A PROTON-PUMP INHIBITOR EXPEDITION: THE CASE HISTORIES OF OMEPRAZOLE AND ESOMEPRAZOLE

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Thirty years ago, disorders associated with inappropriate levels of gastric acid were a major problem for which treatment options were limited, and approaches to the control of gastric acid secretion were thus the focus of considerable drug discovery efforts. Here, we summarize how one such programme led to the development of the proton-pump inhibitor omeprazole (Losec, Prilosec), a conceptually new drug that proved clinically superior to previous antisecretory drugs in the treatment of acid-related disorders, and which became the world's best-selling drug in the late 1990s. We then describe how the antisecretory and clinical effects were further improved by the development of esomeprazole (Nexium), a single enantiomer of omeprazole, which was launched in 2000.

GASTROESOPHAGEAL REFLUX DISEASE
Any symptomatic clinical condition with or without change in tissue structure that results from the reflux of gastric acid into the esophagus.

HEARTBURN
A burning sensation starting in the upper part of the abdomen and moving through the chest towards the throat.

PEPTIC ULCERS
Ulcers in the upper gastrointestinal tract, in which gastric acid is a key promoter.

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Gastric acid has been known for many decades to be a key factor in normal upper gastrointestinal functions, including protein digestion and calcium and iron absorption, as well as providing some protection against bacterial infections. However, inappropriate levels of gastric acid underlie several widespread pathological conditions, including GASTROESOPHAGEAL REFLUX DISEASE (GERD), for which HEARTBURN is the most common symptom, and PEPTIC ULCERS, which cause pain and suffering in millions of people, and which, only thirty years ago, could be life-threatening if untreated. Treatment options then, however, were limited. For example, for peptic ulcers, the main treatment was administration of antacids to neutralize excess gastric acid (which promotes ulcer formation and prevents healing), but this provided only temporary relief. The alternative was an operation (gastrectomy, in which part of the stomach is removed, and/or vagotomy, in which nerves to the stomach are sectioned). The surgery could, however, have serious side effects. Pharmacological control of the complex mechanism of gastric acid secretion has therefore long been desirable.

The medical treatment of acid-related diseases — in particular peptic ulcers and GERD — had a breakthrough in the late 1970s with the introduction of the antisecretory drug cimetidine, an antagonist of the histamine 2 (H_2) receptor, which has a key role in one of the pathways leading to gastric acid secretion. Cimetidine, and later comparable compounds with the same mechanism of action, have a marked gastric acid inhibitory effect, and considerably improved the lives of millions of people, as well as reducing the need for surgery. However, H_2-receptor antagonists have a relatively short duration of action.

From the late 1960s onwards, the pharmaceutical company Astra was also pursuing a programme aimed at finding a drug to inhibit acid secretion. In the 1970s, this led to the development of specific inhibitors of the proton pump in the acid-secreting parietal cells of the stomach, activation of which is now known to be the final step in acid secretion. These compounds were shown to be very potent inhibitors of gastric acid secretion, and demonstrated a surprisingly long-lasting duration of action. Omeprazole — the first proton-pump inhibitor used in clinical practice — was launched in 1988 as Losec in Europe, and in 1990 as Prilosec in the United States. Omeprazole introduced a new approach for the effective inhibition of acid secretion and the treatment of acid-related diseases, and was quite quickly shown to be clinically superior to the H_2-receptor antagonists. None of the subsequently developed proton-pump inhibitors based on the omeprazole structure (but outside the original chemical patents) introduced by other companies have been shown to be significantly superior to omeprazole in clinical practice.

During the 1990s, Astra tested several hundreds of compounds chemically based on the parent compound of omeprazole in order to find a proton-pump inhibitor with properties superior to omeprazole. Finally, esomeprazole emerged. Omeprazole is a racemate consisting of two optical isomers (enantiomers), one being the mirror image of the other. The *S* isomer — *es*omeprazole — subsequently proved to be the first drug that is signficantly superior to omeprazole both as a gastric-acid inhibitor and for the clinical management of GERD. As predicted, the cause of the superiority of esomeprazole was higher bioavailability, which resulted in higher plasma concentrations than achievable with the *R* isomer. At the parietal-cell level, both isomers are equally effective, as both are transformed to the same active inhibitor within the parietal cell. Esomeprazole was launched as Nexium in 2000 by AstraZeneca. In this article, we summarize the development of omeprazole, focusing on the key discoveries and challenges, and then describe the subsequent development of esomeprazole (a more detailed history of the development of omeprazole can be found in the book *Proton Pump Inhibitors*[1]; see also REF. 2).

Background

In the late 1960s, the pharmaceutical company Hässle (a research company within Astra) decided to start a gastrointestinal research division with the aim of finding a potent drug for the inhibition of gastric acid secretion to be used in patients with peptic ulcers. To this end, a gastrointestinal laboratory was created, and the first project in this laboratory resulted in an antisecretory compound that was very effective in the rat, which was used as a screening model. However, the compound was completely ineffective in man, indicating that new screening models were needed.

