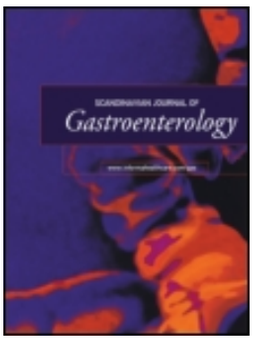

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Mechanism of Action of Omeprazole

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The inhibitory effect of omeprazole on gastric acid secretion *in vivo* and *in vitro* is presented. In the gastric fistula dog omeprazole was found to be about 10 times more potent than cimetidine. When omeprazole was administered *in vivo*, the inhibition of acid secretory rates was found to correlate with the degree of inhibition of the gastric H^+K^+ATPase purified from the omeprazole treated animals. The inhibitory action of omeprazole was found to depend on acid induced transformation of omeprazole into an active inhibitor of the gastric H^+K^+ATPase, as no inhibition was obtained when omeprazole was incubated under neutral conditions with either the isolated gastric mucosal or the H^+K^+ATPase preparations. A model is proposed in which the inhibition of acid formation is mediated by an inhibitory compound generated from omeprazole within the acid compartment of the parietal cell.

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Omeprazole (Fig. 1) belongs to a new class of gastric acid secretion inhibitors, the substituted benzimidazoles. The compound has proved to be an effective anti-ulcer agent and inhibitor of acid secretion in several animal models, including man (1). In the gastric fistula dog (2), a relationship has been demonstrated between inhibition of gastric acid secretion and the dose of drug administered (Fig. 2). The antisecretory effect on histamine stimulated secretion was measured *in vivo* for both omeprazole and cimetidine; omeprazole was found to be about 10-fold more potent than cimetidine.

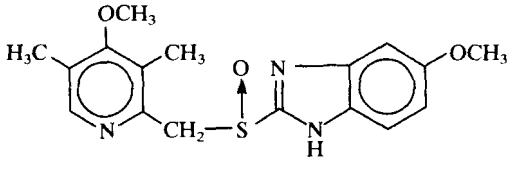

Fig. 1. The structure of omeprazole.

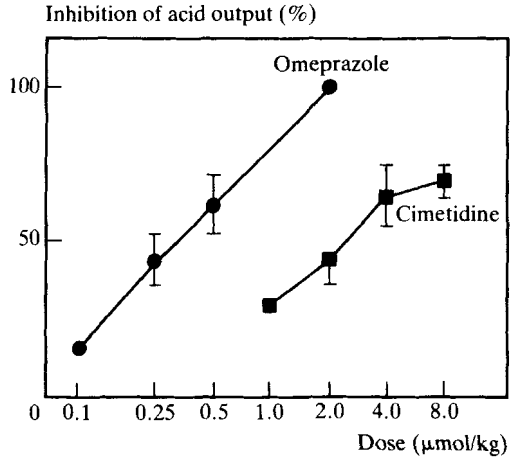

Fig. 2. Inhibition of histamine stimulated gastric acid secretion in the gastric fistula dog. The drugs were administered intraduodenally.

MECHANISM OF ACTION OF OMEPRAZOLE

In order to understand the mechanisms underlying the antisecretory effect of omeprazole, its inhibitory action has been extensively studied in several *in vitro* preparations. The effectiveness of omeprazole and cimetidine *in vitro* is shown in Table I (3–8). Both omeprazole and cimetidine were capable of inhibiting histamine stimulated acid formation in isolated intact gastric glands, isolated parietal cells and isolated mucosal preparations. Under all other conditions cimetidine was without inhibitory effect. In contrast, omeprazole inhibited acid formation in all the preparations tested, regardless of the stimulus. Furthermore, omeprazole inhibited partly purified

Table I. Effect of omeprazole and cimetidine on acid formation in different gastric *in vitro* test models.

