Relief of Duodenal Ulcer Symptoms by Oral Metiamide

R. E. POUNDER, J. G. WILLIAMS, G. J. MILTON-THOMPSON, J. J. MISIEWICZ

British Medical Journal, 1975, 2, 307-309

Summary

Thirty patients with symptoms of duodenal ulceration were treated for five to eight weeks in a double-blind trial with either metiamide 1 g daily by mouth or a placebo. In the 15 patients receiving metiamide there were significant reductions in nocturnal pain and antacid consumption. Daytime pain was diminished. The results suggest that histamine H₂-receptor antagonists are likely to be useful in the medical management of the symptoms of duodenal ulceration.

Introduction

Metiamide is a histamine H₂-receptor antagonist¹ which inhibits human gastric acid secretion in response to various stimuli.²⁻⁷ Though metiamide has been shown to reduce strikingly overnight gastric secretion in patients with duodenal ulcer,⁸ there have been no studies of its clinical efficacy in this disease. To assess its effects on the symptoms and antacid consumption of patients with duodenal ulcer we performed a double-blind clinical trial of oral metiamide and a placebo.

Patients and Methods

The trial was carried out simultaneously in the M.R.C. gastroenterology unit, Central Middlesex Hospital, and the Royal Naval Hospital, Plymouth. All patients included in the trial had typical symptoms of active duodenal ulceration with epigastric pain related to meals and relieved by antacids, the symptoms being present during the week before entry to the trial. The diagnosis had been established in all patients by x-ray examination or endoscopy. Patients were excluded if they were pregnant or had cardiac, renal, or thyroid disease or a gastric ulcer, hiatus hernia, or pyloric stenosis.

The double-blind trial lasted eight weeks. The patients gave their informed consent and were randomly allocated to the treatment or placebo group. Treatment consisted of metiamide tablets 200 mg three times daily after meals and 400 mg on retiring to bed or the same number of placebo tablets containing lactose. Each patient also received a supply of Nulacin tablets to be taken if necessary for ulcer pain. The patients were seen each week. At each visit the unused drugs from the previous week were counted and a fresh supply of 70 trial and 50 Nulacin tablets dispensed. The patients were also issued each week with a diary card to record daytime and nocturnal ulcer pain and the number of Nulacin and trial tablets taken each day. The severity of ulcer pain was scored as "none," "mild," or "severe." The need to take the trial tablets regularly, the necessity of adequate medication with Nulacin, and the way in which the diary cards were to be completed were carefully explained to each patient.

M.R.C. Gastroenterology Unit, Central Middlesex Hospital, London NW10 7NS

R. E. POUNDER, M.B., M.R.C.P., Honorary Senior Registrar and Research Assistant

J. J. MISIEWICZ, M.B., F.R.C.P., Honorary Consultant Physician and Member of Scientific Staff

Royal Naval Hospital, Stonehouse, Plymouth PL1 3JY

J. G. WILLIAMS, M.B., M.R.C.P., Medical Registrar

G. J. MILTON-THOMPSON, M.B., F.R.C.P., Consultant Physician

The patients were asked at the beginning of the trial to throw away any antiulcer drugs in their possession. Their general practitioners were asked not to prescribe any other treatment during the eight weeks of the trial. No specific advice was offered concerning diet.

At the start of the trial and at each weekly visit the patients were physically examined and haemoglobin, red cell indices, and total and differential white count were checked. Every four weeks plasma electrolytes, urea, serum creatinine, and liver and thyroid function were checked, urine was analysed, and a chest x-ray examination was performed.

The results were analysed in two ways. The overall comparison of the incidence of pain between the two treatment groups was based on the total number of days (and nights) in each week that severe, mild, or no ulcer pain was recorded. The significance of difference between the treatment groups was determined with the χ^2 test. Comparisons of consumption of antacid and the number of pain-free days (and nights) in individual patients during each week of the trial were made with the Wilcoxon rank sum test.

Results

Seventy-four patients with duodenal ulcer were referred for treatment in the trial; 37 were excluded: 12 had coincidental gastrointestinal disease, two needed surgery for pyloric stenosis, 15 were in remission, and eight were unsuitable because they were unable to attend regularly or were unlikely to co-operate. Of the remaining 37 patients 19 were randomly allocated to the metiamide and 18 to the placebo group. Fourteen patients were withdrawn from the trial (see table), but seven had completed five or more weeks' treatment. The analysis of results is based on observations in the 30 patients (15 on metiamide, 15 on placebo) who completed five or more weeks in the trial. Twenty-three patients were treated for the full eight weeks.

There were no significant differences between the two treatment groups in age, incidence of smoking, number of attacks of daytime or nocturnal pain during the week before the trial, or severity of pain in that week. There was only one woman—in the metiamide group. The mean lengths of ulcer history ($\pm$ S.E. of mean) in placebo and metiamide groups were, respectively, 4.9 ± 1.3 and 5.7 ± 1.3 years and the mean lengths of relapse before entry to the trial 8.1 ± 2.0 and 6.2 ± 2.0 weeks.