The omeprazole project

In 1972, the gastric acid inhibitory project was restarted with a new approach. Anesthetized dogs were used as an initial screening model, followed by tests on conscious GASTRIC FISTULA DOGS. A literature search found a paper describing an antisecretory compound (CMN 131) developed by the pharmaceutical company Servier[3]; this compound, however, showed severe acute toxicity, and further research into this compound was consequently cancelled. As it seemed a reasonable assumption that the thioamide group in the chemical structure of CMN 131 (FIG. 1) was responsible for the toxicity, the new approach aimed to eliminate this group by incorporating it into, or in between, heterocyclic ring systems. By 1973, the first hit was discovered — the benzimidazole H 124/26 (FIG. 1), which was a powerful antisecretory compound without acute toxicity, and which therefore became the lead compound.

GASTRIC FISTULA DOGS
Dogs provided with a cannula into the stomach or into separated pouches of the stomach.

NECROTIZING VASCULITIS
An immunologically induced process causing an inflammatory reaction and necrosis in blood vessels.

Patent problem. After H 124/26 had been identified, it was discovered that it was already covered by a patent owned by an Hungarian company, which described the compound as a drug for the treatment of tuberculosis. However, a metabolite of H 124/26, which was not included in the Hungarian patent, was found to be an even more potent antisecretory compound[4]. The metabolite H 83/69 was the sulphoxide of H 124/26 — named timoprazole (FIG. 1) — and it became the new lead compound. At this stage, the site of inhibitory action in the pathway leading to acid secretion was not known.

Toxicological challenges. Long-term toxicological studies of timoprazole revealed that it caused enlargement of the thyroid gland — later shown to be due to inhibition of iodine uptake — as well as atrophy of the thymus gland. Thiourea compounds are well-known inhibitors of iodine uptake in the thyroid. A literature search of the chemistry of thiourea compounds showed a few substituted mercapto-benzimidazoles having no effect on iodine uptake, and the introduction of these substituents into timoprazole resulted in elimination of the effects on the thyroid and thymus, without reducing the antisecretory effect. Tests on several substituted benzimidazoles showed that separation of the inhibition of acid secretion from the inhibition of iodine uptake was obtained in a specific range of lipophilicity of these compounds[5]. The most potent antisecretory compound without thyroid/thymus effects was H 149/94, which was named picoprazole (FIG. 1).

However, in extended toxicological studies of picoprazole, as well as one previous compound, a few treated dogs developed NECROTIZING VASCULITIS. Fortunately from the perspective of the project, one of the control dogs also developed necrotizing vasculitis. It was shown that all the dogs with vasculitis emanated from one male dog, and all had antibodies against intestinal worms, which were probably obtained after deworming. New toxicological studies in another beagle strain, and in non-parasitized dogs in another laboratory, were completely clean. Picoprazole was used in a concept study in human volunteers, and showed a potent antisecretory action of very long duration[6].

Compound optimization. Simpler *in vitro* techniques were essential in order to test a large number of different substituted benzimidazoles for the optimal inhibition of gastric acid secretion. The isolated gastric-acid-secreting mucosa of the guinea pig was introduced as an appropriate *in vitro* model[7]. Later on, isolated rabbit acid-secreting glands were used[8], and a micromethod for isolating acid-secreting glands from human gastric biopsies was developed[9]. These techniques allowed the testing of a large number of compounds, including tests on the human target tissue.

At about this time, evidence was emerging that the activation of a newly discovered proton pump (an H^+K^+-ATPase) in the secretory membranes of the parietal cell was the final step in acid secretion[10,11]. Immuno-histological data obtained using antibodies against a crude preparation from the secretory membranes of

