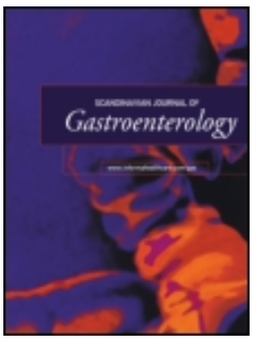

Scandinavian Journal of Gastroenterology

ISSN: 0036-5521 (Print) 1502-7708 (Online) Journal homepage: https://www.tandfonline.com/loi/igas20

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To cite this article: L. Olbe, C. Cederberg, T. Lind & M. Olausson (1989) Effect of Omeprazole on Gastric Acid Secretion and Plasma Gastrin in Man, Scandinavian Journal of Gastroenterology, 24:sup166, 27-32, DOI: 10.3109/00365528909091240

To link to this article: https://doi.org/10.3109/00365528909091240

Effect of Omeprazole on Gastric Acid Secretion and Plasma Gastrin in Man

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Olbe L, Cederberg C, Lind T, Olausson M. Effect of omeprazole on gastric acid secretion and plasma gastrin in man. Scand J Gastroenterol 1989, 24(suppl 166), 27–32

Single doses of omeprazole inhibit pentagastrin-stimulated gastric acid secretion and almost complete inhibition can be achieved for 4–6 hours with a single dose of 80 mg. Acid secretion then slowly returns and reaches normal levels after 3–4 days. Omeprazole also dose-dependently inhibits basal acid secretion as well as acid secretion stimulated with histamine, peptone and modified sham feeding, with similar efficiency. During repeated once-daily dosing with an enteric-coated granule capsule formulation, inhibition of acid secretion increased initially, and stabilized within about 4 days. Dose-response studies in patients with duodenal ulcers and healthy subjects have shown that 20–40 mg/day results in a peak reduction (80–100%) of pentagastrin-stimulated acid secretion 6 hours after dose. Studies of 24-hour intragastric acidity in duodenal ulcer patients have shown that 4 weeks of treatment with omeprazole, 20 mg once daily, resulted in a reduction of median intragastric acidity by 97%, which was superior to the 57% median reduction achieved with ranitidine, 150 mg b.d., for 4 weeks in the same patients. During omeprazole treatment, fasting plasma gastrin increased in relation to the degree of inhibition of acid secretion. After discontinuation of treatment, plasma gastrin normalized. Treatment with omeprazole, 20 mg, increased 24-hour plasma gastrin to the same extent as after highly selective vagotomy. Long-term treatment with omeprazole, 20–40 mg, for up to 2 years has not been associated with any progressive rise in fasting plasma gastrin.

Key words: Gastric acid; gastrin; omeprazole

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Omeprazole, a substituted benzimidazole, represents a new class of gastric acid inhibitors – the proton (acid) pump inhibitors. Experimental studies in vitro and in vivo have shown that omeprazole concentrates within the parietal cell and is activated in the acid milieu. This active metabolite binds and inhibits the gastric proton (acid) pump (H^+,K^+-ATPase) in the secretory membrane of the parietal cell.

EFFECT ON GASTRIC ACID SECRETION

Following a single oral dose of omeprazole in buffered suspension, pentagastrin-stimulated gastric acid secretion was rapidly and dose-dependently inhibited, and almost complete inhibition was achieved for at least 4 hours after an 80 mg dose. (Fig. 1) (1). The calculated median effective dose (ED_{50}) was 27 mg. Similar studies have shown that omeprazole dose-dependently inhibits basal acid secretion, as well as acid secretion stimulated by histamine, modified sham-feeding and peptone, with a similar efficiency (2, 3). This finding was expected, because omeprazole acts at the final step in the acid secretion process and, therefore, inhibits gastric acid secretion independently of stimulus.