Experimental preparation and type of stimulation	Omeprazole	Cimetidine	Reference
Isolated intact mucosa			3
Basal	+	−	
Histamine	+	+	
db-cyclic AMP	+	−	
Isolated intact glands			4,5
Basal	+	−	
Histamine	+	+	
db-cyclic AMP	+	−	
High K^+/low Na^+	+	−	
Isolated permeable glands			4,5
ATP, high K^+			
Isolated enriched parietal cells			6,7
Basal	+	−	
Histamine	+	+	
db-cyclic AMP	+	−	
Purified H^+K^+ATPase			4,8
ATP, K^+	+	−	

\+ Inhibition
− No inhibition

H^+K^+ATPase. Based on this pattern of effectiveness, and because of its inhibition of the isolated H^+K^+ATPase, a mechanism has been proposed in which omeprazole inhibits gastric acid secretion by blockade of the gastric H^+K^+ATPase (Fig. 3) (9).

Although the gastric H^+K^+ATPase has been shown to be responsible for acidification of the stomach on the basis of several lines of evidence, no direct correlation between the activity of the enzyme and acid secretion has been reported. The purpose of one of the author's studies was to correlate acid secretory rates in the rat to the activity of the gastric H^+K^+ATPase. Increasing oral doses of omeprazole inhibited the rate of maximally stimulated acid secretion in a dose dependent manner (Fig. 4a). In parallel, the activity of the gastric H^+K^+ATPase and the formation of its phosphoenzyme intermediate were also inhibited (Fig. 4b, c). The ED_{50} value was about 10 μmol/kg for all three parameters.

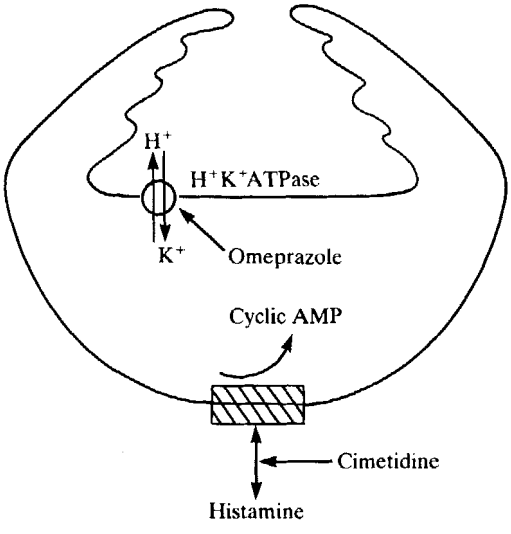

Fig. 3. A model for inhibition of acid secretion in the parietal cell by omeprazole and cimetidine.

The rate of recovery of both acid secretion and H^+K^+ATPase activity was measured following a dose of omeprazole that initially gave total inhibition of acid secretion; both of these parameters followed the same time course (Fig. 5a). When the data were replotted as shown in Fig. 5b, and one higher dose of omeprazole was included, a close correlation between the rate of acid secretion and activity of the gastric H^+K^+ATPase was obtained. This close relationship forms the basis for synthesis of H^+K^+ATPase inhibitors as useful tools in ulcer therapy.

SELECTIVITY OF OMEPRAZOLE

Various factors contribute to the selectivity of omeprazole for inhibition of gastric acid secretion. For example, at neutral or slightly alkaline pH, omeprazole is very stable with a half-life of about 17 hours. However, at a pH approaching the acidity of the gastric juice, that is, pH 1, omeprazole is very labile with a half-life of about 2 minutes (Fig. 6). The stability of omeprazole in isolated stimulated gastric glands can be followed (Fig. 7a). As the concentration of omeprazole decreased in both the isolated gastric glands and in the medium, its reduced form H 168/22 was