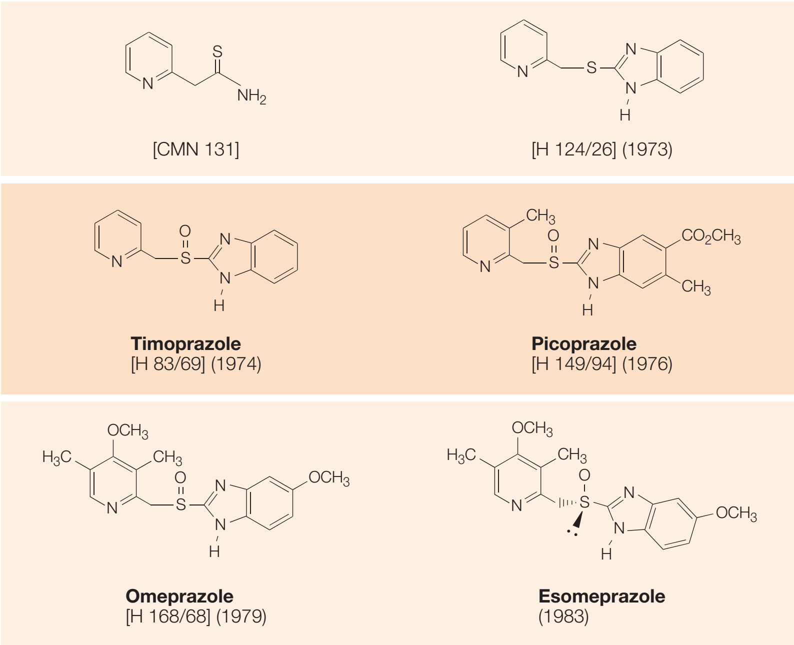

Figure 1 | **Chemical milestones in the development of proton-pump inhibitors and the year of synthesis.**

parietal cells revealed strong immunoreactivity in the parietal cell region of the stomach, but also some activity in the thyroid gland[12]. Coupled with knowledge of the side effects of timoprazole on the thyroid discussed earlier, these findings raised the intriguing possibility that benzimidazoles such as timoprazole could be inhibitors of the H^+K^+-ATPase. Research was initiated in this area in parallel with the further development of benzimidazoles, and it was indeed subsequently shown that substituted benzimidazoles inhibit gastric acid secretion by blocking the H^+K^+-ATPase[13,14]. The mode of action of substituted benzimidazoles, and the implications of this for their clinical benefits, are discussed further in a following section.

How could the antisecretory effect of substituted benzimidazoles be optimized? As weak bases accumulate in the acidic compartment of the parietal cell close to the proton pump, substituents were added to the pyridine ring of timoprazole to obtain a higher pKa value, thereby maximizing the accumulation within the parietal cell. The result was compound H 168/68, which was named omeprazole (FIG. 1). It was later shown in a thorough mechanistic investigation that the higher pKa value of the omeprazole pyridine ring (~1 pKa unit higher than that in timoprazole) also increased the rate of acid-mediated conversion to the active species (the sulphenamide; see the section below on mechanism of action), which is the major factor determining acid inhibitory activity[5]. Also, the 5-methoxy substitution pattern in the benzimidazole moiety of omeprazole made the compound much more stable to conversion at neutral pH compared with, for example, the ester substitution in the benzimidazole moiety of picoprazole (FIG. 1).

Omeprazole was found to be the most potent inhibitor of stimulated gastric acid secretion in rats and dogs *in vivo*[15], and no effects on iodine uptake, no induction of thymus atrophy, no necrotizing vasculitis and no other signs of toxicity were found in initial safety studies. An Investigational New Drug (IND) application was filed in 1980, and omeprazole was taken into human trials in 1982, which had highly encouraging results[16–18]. However, there were still further challenges to address.

Further toxicological problems. Lifelong toxicological studies of very high doses of omeprazole in rats revealed the development of endocrine tumours (carcinoids) in the stomach, which led to the halting of all clinical studies in 1984. The carcinoids originated from enterochromaffine-like (ECL) cells, a type of endocrine cell in the gastric mucosa that synthesize and secrete histamine in response to stimulation by the gastric hormone gastrin. However, longer-term stimulation by gastrin has a potent trophic action on ECL cells. Combining this with the fact that gastrin was known to be released in increasing amounts from the antrum of the stomach as the amount of acid secretion decreases suggested a possible explanation for the observed effects of lifelong very high doses of omeprazole in rats: the elimination of gastric acid secretion, resulting in massive hypergastrinemia. This was shown to be the cause of the ECL cell hyperplasia in omeprazole-treated rats, as the hyperplasia did not occur in rats subjected to resection of the gastric antrum[19]. Furthermore, the ECL cell carcinoids were also produced in lifelong studies of rats administered a H_2-receptor antagonist (ranitidine) in high doses[20], as well as by a surgical procedure that created massive hypergastrinemia[21]. These data allowed clinical studies with omeprazole to be restarted.

Resumption of clinical studies. Omeprazole was found to be significantly superior to previous treatment regimens of H_2-receptor antagonists in patients with duodenal[17,18,22] and gastric ulcers[23]. A particularly notable superiority of omeprazole compared with the H_2-receptor antagonist ranitidine was found in GERD patients[24–26], in which the healing rates were about twice as high with omeprazole. On the basis of these studies, omeprazole was launched in Europe as Losec in 1988.

Clinical doses of omeprazole produce a modest hypergastrinemia in the same range as the surgical procedure vagotomy[27], and neither treatment has produced ECL cell carcinoids over long-term (that is, greater than 10 years) follow-up. Massive hypergastrinemia in man is seen in patients with gastrin-producing tumours, and these patients develop hyperplasia of the ECL cells, but not ECL cell carcinoids. Obviously, the response of the ECL cells to hypergastrinemia is different in man and rat.