The duration of the antisecretory effect following a single oral dose of omeprazole, 20 mg or 40 mg in a buffered suspension, was studied in

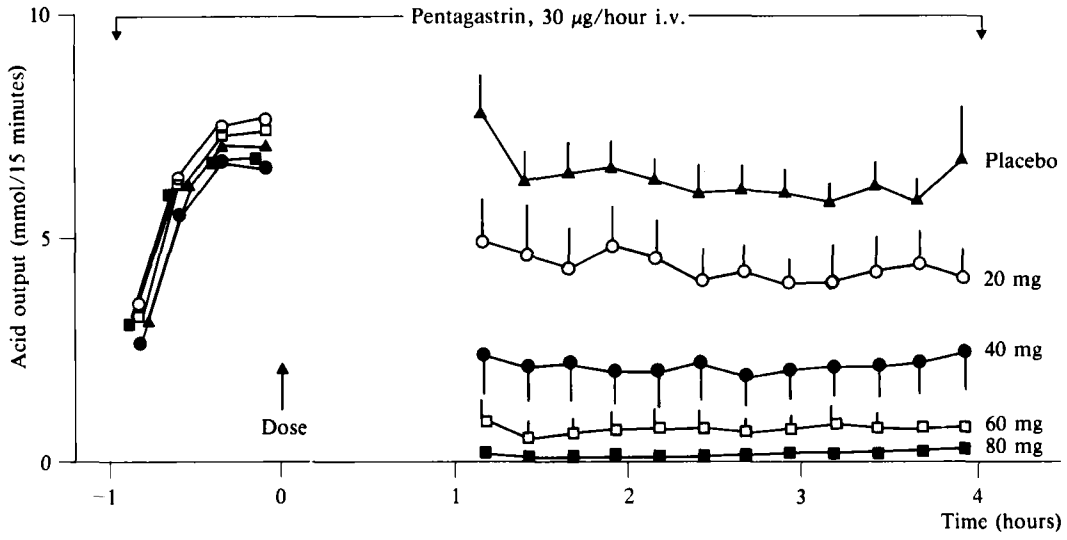

Fig. 1. Mean effects of placebo and different single oral doses of omeprazole on the gastric acid response to an intravenous infusion of a submaximal dose of pentagastrin (30 μg/hour). Redrawn with permission from Lind et al. (1).

six healthy subjects (1). Gastric acid secretion was maximally stimulated by an intravenous infusion of pentagastrin for 1 hour. The pentagastrin stimulation was repeated at intervals of 2 hours, 1 day, 2 days, 3 days and 14 days after the administration of the single dose of omeprazole. Both 20 mg and 40 mg doses of omeprazole produced a marked inhibition of gastric acid secretion 2 hours after dosage, and the degree of acid inhibition then gradually decreased over the next 3 days. After the single 20 mg dose of omeprazole, acid secretion had reached normal levels within 3 days. However, after the 40 mg dose, there was still a small, but significant, inhibition of acid secretion after 3 days. The acid response to pentagastrin was found to be back to control levels 14 days after the omeprazole, 40 mg, dose.

With a repeated daily dose of omeprazole, 15 mg in a buffered suspension, the maximal acid response to pentagastrin was markedly reduced 2 hours after dosing and slightly reduced after 24 hours. The antisecretory effect of omeprazole increased over the first few days and stabilized after 3 days (1). The level of acid inhibition produced by omeprazole at this dose, 15 mg, varied between 40% and 80% over 24 hours. During repeated once-daily administration of omeprazole, 30 mg as enteric-coated granules, inhibition of gastric acid secretion increased during the first few days of treatment, and stabilized within about 4 days (4). Continued treatment produced no further increase in the degree of acid inhibition, and after treatment was discontinued, acid secretion returned to control levels within 3–5 days without any rebound hypersecretion (5). This rate of acid recovery after prolonged antisecretory treatment with omeprazole is similar to that observed after a single 40 mg dose of omeprazole (1). The increase in the antisecretory effect of omeprazole during the first few days of daily treatment is probably due to the slow elimination of the enzyme bound active inhibitor from the parietal cells, resulting in an initial increase in the number of inhibited enzyme molecules.