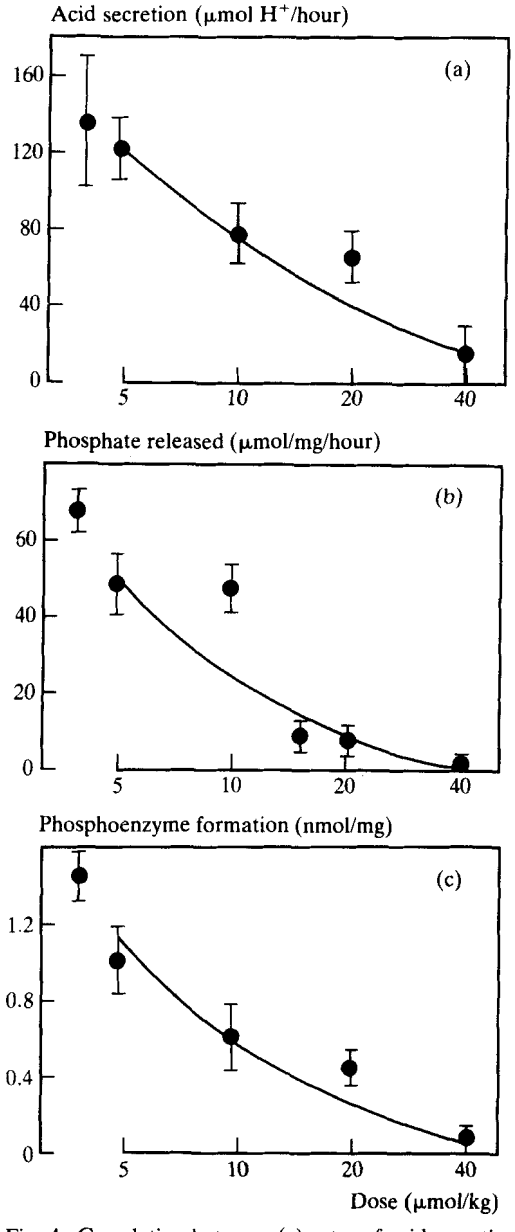

Fig. 4. Correlation between (a) rates of acid secretion in the chronic fistula rat (b) inhibition of H^+K^+ATPase activity and (c) phosphoenzyme formation in rat gastric mucosa, during omeprazole treatment.

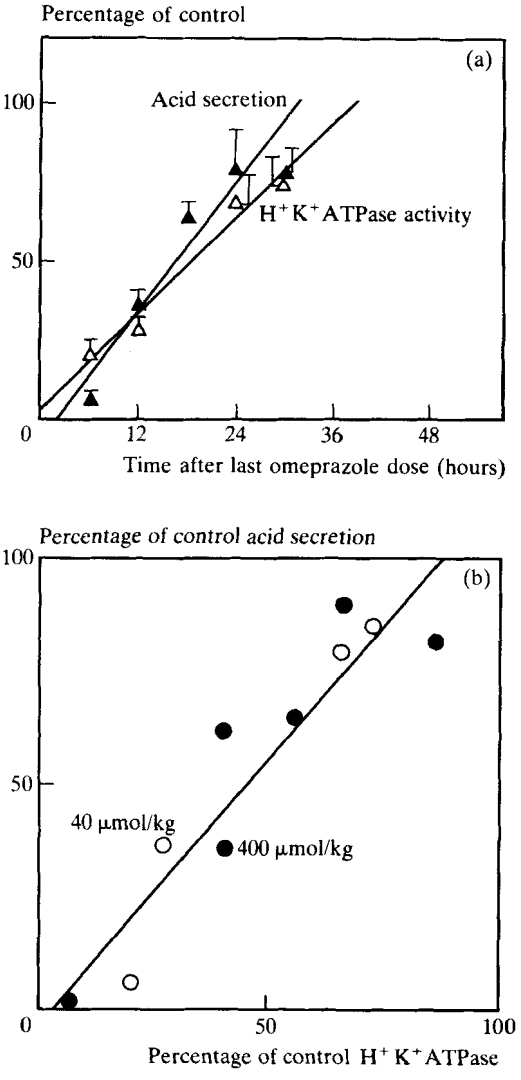

Fig. 5. (a) Recovery of acid secretion and H^+K^+ATPase activity following administration of omeprazole, 40 μmol/kg p.o. (b) Correlation between inhibition of acid secretion and H^+K^+ATPase activity under the influence of two different doses of omeprazole.

