Double blind comparative study of omeprazole 10 mg and 30 mg daily for healing duodenal ulcers

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Abstract

Healing of duodenal ulcers was assessed in 66 patients who received omeprazole either 10 mg or 30 mg daily for four weeks in a double blind study. Healing was rapid in both groups. At two weeks the ulcers in 15 of the 30 patients taking 10 mg daily had healed compared with 28 of the 36 (78%) taking 30 mg daily ($p < 0.03$). At four weeks the respective proportions had risen to 83% (25/30) and 94% (33/35) ($p > 0.05$). In non-smokers the proportion of ulcers healed did not differ significantly with the two doses, although there was a trend for less healing at two weeks with 10 mg daily; in smokers significantly fewer ulcers ($p < 0.05$) were healed with 10 mg than 30 mg daily at two weeks (7/16 (44%) v 17/21 (81%)) and at four weeks (12/16 (75%) v all 21 (100%)). Adverse reactions were few and transient and were considered unlikely to be due to omeprazole.

Introduction

Omeprazole is a substituted benzimidazole that acts selectively at the secretory surface of the parietal cell.^{1,2} Although this particular compound is being reassessed because of a recent suggestion of toxicity in animals at high dosage, this new class of gastric acid inhibitors could be a potent alternative to H_2 receptor blocking drugs in the treatment of peptic ulcers. With all forms of antisecretory treatment problems may arise when doses that totally suppress acid secretion are used for a long time. Thus studies that define the clinical response to smaller doses are important. The optimal regimen for treatment with omeprazole is still uncertain. Three recent comparative dose studies in small groups of patients showed rapid healing of duodenal ulcers treated with 20, 30, 40, or 60 mg daily for four weeks.³⁻⁵ We report a double blind study comparing a lower dose of omeprazole than has been studied previously (10 mg daily) with an intermediate dose (30 mg daily).

Patients and methods

The study was conducted at two teaching hospitals in Melbourne. Patients included in the study had active duodenal ulceration of at least 5 mm diameter that had been verified at endoscopy within the previous three days. We excluded patients aged below 18 or above 80;

women of childbearing potential; patients treated in the previous three days with either anticholinergic agents or histamine H_2 receptor antagonists; and patients with concurrent gastric ulceration, pyloric stenosis, severe reflux oesophagitis, previous gastric surgery, chronic alcoholism, or drug abuse (including analgesic abuse). Each patient gave signed, informed consent before inclusion, and approval for the study was obtained from the human research committee of each hospital.

Sixty seven patients entered the study and were randomised to receive either 10 mg or 30 mg omeprazole (formulated as enteric coated granules in hard gelatin capsules) each morning for four weeks. With this number of patients we calculated that a 35% difference in the proportions of ulcers that healed with the two dosages would be detected ($\alpha = 0.05$, power = 0.8). As the 10 mg and 30 mg capsules differed in appearance a double dummy technique was used to ensure blinding (each patient received one active and one placebo each day). Separate randomisation lists generated by computer were prepared for each centre and put in groups of six to minimise the influence of any variables related to time. Treatment was allocated so that there were similar proportions of smokers in each group, and patients were advised to maintain their previous intake of tobacco throughout the trial. Antacid tablets (Mylanta, buffering capacity 12.5 mmol for each tablet) were allowed ad libitum to relieve ulcer pain. Endoscopy was done by a trained observer who was unaware of the treatment given.

Healing of ulcers was assessed by endoscopy at two weeks and again at four weeks if the ulcers had not healed. Healing was defined as complete re-epithelialisation of the site of the ulcer. During the trial patients were reviewed weekly to assess symptoms, compliance, and possible adverse events. Laboratory investigations were carried out before and on days eight and 29 of treatment. These included assessment of serum electrolyte, urea, and creatinine concentrations; liver function (bilirubin concentration and alkaline phosphatase, serum aspartate aminotransferase, and serum alanine aminotransferase activities); glucose and haemoglobin concentrations; white cell and platelet counts; and analysis of urine. Thyroid function tests (measurement of serum triiodothyronine, thyroxine, and thyroid stimulating hormone concentrations) were performed before the trial started and on day 29. Measurement of serum alanine aminotransferase activity was not included in the initial group of tests but was included after the trial began because of a report of raised activity in some patients.⁴

Results in the two treatment groups were compared with Fisher's test of exact probability (two tailed).⁶ When p exceeded 0.05, 95% confidence limits for differences in the proportions of healed ulcers were also calculated.⁷

Results

Of the 67 patients initially entered into the trial, one, who was treated with 10 mg omeprazole, was lost to follow up before the review on day eight and could not be contacted. One further patient (taking 30 mg omeprazole) refused endoscopy on day 29 and was therefore not included in the analysis of healing at four weeks.