The effect of repeated daily doses of omeprazole, administered as enteric-coated granules in gelatine capsules, on gastric acid secretion has been studied in both healthy

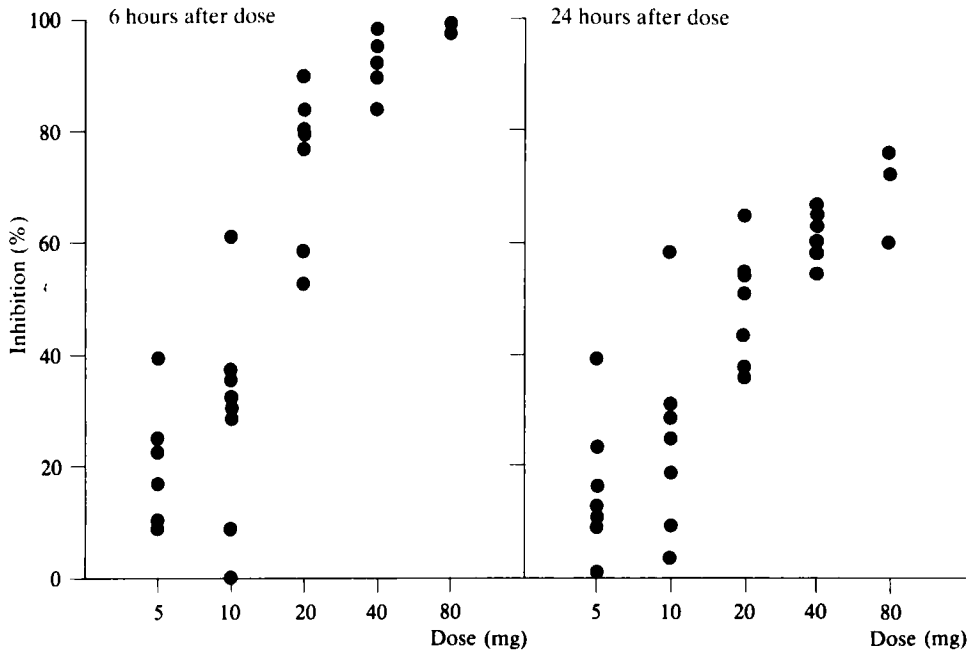

Fig. 2. The individual inhibitory effect of 5 days of treatment with different doses of omeprazole on the maximal acid response to pentagastrin. (a) 6 hours after dose. (b) 24 hours after dose. Redrawn with permission from Lind et al. (14).

subjects and duodenal ulcer patients (6, 7) in order to find a clinically relevant dose. Each dose of omeprazole (5, 10, 20 or 40 mg) was given to all subjects in a randomized order for 5 days, to stabilize the inhibitory effect of each dose. Gastric acid secretion was then maximally stimulated by pentagastrin 6 hours and 24 hours after the last dose of each 5-day period of treatment. Daily treatment with omeprazole, 5 mg and 10 mg, did not produce an adequate inhibition of gastric acid secretion in all patients, while daily doses of 20 mg and 40 mg resulted in 80–100% reduction of pentagastrin-stimulated acid secretion 6 hours after dose and 50–60% inhibition after 24 hours (Fig. 2). Thus, it seems that a daily dose of 20–40 mg omeprazole produces a marked inhibition of gastric acid secretion without producing anacidity.

The effect of a once-daily dosing of omeprazole on 24-hour intragastric acidity has been investigated in several studies (8–12). These studies have shown that omeprazole dose-dependently inhibits 24-hour intragastric acidity in duodenal ulcer patients. Omeprazole, 20–40 mg, resulted in a marked reduction in intragastric acidity while a 10 mg dose was less effective and the response more variable (Fig. 3) (8). Treatment with omeprazole, 20 mg once daily for 4 weeks, resulted in a 97% median reduction in the 24-hour intragastric acidity, compared to treatment with ranitidine 150 mg b.d., which produced a 57% median reduction (12).