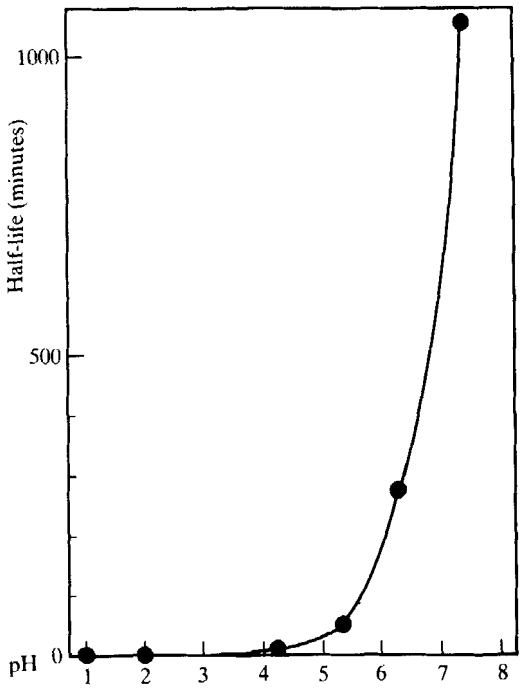

Fig. 6. Stability of omeprazole at different pH values.

produced. In contrast, when the concentrations of omeprazole and its reduced form were measured in inhibited glands (Fig. 7b), omeprazole was found to be comparatively stable. Thus, omeprazole decomposed as a function of the intraglandular acidity, that is, the degree of glandular stimulation.

Neutralization of the gastric mucosa

This section will deal with the question of the relationship between acid induced transformation of omeprazole and inhibition of acid secretion. The effect of neutralization of the gastric mucosa was studied by the use of a permeable weak base. This weak base enters the acidic compartment of the parietal cell in its neutral form. If the pH there is below the pK_a of the weak base, it will be protonated to a large extent. Biological membranes are relatively impermeable to the protonated form of the base which will therefore diffuse into the secretory solution. Provided that the pH of the secretory