Mechanism of action of omeprazole. The success of omeprazole in the clinic can be ascribed to the very effective inhibition of gastric acid secretion achieved through specific inhibition of the gastric H^+K^+-ATPase. This proton pump is located in the secretory membranes of the parietal cell of the gastric mucosa and constitutes the final step of acid secretion[28] (FIG. 2a). Therefore, blockade of this pump results in a more specific inhibition of acid secretion compared with blockade of the more widely distributed H_2 and cholinergic receptors. Furthermore, as omeprazole interacts with the final step of acid production, the inhibition of gastric acid secretion is independent of how acid secretion is stimulated[29,30] — an important advantage over other pharmacological approaches to inhibiting acid secretion. For example, the inhibition of acid secretion by H_2-receptor antagonists can be overcome by food-induced stimulation of acid secretion via gastrin or cholinergic receptors.

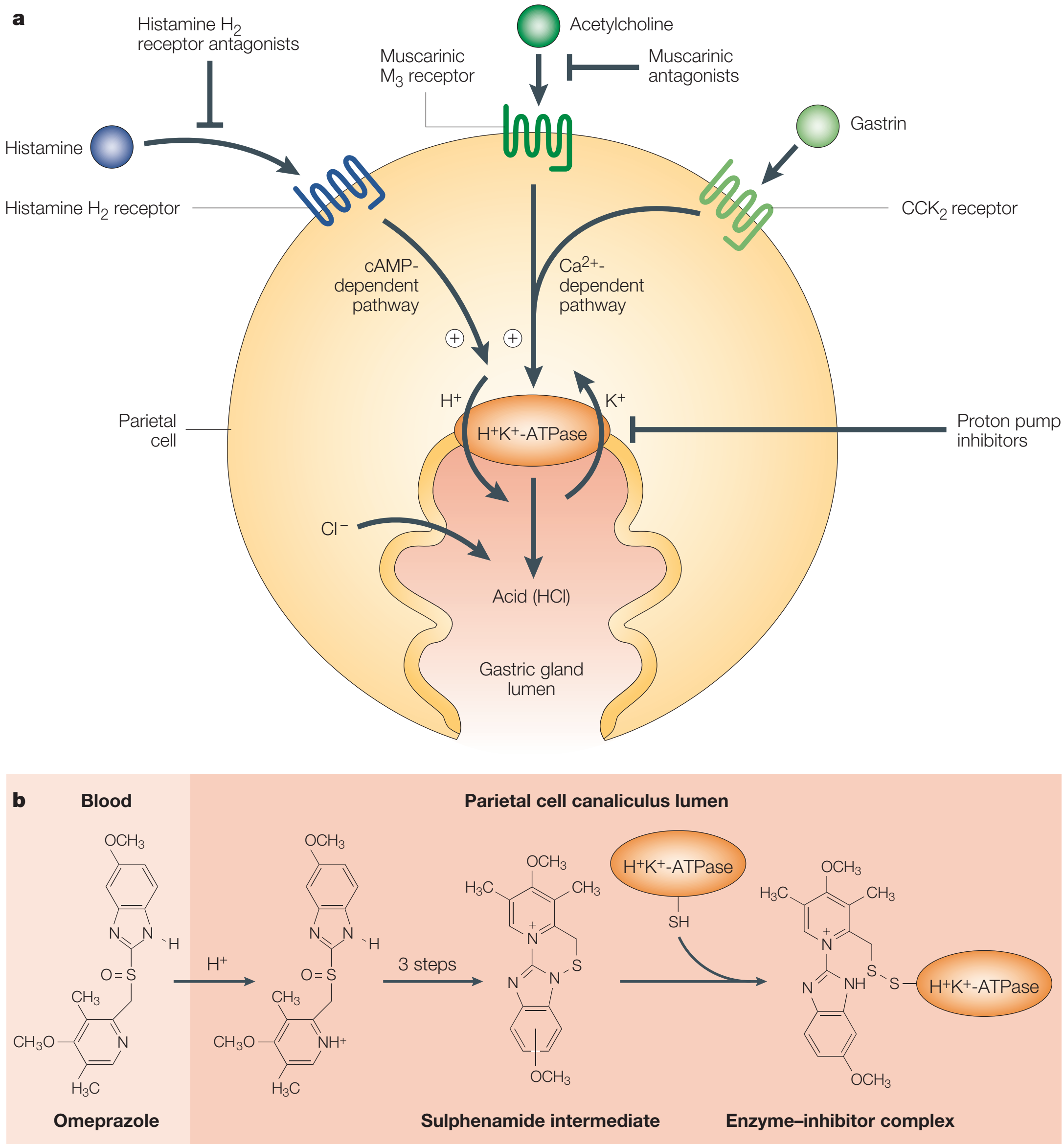

Figure 2 | **Proton-pump inhibition. a** | Gastric acid is secreted by parietal cells of the stomach in response to stimuli such as the presence of food in the stomach or intestine and the taste, smell, sight or thought of food. Such stimuli result in the activation of histamine, acetylcholine or gastrin receptors (the H_2, M_3 and CCK2 receptors, respectively) located in the basolateral membrane of the parietal cell, which initiates signal transduction pathways that converge on the activation of the H^+K^+-ATPase — the final step of acid secretion. Inhibition of this proton pump has the advantage that it will reduce acid secretion independently of how secretion is stimulated, in contrast to other pharmacological approaches to the regulation of acid secretion; for example, the inhibition of acid secretion by H_2 receptor antagonists can be overcome by food-induced stimulation of acid secretion via gastrin or acetylcholine receptors. **b** | Proton-pump inhibitors such as omeprazole are prodrugs that are converted to their active form in acidic environments. Omeprazole is a weak base, and so specifically concentrates in the acidic secretory canaliculi of the parietal cell, where it is activated by a proton-catalysed process to generate a sulphenamide[29]. The sulphenamide interacts covalently with the sulphydryl groups of cysteine residues in the extracellular domain of the H^+K^+-ATPase — in particular Cys 813 — thereby inhibiting its activity[30]. The specific concentration of proton-pump inhibitors such as omeprazole in the secretory canaliculi of the parietal cell is reflected in their favourable side-effect profile.