Table I shows the initial characteristics of the patients after randomisation. The differences in these characteristics between the two groups were not significant ($p > 0.05$). Table II gives the proportions of patients whose ulcers healed. At two weeks significantly more ulcers had healed in patients treated with 30 mg daily than in those treated with 10 mg daily (78% v 50%; $p < 0.03$). The difference in healing between groups at four weeks was not significant (94% v 83%). Even large ulcers (≥ 15 mm) healed rapidly. Duodenitis was present at initial endoscopy in 25 (83%) of the group taking 10 mg omeprazole and in 24 (67%) of the group taking 30 mg ($p = 0.2$). At endoscopy after two weeks duodenitis was still evident in 22 (73%) of those given 10 mg compared with only 14 (39%) given 30 mg ($p < 0.05$).

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Smokers responded differently from non-smokers. In non-smokers the proportions of ulcers healed after two and four weeks were similar at both doses, but among smokers fewer ulcers had healed at two and four weeks in those taking the lower dose ($p < 0.05$) (table III). Compliance was good; only one patient missed more than two doses throughout the entire trial. Exclusion of that patient did not influence the significance of the differences in healing between the two groups.

TABLE I—Characteristics of patients at randomisation

	Omeprazole 10 mg/day (n = 30)	Omeprazole 30 mg/day (n = 36)
Mean (range) age (years)	49 (24-73)	46 (21-75)
Men:women	22:8	24:12
No (%) of smokers	16 (53)	21 (58)
No (%) taking regular alcohol	5 (17)	9 (25)
No (%) with ulcer size:		
5-9 mm	10 (34)	13 (36)
10-14 mm	13 (43)	14 (39)
≥15 mm	7 (23)	9 (25)

TABLE II—Proportions of patients whose ulcers had healed after two and four weeks (figures in parentheses are percentages)

Ulcers healed after:	Initial size of ulcer (mm)			Total	95% confidence limits of % healed ulcers
	5-9	10-14	≥15		
Omeprazole 10 mg daily					
Two weeks	5/10 (50)	8/13 (62)	2/7 (29)	15/30 (50)	31-69
Four weeks	9/10 (90)	11/13 (85)	5/7 (71)	25/30 (83)	65-94
Omeprazole 30 mg daily					
Two weeks	13/14 (93)	10/15 (67)	5/7 (71)	28/36 (78)	61-90
Four weeks	14/14 (100)	13/14 (93)	6/7 (86)	33/35 (94)	81-99

TABLE III—Proportions of smokers and non-smokers whose ulcers healed (figures in parentheses are percentages and 95% confidence limits)

Duration of treatment	Smokers	Non-smokers
<i>Omeprazole 10 mg daily</i>		
2 weeks	7/16 (44, 20-70)	8/14 (57, 29-82)
4 weeks	12/16 (75, 48-93)	13/14 (93, 66-100)
<i>Omeprazole 30 mg daily</i>		
2 weeks	17/21 (81, 58-95)	11/15 (73, 45-92)
4 weeks	21/21 (100, 84-100)	12/14 (86, 57-98)

TABLE IV—Number of patients with pain

Day	Dyspeptic pain			
	Absent	Mild	Moderate	Severe
<i>Omeprazole 10 mg daily</i>				
1	5	4	11	10
8	23	5	1	1
15	23	5	2	
22	27	2	1	
29	28	2		
<i>Omeprazole 30 mg daily</i>				
1	2	5	10	19
8	25	7	4	
15	30	5	1	
22	32	3	1	
29	33	2	1	

Dyspeptic symptoms (epigastric pain and nausea) were present at the start of the trial in 25 (83%) of the group given 10 mg omeprazole and in 34 (94%) of those given 30 mg. Symptoms were relieved rapidly (table IV), and at the end of the first week only seven patients (23%) taking 10 mg daily and 11 (31%) taking 30 mg daily continued to experience symptoms and only one patient (given 10 mg) still had severe pain. By four weeks only five patients (8%) had any dyspeptic symptoms. Two of these (one in each group) had an ulcer that did not heal (the five other patients with ulcers that did not heal were asymptomatic). Consumption of antacid during the first week

averaged 4.1 and 3.3 tablets for each person in the groups taking 10 mg omeprazole and 30 mg respectively (not significant). Thereafter, consumption was negligible.

The adverse reactions that were reported were few and transient. They included two episodes of diarrhoea and single episodes of abdominal colic and palpitations in the group taking 30 mg omeprazole, and oral aphthous ulceration and haemorrhoidal bleeding in the group taking 10 mg. All adverse reactions settled despite continued dosage, and none could be attributed to omeprazole. No appreciable changes in blood biochemistry, haematology, or urinary analysis occurred, except in one patient, whose serum alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase activities rose threefold to fourfold at the end of the first week of treatment, nine days after a blood transfusion of four units. The abnormal values returned towards normal over the next three weeks despite continued treatment with omeprazole.

Discussion

Omeprazole is the first antisecretory drug studied in a clinical trial to produce a sustained reduction of gastric acidity for 24 hours after a single dose. We had previously found that although gastric acidity over 24 hours is noticeably reduced by a dose given either in the morning or in the evening, the overall reduction is greater with the dose given in the morning⁸; hence our choice of giving omeprazole in the morning in this study.