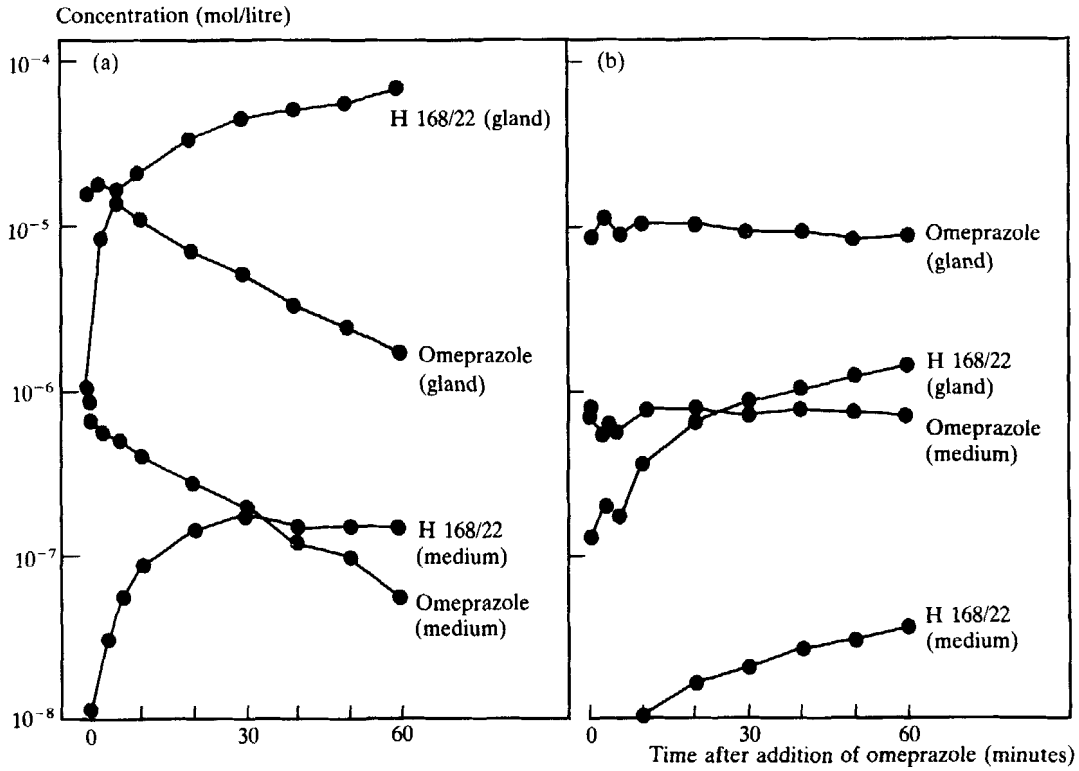

Fig. 7. Stability of omeprazole in isolated gastric glands. Omeprazole, 1 μmol/litre, was added at time zero, and the concentration of the parent compound and its reduced form H168/22 followed in (a) stimulated gastric glands (b) inhibited gastric glands.

solution is above the pK_a value of the weak base, it will be deprotonated and the secreted proton can be titrated. If the pH of the secretory solution is below the pK_a value of the weak base, however, the proton will still be bound and cannot be measured. This will lead to an apparent inhibition of acid secretion.

The effect of neutralization of the mucosa by the weak base, 4-aminoantipyrine, on omeprazole inhibition in the isolated guinea-pig mucosal preparation is shown in Fig. 8. In this experiment, the secretory side pH was maintained at 7.4, and 4-aminoantipyrine was added to the nutrient side 30 minutes before omeprazole. In the control, 4-aminoantipyrine was omitted. The results shown are acid secretory rates at 120 minutes, after stimulation with histamine. In the absence of 4-aminoantipyrine, omeprazole induced a strong inhibition of acid secretion. Inclusion of the weak base before omeprazole, however, reduced the inhibition substantially. This indicates that when the mucosa is neutralized prior to addition of omeprazole, the inhibitory capacity of the benzimidazole is lost.

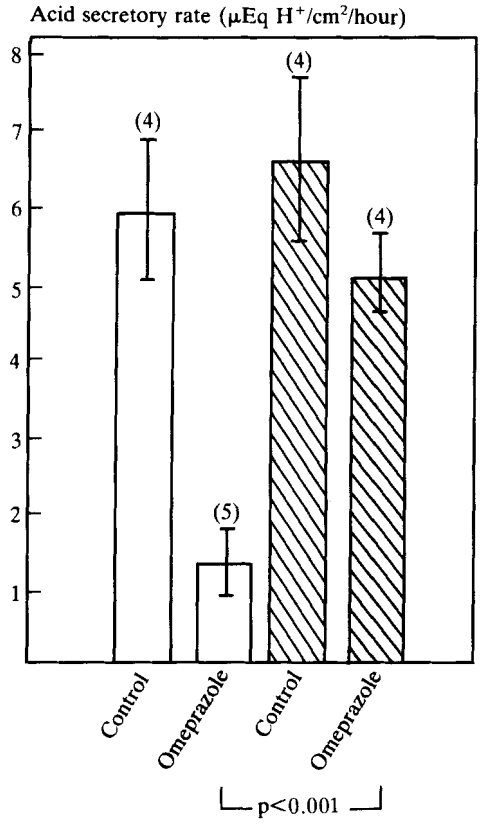

Fig. 8. Effect of neutralization of the gastric mucosa on inhibition of acid secretion by omeprazole. The secretory side was maintained at pH 7.4 and 4-aminoantipyrine, 20 mmol/litre, was added to the nutrient side, as was omeprazole, 5×10^{-6} mol/litre. The cells were stimulated by histamine, 2×10^{-5} mol/litre, on the nutrient side.