EFFECT ON PLASMA GASTRIN

It is well established that the release of gastrin from the G cells in the gastric antrum is regulated by the acidity of the gastric juice, though the precise inhibitory mechanism of action is not known. It is, therefore, not suprising that treatment with histamine H_2-receptor antagonists causes a slight rise in plasma gastrin concentrations (13). This effect has also been seen with omeprazole (3, 8, 10, 13–17). During treatment with omeprazole once daily, there was a modest

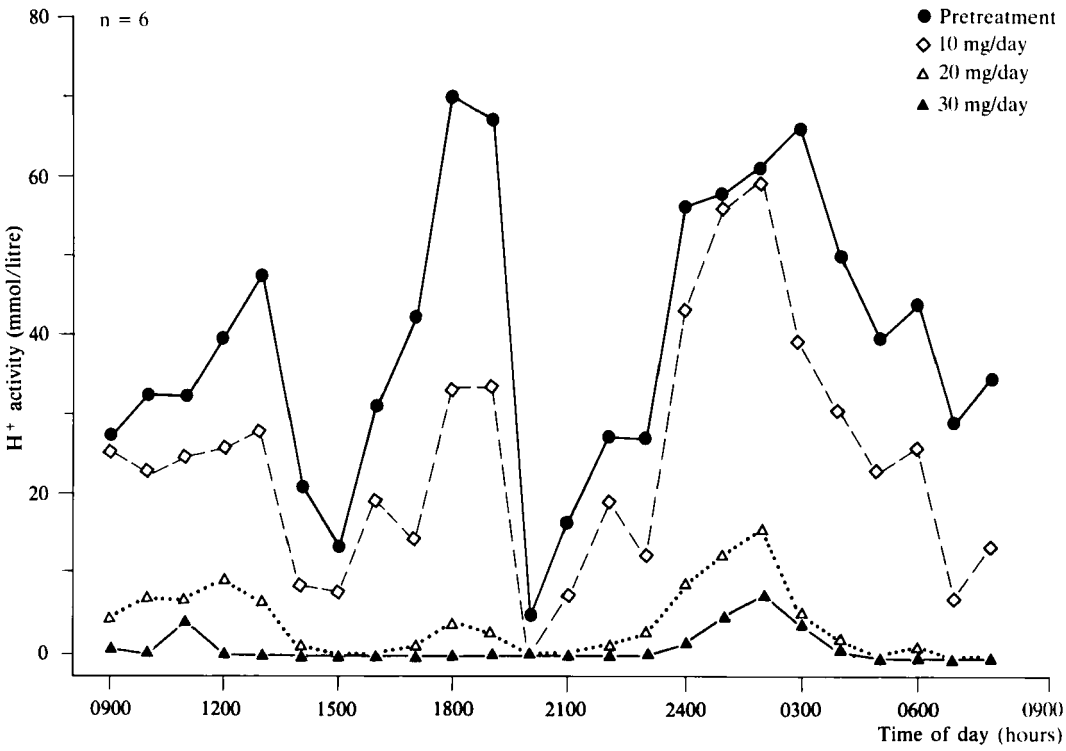

Fig. 3. The inhibitory effects of 1 week of treatment with different daily doses of omeprazole on the 24-hour intragastric acidity. Redrawn with permission from Sharma et al. (8).

increase in the fasting plasma gastrin levels and in the gastrin response to meals (8, 16).

The relationship between the dose of omeprazole, the degree of acid reduction and the increase in fasting plasma gastrin levels has been studied both 6 hours and 24 hours after 5 days of treatment (14). As previously stated, the degree of acid reduction was dose dependent, and was more marked 6 hours after dosing than after 24 hours. The level of fasting plasma gastrin showed a corresponding pattern and was thus higher 6 hours after dosing than after 24 hours. There was a relationship between inhibition of acid secretion and fasting plasma gastrin. Gastrin levels did increase in relation to the degree of inhibition of acid secretion, but inhibition had to exceed 80% before this occurred.

After short-term treatment with omeprazole resulting in an increased fasting plasma gastrin level, plasma gastrin concentrations returned to normal within 1 week of discontinuation of therapy (16). During long-term treatment with omeprazole, fasting plasma gastrin levels increased modestly over the first few weeks of treatment, but no further increase occurred during the following treatment period of up to 2 years (13).