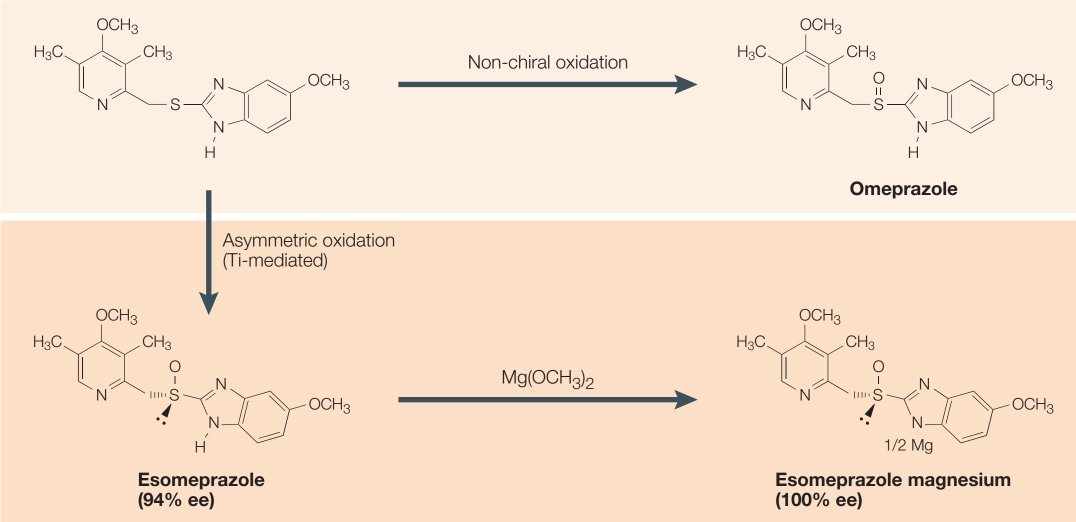

Figure 3 | **Synthesis of omeprazole and esomeprazole.** The large-scale production of esomeprazole is achieved by asymmetric oxidation of the same sulphide intermediate as is used in the production of omeprazole, which gives a 94% enantiomeric excess (ee). This is increased to 100% by preparing a magnesium salt of of esomeprazole and then performing a crystallization.

So, how does omeprazole inhibit the H^+K^+-ATPase? In whole-body autoradiographic studies in mice, omeprazole was found to label only the tubulovesicles and secretory membranes of the parietal cell, which contain the H^+K^+-ATPase[5]. Electrophoretic analyses of such membranes, purified after administration of radio-labelled omeprazole, demonstrated that the radiolabel specifically associated with the 92-kDa proteins known to hold the catalytic subunit of H^+K^+-ATPase[5]. From this, it could be concluded that omeprazole binds only to the H^+K^+-ATPase in the gastric mucosa and nowhere else in the body.

However, omeprazole itself is not the active inhibitor of the H^+K^+-ATPase. The transformation of omeprazole in acid is required to inhibit the H^+K^+-ATPase (FIG. 2b) *in vitro* and *in vivo*, whereas intact omeprazole is devoid of inhibitory action. Isolated H^+K^+-ATPase is blocked by omeprazole only after pretreatment of omeprazole with acid, and neutralization of the acidic secretory canaliculi of isolated gastric gland and parietal cell preparations by permeable buffers, which blocks the acid-catalysed transformation of omeprazole, prevents the inhibition of acid secretion. Furthermore, *in vivo* blockade of acid secretion using an H_2-receptor antagonist prior to omeprazole administration decreases the inhibitory action of omeprazole. Investigations of the acid decomposition of omeprazole have revealed an intermediate compound — a sulphenamide — that effectively inhibits the H^+K^+-ATPase preparation *in vitro*[31] and which reacts rapidly with mercaptans (for example, β-mercaptoethanol) to form a disulphide adduct. As the H^+K^+-ATPase inhibition is associated with the modification of mercapto groups in the enzyme, such disulphide adducts can be considered as models of the enzyme–inhibitor complex, and the sulphenamide formed from omeprazole can be considered to be the active inhibitor, which binds covalently to the cysteine residues (in particular, Cys 813) of the H^+K^+-ATPase (FIG. 2b).