The number of days (or nights) in each week that pain (severe, mild, or none) was recorded is shown in fig. 1. Treatment with metiamide produced a significant reduction of both day and night pain, though the effect on daytime symptoms was not apparent during the first two weeks of treatment. The patients receiving placebo experienced more severe pain than those on metiamide. Two patients in the control group were withdrawn from the trial because of severe symptoms requiring admission to hospital (see table). The number of pain-free days (and nights) experienced by every patient during each week of the trial is shown in fig. 2. Though all but three patients on metiamide were free of daytime pain during the last three weeks of treatment the difference from the control group is not significant. Nocturnal pain, however, was significantly improved during most weeks of the trial.

Patients on metiamide consumed significantly less antacid during the second, third, and fifth week of the trial than patients in the placebo group (fig. 3). During the last three weeks of treatment antacid consumption was reduced in the placebo group, most probably because of spontaneous remission of symptoms, thus obliterating the difference between the treated and the control patients.

No abnormal physical signs were found in any patient during the trial. There was no significant change in any of the results of laboratory investigations except in three patients on metiamide and one receiving placebo who developed mildly raised alanine and aspartate transaminases. Results of the other liver function tests were normal. The haematological results remained normal in all the patients who received metiamide. Mild systemic unwanted effects, such as sedation, headache, and dizziness, were reported by 10 patients on metiamide and five on placebo, but none of the effects were severe enough to stop treatment.

TABLE 1—Reasons for Withdrawing Patients from Trial

Case no. Treatment No. of weeks in trial	Metiamide Withdrawn from General Use							Severe unrelieved Symptoms		Irregular Taking of Drug			Atrial Fibrillation	Severe Depression Needing Treatment
	1 P. 1	2 M. 3	3 M. 5	4 M. 5	5 M. 5	6 M. 5	7 P. 6	8 P. 5	9 P. 6	10 M. 1	11 M. 1	12 P. 1	13 P. 1	14 M. 3

P. = Placebo. M. = Metiamide.

FIG. 1—Incidence of daytime and nocturnal pain in both groups in each week of trial. Significances were calculated from number of days or nights a week with or without pain (χ^2 test).

FIG. 2—Number of days and nights free of pain in individual patients during each week of trial. Differences between groups in daytime were never significant (Wilcoxon rank sum test). ○ = Placebo group. ● = Metiamide group.

Discussion

The clinical trials certificate for metiamide was temporarily suspended during the course of the investigation because of reports from other centres of two cases of reversible granulocytopenia occurring during the administration of metiamide, but none of our patients who received metiamide developed any serious unwanted effects.

Metiamide produced a rapid remission of night pain, which supported the observation of Milton-Thompson *et al.*⁸ that 400 mg taken on retiring effectively suppresses nocturnal acid secretion in patients with duodenal ulcer. As a group the patients treated with metiamide had significantly less daytime pain than those receiving the placebo, though this improvement was insignificant when results in individual patients were compared.

FIG. 3—Number of Nulacin tablets consumed weekly by individual patients. ○ = Placebo group. ● = Metiamide group.

Nevertheless, the metiamide-treated patients consumed significantly less antacids than the controls and all but three of them were free of pain during the last three weeks of the trial. Experience suggests that absorption of metiamide can be variable,⁸ which may account for the lack of response in some patients. Larger doses or the addition of an anticholinergic drug⁹ might further improve the results.

We made no attempt to assess the effect of metiamide on ulcer healing; progress was assessed entirely on the patients' subjective relief of pain and their antacid consumption. Serial endoscopic observation of ulcer healing within the framework of a therapeutic trial is feasible, but the correlation between ulcer healing and relief of symptoms is not exact.⁹ Our approach was appropriate as a preliminary exploration of the clinical usefulness of metiamide, and the results in this small group of patients suggest that treatment with an H_2 -receptor antagonist produces an early remission of symptoms of duodenal ulcer. Confirmation of an incidence of granulocytopenia due to metiamide may make treatment with the drug unjustifiable, however, except in selected patients. We hope, therefore, that

other H_2 -receptor antagonists will soon be available for clinical evaluation.

We thank Dr. A. C. Flind and Dr. R. A. Wiseman (Smith, Kline and French Laboratories Ltd.) for supplies of metiamide and placebo tablets, and staff nurse Sue Pittkin, and chief medical technician M. Townsend for their help in the duodenal ulcer clinics. We are grateful to the laboratory staff of both hospitals for their help.

References

¹ Black, J. W., and Spencer, K. E. V., in *International Symposium on*

Histamine H_2 -Receptor Antagonists, ed. C. J. Wood and M. A. Simkins, p. 23. Welwyn Garden City, Smith, Kline and French Laboratories Ltd., 1973.

² Wyllie, J. H., and Hesselbo, T., in *International Symposium on Histamine H_2 -Receptor Antagonists*, ed. C. J. Wood and M. A. Simkins, p. 371. Welwyn Garden City, Smith, Kline and French Laboratories Ltd., 1973.

³ Thjodleifsson, B., and Wormsley, K. G., *British Medical Journal*, 1974, 2, 304.