The finding that an acid environment is a necessary condition for inhibition by omeprazole was supported by the results of an experiment in which omeprazole was decomposed in buffer, pH 5.2. After various time intervals, its inhibitory action on the isolated H^+K^+ATPase was investigated. At zero time, no decomposition of omeprazole had occurred and no inhibition was observed (Fig. 9). However, as omeprazole

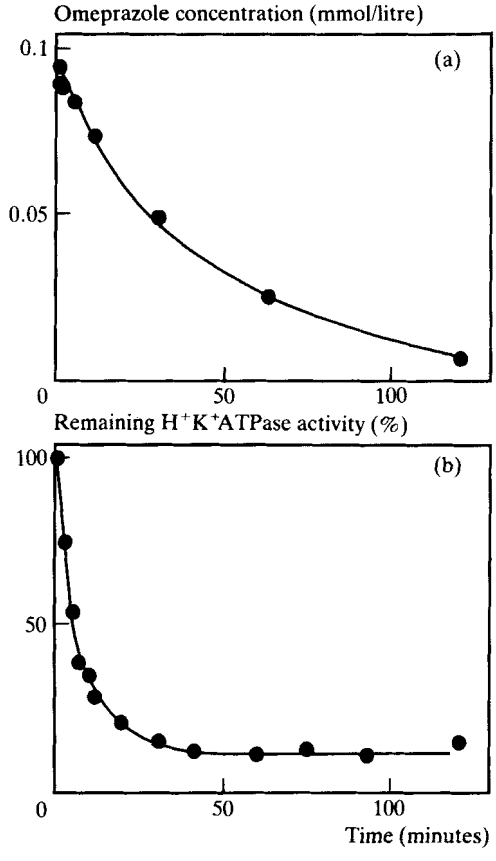

Fig. 9. Effect of acid treatment of omeprazole on its inhibition of H^+K^+ATPase activity.

gradually decomposed, progressive inhibition of the H^+K^+ATPase activity was obtained.

POSTULATED MECHANISM OF ACTION OF OMEPRAZOLE

A model for the events leading to inhibition of acid secretion by omeprazole is presented in Fig. 10. Omeprazole in intact form enters the parietal cell from the serosal side. When it enters the acid compartment of the parietal cell, it will be protonated and accumulated, provided the pH of the acid compartment is below the pK_a value of omeprazole. Subsequently the protonated form of omeprazole is transformed into its active inhibitor, which reacts with the gastric H^+K^+ATPase. In this way, acid induced transformation is necessary in order to produce inhibition. The fact that omeprazole is activated close to the H^+K^+ATPase, an enzyme that appears unique for the gastric mucosa, enhances the selectivity of the inhibitor.

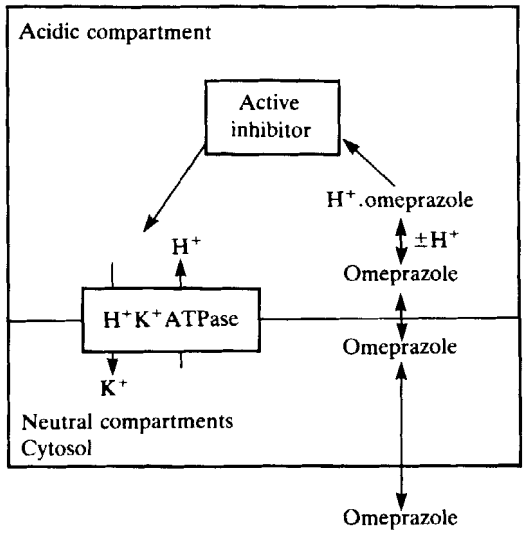

Fig. 10. A scheme for acid induced transformation of omeprazole into an active inhibitor of acid secretion within the parietal cell.

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