The proportion of ulcers healed at two weeks in patients given a dose of 30 mg daily was striking. When our data at two weeks are combined with those of Gustavsson *et al.*¹ and Walan *et al.*,³ a dose response relation becomes apparent, the proportion of ulcers healed with 60, 40, 30, 20, and 10 mg daily being 100, 93, 78, 63, and 50%, respectively. In the study by Gustavsson *et al.*¹ smokers were unevenly distributed between the two study groups, which slightly complicates the comparison of the 60 mg and 20 mg daily regimens. Nevertheless, there are probably now sufficient data on which to base a choice of dosage for trials in the future, in which omeprazole needs to be compared directly with histamine H₂ antagonists. Based on our finding that half the ulcers were healed at two weeks, 10 mg omeprazole appears comparable with 1 g of cimetidine daily, which has produced a median healing at two weeks of 48% in several trials.⁹ If omeprazole is to promote appreciably faster healing than the H₂ antagonists our results suggest that a dose of at least 30 mg daily may have to be given.

Our results, in agreement with those of other studies of drugs acting against ulcers,^{10,11} indicated that ulcers are more difficult to heal in smokers than non-smokers. In non-smokers daily doses of 10 mg and 30 mg omeprazole were almost equipotent, but in smokers the lower dose was less effective.

Finally, in view of the rise in serum alanine aminotransferase activities in some of the patients studied by the Uppsala group¹ it is reassuring that, with the exception of one patient who developed an unexplained rise in serum aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase activities after blood transfusion, no appreciable changes in liver function were detected in this group of 66 patients. Thus it appears that omeprazole, like the H₂ antagonists, is well tolerated when given in short courses.

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SHORT REPORTS

Absence of response of prolactin to hypoglycaemia induced by insulin in obese children

Kopelman *et al* found that in adults with a history of obesity from early childhood there was no response of plasma prolactin concentration to symptomatic hypoglycaemia induced by intravenous injection of insulin.^{1,2} In contrast, release of prolactin was unimpaired in patients in whom the obesity had occurred either during teenage years or later. These findings suggested that in obese children there should be no response of prolactin to induced hypoglycaemia. We carried out a study to test this.

Subjects, methods, and results

We studied six obese children aged 4-13 and five obese adults aged 23-38 whose mean (SD) body weight was 127.2 (7.9)% and 147.0 (30.8)% of the ideal, respectively. Seven non-obese children aged 6-12 and 11 non-obese adults aged 19-23 were also studied as controls. Endocrinological examination of the 11 obese subjects yielded normal results. Five of the six obese children had a family history of obesity in their mother or father, or both. Obesity in the five adults had ensued after adolescence. In all subjects the response of plasma prolactin concentration to hypoglycaemia was monitored at 0, 15, 30, 45, 60, 90, and 120 minutes after an intravenous injection of insulin (0.1 units/kg body weight). The blood glucose concentration 30 minutes after administration of insulin in each subject decreased to less than half the basal concentration for that subject and was lower than 2.8 mmol/l (50 mg/100 ml). Plasma prolactin concentrations were measured by radioimmunoassay.

The response of plasma prolactin concentration to stimulation by thyrotrophin releasing hormone (500 µg) intravenously was normal in six obese children. The response patterns of plasma prolactin concentration to the induced hypoglycaemia were within normal limits in the obese adults and non-obese adults and children but not in the obese children, in whom

the mean plasma prolactin concentration, expressed as the mean percentage of the basal plasma concentration, was lower than basal values (100%) 30 and 120 minutes after the administration of insulin (figure).

As the highest mean percentage occurred in the obese adults and non-obese adults and children 45 minutes after the insulin was administered we compared the mean percentage at 45 minutes in obese children with that in the three other groups. The mean percentage in the obese children was significantly lower than that in the non-obese children ($p < 0.01$), obese adults ($p < 0.05$), and non-obese adults ($p < 0.02$) (Student's *t* test).

Comment

Hypoglycaemia normally acts via the hypothalamus to increase secretion of prolactin by the pituitary. Our findings indicate that this mechanism is disturbed in obese children.

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Mean response of prolactin concentration to stimulation by hypoglycaemia induced by insulin in obese and non-obese children and adults. Bars represent SEM.

Cutaneous manifestations of zinc deficiency during treatment with anticonvulsants

Two primary zinc deficiency states occur in man—namely, endemic nutritional zinc deficiency and acrodermatitis enteropathica, an inherited defect of zinc absorption.¹ Symptomatic secondary zinc deficiency is rare and has occurred after total parenteral nutrition and jejunoileal bypass operations and in chronic alcoholism.¹ To our knowledge it has not been reported in patients receiving anticonvulsants or in ulcerative colitis per se. Zinc deficiency produces widespread disturbances in growth, behaviour, and gastrointestinal function.¹ Skin manifestations include an erosive anogenital dermatitis and a condition similar to seborrhoeic dermatitis of the face with candidal cheilitis. In chronic deficiency well demarcated scaly red-brown plaques develop over bony prominences.

Case reports

CASE 1

In 1983 a 37 year old subnormal epileptic woman presented with a non-itchy rash on one hand of two weeks' duration, which was unresponsive to