⁴ Mainardi, M., et al., *New England Journal of Medicine*, 1974, 291, 373.

⁵ Richardson, C. T., and Fordtran, J. S., *Gastroenterology*, 1974, 66, 861.

⁶ Carter, D. C., et al., *British Medical Journal*, 1974, 3, 554.

⁷ Konturek, S. J., Biernat, J., and Oleksy, J., *American Journal of Digestive Diseases*, 1974, 19, 609.

⁸ Milton-Thompson, G. J., et al., *Lancet*, 1974, 1, 693.

⁹ Brown, P., et al., *British Medical Journal*, 1972, 3, 661.

Clinical Trial of Mebendazole, A Broad-spectrum Anthelmintic

J. G. P. HUTCHISON, NATALIE M. JOHNSTON, MARY V. P. PLEVEY, IRENE THANGKHIEW, CONSTANCE AIDNEY

British Medical Journal, 1975, 2, 309-310

Summary

Eighty-five children aged 5-14 years who were infested with worms were treated with mebendazole 100 mg twice daily for three days. The percentage cure rates were ascaris 100%, trichuris 94%, hookworm 82%, and hymenolepis 39%. The drug was well tolerated and with its broad activity should be very useful in treating those with multiple infestations.

Introduction

Mebendazole has a wide spectrum of action and high activity against the helminths, particularly *Ascaris lumbricoides*, *Trichuris trichiura*, taenia, enterobius, hookworm, and to a lesser degree *Hymenolepis* spp.¹⁻³ It also has a definite effect against strongyloides.⁴

In Birmingham many immigrant children from all parts of the globe are examined before they enter school, and faecal examinations have shown that they are often infested.⁵ The treatment of these children, however, has proved virtually impossible because of the lack of satisfactory drugs (the worm species commonly found were not particularly sensitive to a single agent), because many of the immigrants lacked general practitioners to take over their treatment, and because a language barrier made adequate communication very hard. Attempts were made to organize a single treatment session at a hospital when results of the faecal examinations were known, but the outcome of any treatment remained completely unknown because few of the treated patients ever returned to the hospital clinic.

We report here the results of a trial of mebendazole (performed under D.H.S.S. Licence) in a small series of children of 5-14 years old. Reports had suggested that the drug was only slightly absorbed (5-10%) and no toxicity had been shown in extensive foreign studies.^{2,4}

Methods

Children of both sexes aged 5-14 years were examined at the school clinic and brought with them a faecal specimen. As part of the examination they were given a Heaf test, and they returned seven days later for the test to be read, by which time the results of faecal examination were available. The modified formol-ether method⁶ was used for detecting ova. If helminth ova were found the parent or guardian was given six 100-mg tablets of mebendazole with instructions to give one tablet to the child night and morning for three days; the first dose was given at the clinic. Between seven and 21 days later (median 14 days) a second faecal specimen was obtained by a home visit (M.V.P.P.) and inquiries were made about any possible ill effects of the drug. Results of the second examination were then collated with the first to assess drug efficacy. If ova were present in the second specimen which had not been detected in the first we assumed that they had been missed on first examination, as cross-infestation and its manifestation in so short a time is unlikely in Britain. The formol-ether method gives a positive result on a single examination in about 75% of infestations. The finding of *Giardia lamblia* cysts in faeces is capricious and stools may be repeatedly negative in spite of known infection. Nevertheless 25 children who had cysts of *G. lamblia* only were also treated. No attempt was made to control the trial with untreated cases.

Results

Eighty-five children harbouring helminths submitted a follow-up faecal specimen and were believed to have taken the tablets. Of these 65 (76%) seemed to have been dewormed. Of those with a single infestation the cure rates were ascaris 100%, trichuris 91%, hookworm 94%, and hymenolepis 50% (see table). Only a few children had multiple infestations. All four children with ascaris and trichuris were cured, as were all three with ascaris, trichuris, and hookworm. Of the three with ascaris and hookworm one was cured, of the three with trichuris and hookworm one was cured, but of the seven with hookworm and hymenolepis only one was cured. The large variations in percentage cures probably reflected a large standard error ($\pm 27\%$ in the cases of mixed ascaris/hookworm and trichuris/hookworm infestations) rather than a real difference in the drug's effectiveness. This view is to some extent supported by the fact that the cure rate for the triple infestation ascaris/trichuris/hookworm was 100%. Except for hymenolepis the cure rates were most promising and similar to those of the single infestation group.

Regional Public Health Laboratory, East Birmingham Hospital, Birmingham, B9 5ST

J. G. P. HUTCHISON, M.D., F.R.C.PATH, Director
MARY V. P. PLEVEY, S.R.N., Research Assistant
IRENE THANGKHIEW, M.B., DIP. BACT., Assistant Bacteriologist

Area Health Authority (T), Birmingham

NATALIE M. JOHNSTON, L.R.C.P. & S., M.F.C.M., Specialist in Community Medicine (Child Health)
CONSTANCE AIDNEY M.B., M.F.C.M., Deputy Senior Administrative Medical Officer for Child Health