Omeprazole has several characteristics that are important for its unique mechanism of action. First, omeprazole is lipophilic, which means that it easily penetrates cell membranes. Second, it is a weak base, which means that it concentrates in acid compartments. Third, it is very unstable in an acidic solution. The half-life of omeprazole at pH 1 is ~2 minutes, whereas at pH 7.4 it is ~20 hours. So, omeprazole is a prodrug that accumulates within the acid space of the target cell, where it is transformed to the active inhibitor.

Whereas the half-life of omeprazole in blood plasma is rather short — 1–2 hours in man — the half-life of the inhibitory complex is much longer. On the basis of the duration of action in humans, the half-life at the site of action is estimated to be ~24 hours. Dissociation of the enzyme–inhibitor complex is probably a result of the effect of endogenous glutathione[32,33], which leads to reactivation of the enzyme and the release of the omeprazole sulphide. The fact that the sulphide is found in the gastric juice is consistent with this idea. Reactivation of the acid-producing capacity may also in part be due to *de novo* synthesis of enzyme molecules[34].

Esomeprazole (Nexium)

Omeprazole — need for improvement? Omeprazole showed a significant inter-individual variability, both regarding its pharmacokinetics and effect on acid secretion, and a significant number of patients with acid-related disorders needed higher or multiple doses to achieve symptom relief and healing. This difference in response was especially pronounced between slow and rapid metabolizers.

In western countries, ~2–4% of individuals lack one of the isoenzymes — 2C19 — of the P450 enzyme family in the liver[35]. This isoenzyme is important for the metabolism of a number of drugs, including omeprazole[35]. Individuals lacking this isoenzyme metabolize these drugs at a slower rate and are therefore called slow metabolizers. Among people from South East Asia and Japan, up to 20% are slow metabolizers[35].

On the basis of this knowledge, Astra started a new acid inhibitor research program in 1987 with the aim of finding a compound with reduced clearance by the liver — that is, increased bioavailability. Chemical approaches were used to change the substitution pattern on the pyridine and benzimidazole rings. More than 30 scientists synthesized and screened several hundred compounds in the search for one that could possibly surpass omeprazole. During 1989–1994, four compounds passed the hard preclinical tests and demonstrated superior bioavailability compared with omeprazole in rats, and were then tested in humans. When all the key parameters — pharmacokinetic properties, acid inhibitory effect and safety issues — were assessed, only one compound exceeded omeprazole: it was one of its optical isomers, the *S* isomer or esomeprazole.

Optical isomers and consequences in biology. Around 150 years ago, Louis Pasteur found that a solution of deposits from old wine casks could either rotate a beam of plane-polarized light to the right, to the left or not at all. He also found that an organic acid isolated from this tartar crystallized in two forms, and that a solution of one crystal form rotated the light to the left and the other form to the right, whereas a mixture of equal amounts of the two forms did not rotate the beam of light at all. Pasteur had detected isomerism and is, therefore, the pioneer of stereochemistry. Chemical compounds containing an atom (usually sulphur or carbon) bound to four different groups can occur in two forms, each of which is a non-superimposable mirror image of the other. Except for this ability to rotate plane-polarized light, their chemical structures and physicochemical properties are the same[36].

In biology, stereochemistry is very important. Drug targets, such as enzymes and ion channels, as well as their endogenous ligands, hormones and signal substances, are the results of stereoselective biosynthesis. This means that drug targets recognize drug isomers and that the two isomers of a racemate often differ in their potency owing to different affinities for the target receptor, have different pharmacokinetic properties owing to different affinity for metabolizing enzymes or have different toxicological properties. Against this background and progress in chemical technology[37,38], which has made it possible to synthetically produce pure isomers on a large scale, the regulatory authorities now require the development of a pure isomer whenever possible.

Omeprazole is a racemate. The chemical structure of omeprazole contains a sulphoxide group (FIG. 1) and is therefore a racemate composed of the two isomers *S* and *R* in the proportion 1:1. As the two isomers of omeprazole have the same physicochemical properties, they both undergo a non-enzymatic, proton-catalysed transformation to the active molecular species — the non-chiral sulphenamide (FIG. 2b). In accordance with this, we also found that the two isomers showed identical dose–response curves when tested *in vitro* for the inhibition of acid production in isolated gastric glands[39].

