and a histamine receptor antagonist both inhibit food-stimulated acid secretion, the effect of the combination of isopropamide and metiamide was also measured. Isopropamide alone reduced acid secretion during the 3 h after the meal from 98 to 74 meq (24 meq reduction). 300 mg metiamide alone reduced this secretion from 98 to 35 meq (63 meq reduction). The combination of these drugs reduced secretion from 98 to 10 meq (88 meq reduction). Thus, a maximum tolerated dose of isopropamide and 300 mg of metiamide were additive in suppressing food-stimulated acid secretion in these patients.

Since metiamide has such a marked effect on food-stimulated acid secretion, experiments were performed to evaluate the effect of this drug on two other gastric functions, emptying of a meal and antral release of gastrin. The results indicated no effect of metiamide on either of these activities. Therefore, as far as can be determined, metiamide has a specific inhibitory effect on acid secretion, and this is not mediated through an inhibition of gastrin release. The effect of histamine H_2-receptor blockade on pepsin and intrinsic factor secretion has not to our knowledge been reported.

From a clinical standpoint, several additional conclusions based on our data seem justified. First, metiamide is a potent inhibitor of food-stimulated acid secretion in patients with duodenal ulcers. Even the smallest dose we used, 50 mg, is more powerful than the largest dose of an anticholinergic drug that patients can tolerate on a chronic basis, and a 400-mg dose suppresses 3-h acid secretion by 87% (Fig. 3) after a high protein meal. Second, the effect of metiamide on food-stimulated acid secretion is consistent. In each of our patients, even the severe hypersecretors, metiamide effectively suppressed food-stimulated acid secretion (Table II). Third, the onset of action, duration of action, and peak effect of the drug have been established. If metiamide is given before meals, it is most effective during the early postprandial period, whereas if it is given after meals, it is most effective during the 2nd h after eating. The duration of action is at least 3 h, but at the end of this period even large doses are beginning to lose their effectiveness. This is in contrast to the anticholinergics which have a duration of action of from 5 to 8 h. Finally, combination therapy with metiamide and an anticholinergic may be especially useful, since perhaps smaller doses of both agents could be used rather than larger doses of either agent alone.

Two cases of agranulocytosis have been reported after chronic metiamide therapy for duodenal ulcer disease, and further trials in the United States have been limited to selected patients with severe ulcer disease not amenable to other methods of therapy (personal communication, Smith Kline & French Laboratories). However, another H_2-receptor antagonist has been recently developed. It is anticipated that this drug will prove to be as effective in inhibiting gastric acid secretion and hopefully will not have an adverse effect on granulocytes.

ACKNOWLEDGMENTS

We wish to thank Martha Hicks and Vickie Jones for their excellent technical assistance and Carolyn Tirado for typing the manuscript.

This study was supported in part by research grants 16816 and 17328 from the National Institute of Arthritis and Metabolic Diseases; a grant from Smith Kline & French Laboratories, Philadelphia, Pa., and General Clinical Research Center grant 00633.

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