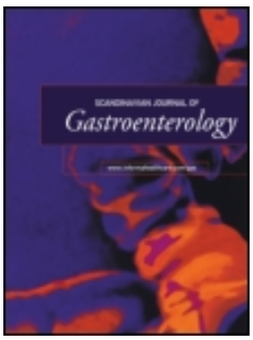

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Omeprazole in the Zollinger–Ellison Syndrome

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Treatment with omeprazole was evaluated in nine patients with the Zollinger–Ellison syndrome, in whom the effect of H_2-receptor antagonists had become inadequate. Treatment with 20–80 mg omeprazole daily reduced basal acid secretion by 77–100%. The effect persisted during a continuous treatment of up to 2 years. In five patients the initial dose could be reduced after some time of treatment. In eight patients the treatment promptly relieved all symptoms, and in the last patient, who had disseminated metastatic disease and large anastomotic ulcers, the symptoms disappeared gradually over a period of 10 weeks. No adverse events were seen. We conclude that omeprazole is an effective inhibitor of the acid hypersecretion in Zollinger–Ellison patients, also when H_2-receptor antagonists have failed.

Key words: Omeprazole; Zollinger–Ellison syndrome

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Omeprazole is a substituted benzimidazole and a potent antisecretory drug (1–3). It acts by blocking the H^+/K^+ ATPase, which is located on the secretory surface of the parietal cell and involved in the terminal steps of proton secretion (4). The drug is not commercially available but is under clinical investigation in several countries. We have investigated the effect of omeprazole treatment in nine Zollinger–Ellison patients who had become resistant to H_2-receptor antagonists.

PATIENTS AND METHODS

The features of the nine patients before treatment with omeprazole are shown in Table I. Patient 4 had had a truncal vagotomy with a gastrojejunostomy 5 years previously, and patient 7 a noncurative pancreaticoduodenectomy and antrectomy 7 years previously. He now had widespread metastases and a stomal ulcer. All other patients had an intact stomach and no signs of metastatic disease. Two of the patients (nos. 1 and 8) had multiple endocrine neoplasia syndrome type I (MEN I syndrome), with multiple gastrinomas in the pancreas and duodenum in one of them. In seven of the patients attempts to locate the gastrinoma to perform radical surgery have so far been unsuccessful. The basal acid secretion was measured during H_2-receptor antagonist treatment before the first morning dose and 8–10 h after the last medication, except in one patient (no. 8), who was given 800 mg cimetidine 2 h before measurements. The investigations performed during omeprazole treatment are shown in Table II. On day 1, H_2-receptor antagonist treatment was continued unaltered, and the first dose of 60 mg omeprazole was given at 2000 h. Basal acid output (BAO) was measured the next morning before any medication. H_2-receptor antagonists were then withdrawn, and omeprazole was thereafter given once or twice a day. After measurements of BAO the dose was adjusted to avoid achlorhydria and to keep BAO below 10 mmol/h. On days with BAO measurements the drug was given shortly after the measurements.

Gastric juice was collected by intermittent pump suction through a nasogastric tube. The aspirate was titrated to pH 7.0 with an autotitrator TTT (Radiometer, Copenhagen). Gastrin was determined radioimmunochemically with antiserum 2604 (5), as described previously (6).

Table I. Features of nine patients with the Zollinger–Ellison syndrome before treatment with omeprazole