At this stage, however, we could not dismiss the idea of a possible difference in metabolism between the two isomers, but we needed larger amounts of the pure isomers. Isomer-selective production using microbial and enzymatic systems were only partly successful. We became more focused on the new idea of separating isomers via chromatography of diastereomers[40]. As a spin-off from our previous work, we identified a technique to use a temporary covalent diastereomeric complex with mandelic acid for chromatographic separation. Not only did we obtain hundreds of milligrams of the single isomers, but we also realized that alkaline salts, as opposed to the neutral forms, were crystalline and, moreover, that they were stable against racemisation. We now had the prerequisites for *in vivo* testing.

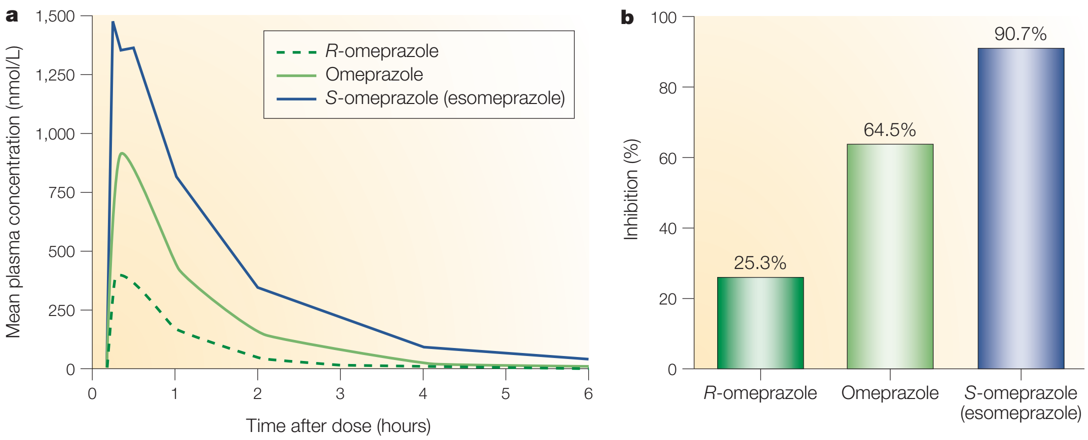

Figure 4 | **Effects of racemic omeprazole and its enantiomers. a** | Drug plasma concentrations and **b** | inhibition of pentagastrin-stimulated gastric acid secretion in healthy subjects ($n = 4$) after oral administration of 15 mg of *R*-omeprazole, omeprazole and esomeprazole at time 0 (REF. 42).

ENANTIOMERIC EXCESS
If one enantiomer is present to a greater extent, an enantiomeric excess exists where: enantiomeric excess = (measured specific rotation of mixture/specific rotation for the pure enantiomer) × 100.

The large-scale production of esomeprazole is now successfully achieved by asymmetric oxidation of the same sulphide intermediate as is used in the production of omeprazole (FIG. 3). Drawing inspiration from the work on titanium-mediated asymmetric oxidation reported by K. Barry Sharpless, who won the Nobel Prize for Chemistry in 2001, and H.B. Kagan, and on the basis of some key changes in the process parameters, the ENANTIOMERIC EXCESS could be increased from 4% to 94%. In the production method, the optical purity is further enhanced by the preparation of esomeprazole magnesium salt with subsequent crystallization[41].

Isomer pharmacokinetics and pharmacodynamics. Initial *in vivo* experiments were carried out with the pure isomers and the racemates in rats and dogs to assess the the plasma concentration following oral doses and the effects on stimulated acid secretion. In the rat, the *R* isomer showed significantly higher bioavailability and more potent inhibition of acid secretion than the *S* isomer and the racemate. In the dog, however, no differences could be detected between the two isomers. If the initial *in vivo* experiments had been performed solely in dogs, we would have probably stopped further work with the isomers. On the basis of the initial findings in rats, however, we took the decision to continue the project and compare the isomers in man. We found about the same magnitude of difference between the isomers as in the rat, but, to our surprise, the *S* isomer had the highest bioavailability and oral potency in inhibiting gastric acid secretion in man[42] (FIG. 4), owing to stereoselective metabolism of omeprazole[43].

In man, 40 mg of esomeprazole taken orally showed much higher and more prolonged plasma concentration curves than 20 mg esomeprazole (FIG. 5). The 40-mg esomeprazole dose also showed significantly more potent inhibition of gastric acid secretion than the 20 mg esomeprazole, 20 and 40 mg omeprazole as well as the standard doses of the other commercially available proton-pump inhibitors[44]. Consequently, 40 mg of esomeprazole was chosen as the standard dose when esomeprazole was launched as Nexium in 2000. Reassurance on the safety of a high standard dose of esomeprazole was provided by the extensive experience of continuous treatment with both 20 mg and 40 mg of omeprazole[45], in contrast to the situation in which the choice of standard 20 mg dose of omeprazole was made. At that time, the safety of the drug was more uncertain, as it was a completely new type of drug, and the choice of dose had to be the lowest possible that still retained sufficient activity.