A crossover study compared the effect of 4 weeks' treatment with omeprazole, 20 mg once daily, with ranitidine, 150 mg b.d., on plasma gastrin (18). Both drugs caused a slight, but significant, rise in the 24-hour plasma gastrin, with omeprazole producing a greater increase than ranitidine. The gastrin levels during treatment with both drugs were, however, far below the levels obtained in patients with achlorhydric pernicious anaemia (Fig. 4). The difference between omeprazole and ranitidine was probably due to the more effective reduction of intragastric acidity during omeprazole treatment, as the

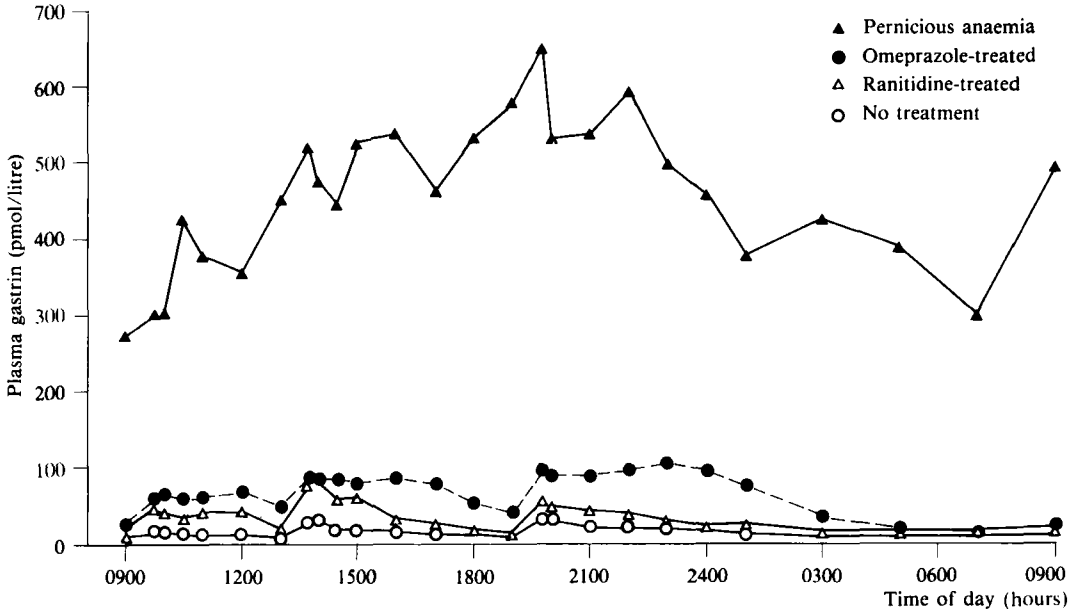

Fig. 4. The 24-hour plasma gastrin profile in non-treated patients, ranitidine-treated (150 mg b.d.) patients, omeprazole-treated (20 mg once daily) patients, and achlorhydric pernicious anaemia patients. Redrawn with permission from Lanzon-Miller et al. (18).

intragastric acidity was inversely correlated to the 24-hour plasma gastrin level, irrespective of treatment.

In a recent study, the effect of omeprazole, 20 mg once daily was compared with the effect of proximal gastric vagotomy on plasma gastrin in a group of patients with severe peptic ulcer disease (19). Nine patients were studied before treatment, after 7 days' treatment with omeprazole and 3–6 months after proximal gastric vagotomy. The median reduction in 24-hour intragastric acidity was 94% during omeprazole treatment and 78% following gastric vagotomy. Both omeprazole treatment and proximal gastric vagotomy increased the 24-hour plasma gastrin levels to about the same degree, though the mechanisms behind the increases may not be the same.

CONCLUSION

Omeprazole, 20–40 mg, provides a once-daily regimen for effective control of gastric acid secretion and intragastric acidity that is more effective than other treatments, such as histamine H_2-receptor antagonists or proximal gastric vagotomy. The reduction of intragastric acidity during omeprazole treatment results in a modest but fully reversible rise in plasma gastrin levels.

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