Patient no.	Sex/Age, years	Serum gastrin, pmol/l	Basal acid output, mmol/h	Treatment, drug/daily dose	Duration of treatment, months	Symptoms and findings
1	M/39	568	106.0	Cimetidine/2.4 g	38	Gastric pain, diarrhea, multiple duodenal ulcerations
2	M/48	331	50.6	Cimetidine/3.0 g	21	Diarrhea, multiple duodenal erosions
3	M/56	785	67.3	Cimetidine/3.6 g	63	Gastric pain, diarrhea, multiple duodenal erosions
4	M/60	360	20.5	Ranitidine/1.2 g	29	Gastric pain, anastomotic ulcer
5	M/45	160	45.1	Ranitidine/1.8 g	36	Gastric pain, multiple duodenal ulcerations
6	M/34	363	84.8	Cimetidine/3.6 g	30	Gastric pain, diarrhea, multiple duodenal erosions
7	M/40	360	20.2	Ranitidine/2.7 g	6	Gastric pain, anastomotic ulcer and stenosis, hepatic metastasis
8	M/47	416	25.7	Cimetidine/4.8 g	53	Gastric pain, large deep duodenal ulcer, prepyloric ulcers
9	M/64	238	62.5	Cimetidine/3.6 g	17	Diarrhea, multiple duodenal ulcers

At every visit the patients were asked about dyspeptic symptoms, diarrhea, and side effects. Before and regularly during treatment routine urine tests for blood, sugar, and albumin were done, and blood samples were taken for the following analyses: hemoglobin, erythrocyte morphology, leukocyte differential count, platelet count, and concentrations of creatinine, urea, sodium, potassium, calcium, albumin, bilirubin, alkaline phosphatase, alanine aminotransferase, T_3, T_4, thyroid-stimulating hormone, glucose, and gastrin.

Endoscopy was performed at regular intervals (Table II).

The patients were fully informed of the experimental nature of the drug, and had all accepted the treatment.

RESULTS

The effect of omeprazole on the basal acid secretion is shown in Fig. 1 and Table III. In all patients there was a significant and strong reduction of acid secretion. The effect was immediate and lasted for more than 24 h in most of the patients, who could be treated with one morning dose. In some patients it was necessary to be treated twice daily to achieve adequate acid reduction. The necessary total daily doses were 20–80 mg. Details appear in Table III.

All patients but one experienced a prompt effect on symptoms and were without dyspeptic symptoms or diarrhea after day 3. Patient 7, with disseminated gastrinomas and large stenosing gastrojejunal ulcers, only gradually improved over a period of months. After 4 months the ulcers were healed, slight stenotic symptoms persisted, but dyspeptic pain had disappeared. In patients 1–6 endoscopy was not performed until after 6 months of treatment, owing to the complete lack of symptoms. At that time all ulcers had healed. Owing to the very severe ulcerations in patient 8, endoscopy was done on day 22, even though the patient was without symptoms. The ulcers were completely healed.

Gastrin values seemed unaffected by the treat-

Table II. Investigations performed on Zollinger–Ellison patients treated with omeprazole

	Measurements of basal acid output	Endoscopy	Blood and urine analyses
Pretreatment	+	+	+
Day 2	+		
Day 3	+		
Day 8	+		+
Day 22	+	(+)*	+
2 months	+	(+)*	+
4 months	+	(+)*	+
6 months†	+	+	+

* Only when dyspepsia.
† Same investigations repeated every 3rd month.

ment, and no side effects were seen in any of the patients.

DISCUSSION

The study shows that omeprazole is a potent inhibitor of acid secretion in patients with the Zollinger–Ellison syndrome (ZES). The spontaneous acid secretion is rapidly reduced by 77–100% by doses from 20 to 80 mg daily, and, if desirable, it seems quite possible to reduce secretion 100% in all patients by slight increases of dosage.

Omeprazole has a prolonged biological effect, also verified in this study. Marked inhibition of acid secretion is seen 24 h after administration, at which time the drug is unmeasurable in circulation (1). It has been suggested that the compound, being a weak base, accumulates at the parietal cells (7). The long duration of action makes it