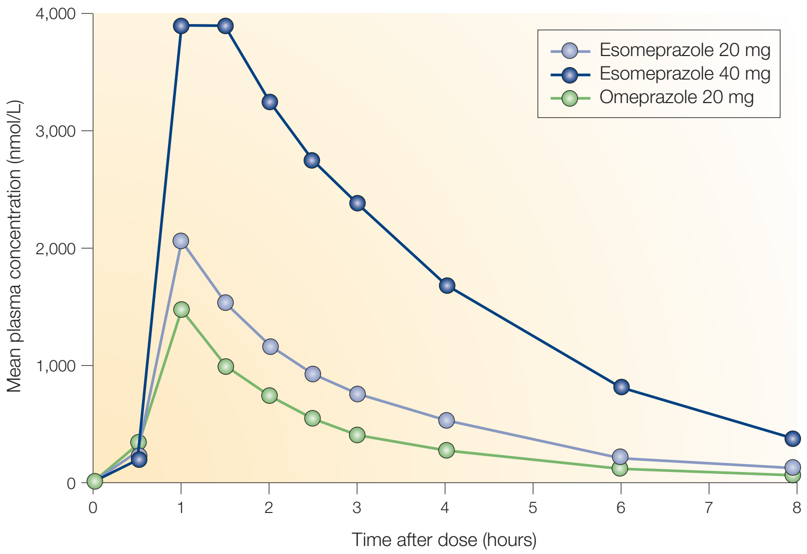

Figure 5 | **Optimal dosing of esomeprazole.** Mean plasma concentration-time profiles on day 5 after daily doses of esomeprazole (40 and 20 mg) and omeprazole (20 mg) in 36 patients with gastroesophageal reflux disease[47]. 40 mg of esomeprazole taken orally showed much higher and more prolonged plasma concentration curves than 20 mg esomeprazole.

Clinical results. In GERD, the most common acid-related disease, esomeprazole has been shown to be clinically superior to other proton-pump inhibitors, such as omeprazole and lansoprazole. There is significantly higher symptom relief during treatment with esomeprazole[46,47], and significantly higher healing rates, which are well above 90% in patients with esophagitis[46,48,49]. The remission rate during maintenance treatment is also significantly higher with esomeprazole in comparison with placebo and lansoprazole[50,51].

It is now known that most peptic ulcers are caused by infection with *Helicobacter pylori*, with gastric acid still being a key promoter. Elimination of *H. pylori* is now the clinical approach of choice[52]. At present, antibiotics alone are not sufficient to achieve high enough cure rates, and so two antibiotics are combined with an antisecretory agent, such as a proton-pump inhibitor, in 'triple therapies'. For esomeprazole, one-week triple therapy results in healing rates of duodenal ulcers above 90%. Esomeprazole-based *H. pylori* eradication therapy is very effective and yields eradication rates around 90% (REF. 53), which is in the range of the best results so far obtained.

Conceivable future drugs

In the future, shorter-acting acid pump antagonists with a rapid onset of action will probably be developed to treat milder or intermittent forms of GERD. Eventually, the antisecretory drugs may be replaced by drugs that act more specifically in the treatment of some acid-related diseases. As GERD is caused by motor abnormalities of the lower esophageal sphincter and the stomach, it is conceivable that new drugs might be developed to block the reflux pattern instead of reducing acid reflux with antisecretory drugs. One possible example is agonists of the GABA (γ-amino-butyric acid) receptor $GABA_B$[54].

Patients with a gastrin-producing tumour — Zollinger-Ellison syndrome — are often treated with rather high doses of a proton-pump inhibitor. A specific antigastrin drug would change the situation, but so far, all efforts to develop such a compound have failed.

Peptic ulcers induced by the use of non-steroidal anti-inflammatory drugs (NSAIDs) are increasing in the elderly population, which has prompted an increase in the use of NSAIDs in combination with a proton-pump inhibitor. This type of ulcer might be reduced by the use of newer NSAIDs, such as the cyclooxygenase 2 (COX2) inhibitors and the nitric-oxide-donating NSAIDs[55]. So far, the results are promising.

Finally, as mentioned above, peptic ulcers induced by *H. pylori* are now treated by a combination of two antibiotics and a proton-pump inhibitor. The eradication rate of the *H. pylori* infection with optimal therapy is 90–95%, and there are few ulcer recurrences after eradication. A vaccine or a specific monotherapy against *H. pylori* might represent a future therapeutic strategy for peptic ulcer treatment, and a possible preventative measure against the development of gastric malignancy.

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