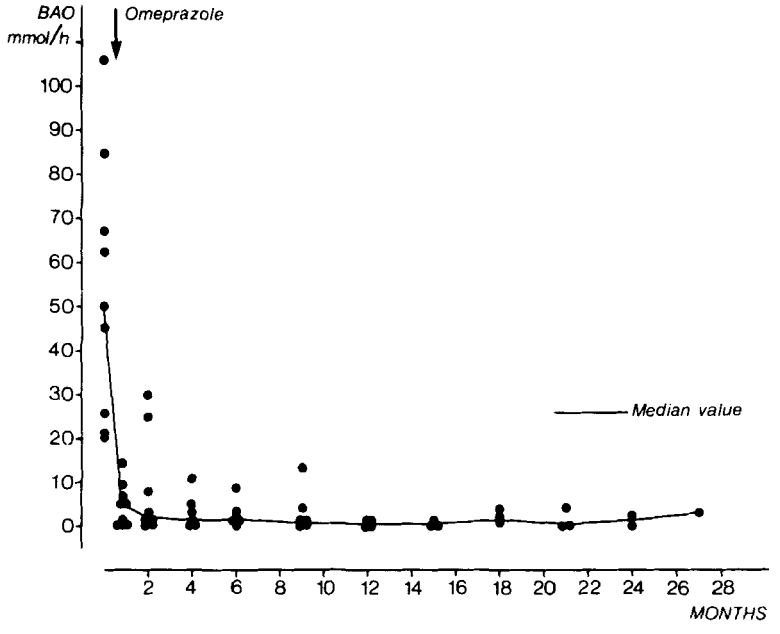

Fig. 1. Basal acid secretion (median) before and during treatment with omeprazole in patients with the Zollinger–Ellison syndrome.

Table III. Daily dose of omeprazole (mg) and basal acid output (BAO) (mmol H^+/h) before next dosing in nine patients with the Zollinger–Ellison syndrome

	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5		Patient 6		Patient 7		Patient 8		Patient 9	
	Dose	BAO	Dose	BAO	Dose	BAO	Dose	BAO	Dose	BAO	Dose	BAO	Dose	BAO	Dose	BAO	Dose	BAO
Pretreatment		106.0		50.6		67.3		20.5		45.1		84.8		20.2		25.7		62.5
Day 2	60	29.0	60	1.7	60	24.1	60	0.0	60	4.2	60	9.5	60	10.7	60	0.8	60	0.0
Day 3	100	5.0	80	5.0	80	12.2	60	0.0	80	8.8	80	21.3	60	9.6	60	2.5	60	14.9
Day 8	80	4.0	80	8.0	80	19.0	60	0.0	80	0.0	40 + 40	11.4	60	5.7	60	18.6	60	10.2
Day 22	80	5.0	80	7.0	60 + 40	0.0	60	0.0	60	0.0	40 + 40	1.1	60	9.4	40 + 40	4.7	60	14.5
2 months	80	8.0	80	1.5	80	25.4	60	0.0	40	0.0	40 + 40	0.9	60	30.4	40 + 40	3.7	40 + 40	
4 months	80	4.7	80	3.2	60 + 40	0.5	40	0.0	40	0.0	60	10.7	80	2.0	40 + 40			
6 months	80	2.4	80	3.1	40 + 40	0.0	20	1.2	40	1.6	60	8.9	80					
9 months	80	1.2	80	4.2	40 + 40	1.6	20	0.0	40	0.0	60	13.6						
12 months	80	0.8	80	0.0	40 + 40	0.7	20	0.0	20		40 + 20							
15 months	60	1.3	60	0.0	40 + 40	0.0	20											
18 months	60	1.7	60	0.8	40 + 20	3.5												
21 months	60	4.8	60	0.0	40 + 20	0.1												
24 months	60	2.7	60	0.0	20 + 20													
27 months	60	3.0	40															

possible to administer the drug only once a day in most patients. We learned from this study, however, that when 80 mg daily was insufficient, a further increase in total dose could be avoided, because a satisfactory inhibition could be obtained by giving half the dose twice daily (patients 3 and 6, Table III).

A gradual decrease in total dose was possible in some patients. Patients 1, 2, and 3 needed less to maintain the inhibition after about a year of treatment. The same was possibly the case in patients 4 and 5, but it is also possible that the dose was unnecessarily high from the beginning in these patients.

We saw no side effects of the drug in any of the patients, and laboratory values were unchanged during long-term treatment. In two patients (nos. 7 and 2) the serum gastrin concentration increased. In patient 7 there was evident progression of the disease at the same time, and in patient 2 the value decreased again later and has always fluctuated considerably. A gradual increase and some variation in serum gastrin values are not unusual in patients with ZES, and in omeprazole-treated patients it will be difficult to verify whether some of these changes can be ascribed to the drug.

Cellular hyperplasia and carcinoid-like tumors consisting of enterochromaffin-like cells have been found to develop in the stomach of rats after long-term treatment with omeprazole (8). The hyperplasia is probably caused by hypergastrinemia, which arises from decreased antral inhibition by acid during treatment with high doses of the drug (8). How these findings in rats apply to man is not known. In theory, the constant hypergastrinemia in ZES patients might also result in hyperplasia of the endocrine cells of the gastric mucosa, and proliferation of gastric endocrine cells has earlier been reported in association with ZES (9). In a recent investigation of ZES patients treated with omeprazole or H_2-receptor antagonists or without medical treatment we found no carcinoid tumors, but some degree of endocrine cell hyperplasia in the gastric body was seen in most of the patients irrespective of treatment. The degrees of hyperplasia were positively correlated with duration of disease (10).

Complete medical control of acid secretion in patients with ZES is of considerable value. Since the primary goal in the treatment of these patients is radical tumor resection, it is an advantage when acute surgery and elective total gastrectomy can be avoided, and repeated investigations in an attempt to locate the gastrinomas can be carried out. Treatment with H_2-receptor antagonists in high doses seemed to be a safe and satisfactory therapy in many cases (11), but a considerable increase in the doses has often been necessary in the long-term treatment, and some patients, as we also have experienced, become gradually resistant (12, 13). It follows that an alternative antisecretory treatment is of great value. Omeprazole seems to control the ulcer diathesis completely, and we found no side effects and no indications that hypergastrinemia would be accentuated during the treatment. However, the findings in treated rats (8) and the long-standing constant hypergastrinemia in gastrinoma patients suggest that regular endoscopic checks with studies of the endocrine cells of the gastric mucosa are appropriate during the treatment.

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REFERENCES

1. Olbe L, Haglund U, Leth R, Lind T, Cederberg C, Ekenved G, Elander B, Fellenius E, Lundberg P, Wallmark B. Gastroenterology 1982, 83, 193–198
2. Lamers CBHW, Lind T, Moberg S, Jansen JBMJ, Olbe L. N Engl J Med 1984, 310, 758–761
3. Öberg K, Lindström H. Lancet 1983, 1, 66–67
4. Fellenius E, Berglindh T, Sachs G, Olbe L, Elander B, Sjöstrand SE, Wallmark B. Nature 1981, 290, 159–161
5. Rehfeld JF, Stadil F, Rubin B. Scand J Clin Lab Invest 1972, 20, 221–232
6. Stadil F, Rehfeld JF. Scand J Gastroenterol 1973, 8, 101–112
7. Fellenius E, Elander B, Wallmark B, Helander HF, Berglindh T. Am J Physiol 1982, 243, G 505–510
8. Ekman L, Hansson E, Havu N, Carlsson E, Lundberg C. Scand J Gastroenterol 1985, 20(suppl 108), 53–69
9. Bordi C, Cocconi G, Togni R, Vezzadini P, Missale G. Arch Pathol 1974, 98, 274–279
10. Bardram L, Thomsen P, Stadil F. Digestion 1986 (in press)
11. McCarthy DM. Gastroenterology 1978, 74, 453–458
12. Deveney CW, Stein S, Way LW. Am J Surg 1983, 146, 116–123
13. Stabile BE, Ippoliti AF, Walsh JH, Passaro E. Am J Surg 1983, 145, 17–23