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# *Review article: esomeprazole – the first proton pump inhibitor to be developed as an isomer*

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## SUMMARY

Omeprazole is a racemate, from which the R- and S-isomers can be isolated. At the cellular level, both of these isomers convert to the same inhibitor of the $H^+$,$K^+$-ATPase and produce the same reduction in gastric acid secretion. However, the S-isomer, esomeprazole, is metabolized more slowly and reproducibly than the R-isomer and omeprazole, and therefore produces higher plasma concentrations for longer and, as a result, inhibits gastric acid production more effectively and for longer. Thus, esomeprazole has the pharmacological properties of a more effective form of treatment for disorders related to gastric acid secretion. Clinical studies have confirmed the anticipated increased efficacy, but have shown no evidence of impaired tolerability or increased toxicity when compared with omeprazole.

## INTRODUCTION

Omeprazole was the first drug to be successfully developed and marketed that reduced gastric acid production by inhibiting the $H^+$,$K^+$-ATPase in the mucosal cells of the stomach. Its impact on gastric pH was greater than, and lasted for longer than, the drugs previously used most extensively, namely the $H_2$-receptor antagonists. As a result of its efficacy and tolerability, omeprazole is extremely widely used and became the best-selling drug in the world. Subsequently, other drugs, also substituted benzimidazoles – namely lansoprazole, pantoprazole and rabeprazole – with similar modes of action, were developed. These drugs are referred to as proton pump inhibitors.

Like many other drugs, all these proton pump inhibitors are racemates, which means that they are a mixture of two compounds containing exactly the same chemical components, but their spatial disposition is such that they are pharmacologically different. The two entities are called isomers. The clinical and therapeutic relevance of drugs being racemates and containing isomers is that it raises the possibility of selecting and developing a new drug consisting solely of the better isomer. The search to find a drug better than omeprazole began in the 1980s, but it was only when the technology to develop isomers became available that it became evident that one isomer was therapeutically preferable. In theory, therefore, all racemate proton pump inhibitors could be replaced, in time, by drugs made from the better isomers of the current proton pump inhibitors. To date, only one such isomer has been developed and marketed; this is esomeprazole.

In this paper, the pharmacological basis of optical isomers will be described, some of the terms used will be defined, and the reason why esomeprazole is more effective than omeprazole will be explained.

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## ISOMERS AND RACEMATES

Jean Baptiste Biot first noted that when light was shone through a solution of some chemical substances the beam was bent or deflected. Subsequently, Louis Pasteur (1822–1895), some 150 years ago, made interesting observations on tartaric and racemic acid.[1] Tartaric

acid rotated light, but racemic acid did not. However, crystallized racemic acid was found to contain two different crystal forms, which were mirror images of each other. When these were separated, one form rotated light to the right and the other rotated light to the left. Since then, the nonrotating mixtures have been called racemates and the light-rotating components have been called stereoisomers or enantiomers.

The molecular basis for the above observations is that many compounds have a centrally placed atom, usually carbon but sometimes other atoms such as sulphur or phosphorus. The carbon atom links to four chemical groupings, which when represented in three dimensions can be arranged to form two structures containing exactly the same chemical components, but which are mirror images of each other (Figure 1). The central atoms are referred to as asymmetric or chiral centres (which is derived from the Greek word 'cheir' for hand), and chirality is used as a descriptive term for this concept. The visual representation of the two enantiomers as two hands or two gloves is helpful, as it is readily apparent that, whereas two gloves have the same component parts, only the left-hand glove will fit on the left hand. It is therefore not surprising that two isomers with the same chemical components but different spatial patterns can bind differently to different receptors or other chemical compounds.

Pharmacologically, it is reasonable to anticipate that when a racemate contains two isomers, one (or other) of them may be more potent, be less or more likely to interact with other drugs, be metabolized more slowly and therefore be longer acting, or be more or less likely to cause particular adverse effects. By developing a drug that contains the more effective or the less toxic isomer, it may be possible in some instances to improve markedly the therapeutic value of a particular drug.

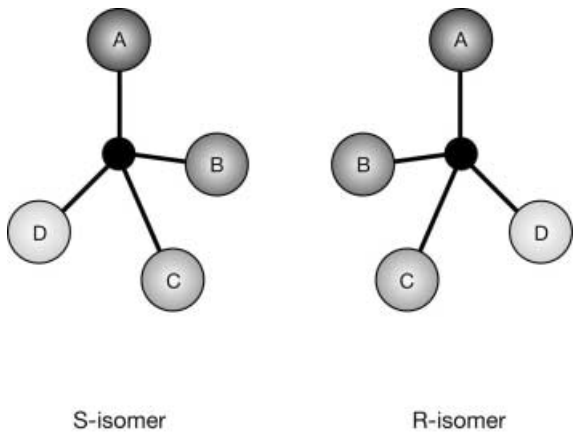


Figure 1. Four chemical groupings (A, B, C and D) attached to a chiral centre (O) arranged to produce two compounds that are mirror images of each other.

The nomenclature used to describe different isomers can be confusing. However, for the clinician, it is probably sufficient to know that D or (+) for dextrorotatory and L or (–) for laevorotatory are used to describe the direction in which a light beam is rotated. By comparison, R (rectus – to the right or clockwise) and S (sinister – to the left or anticlockwise) are used to describe the spatial arrangement of the substituent atoms around the chiral centre.[1]

Chirality, racemates and isomers should not be regarded as a rather exotic aspect of drug chemistry. At least 25% of all drugs are marketed as racemates and, although relatively few compounds have been developed as the better isomer, this approach to drug development is becoming increasingly important. The isolation of esomeprazole was technically extremely difficult and very time-consuming, but was eventually achieved by AstraZeneca. Because of anticipated problems, some companies now specialize in this potentially technically demanding form of pharmaceutical chemistry. In many instances, the isomers may not be significant improvements over the racemates, but there are some good examples of only one isomer being effective or the only safe form of the compound. Carbohydrates and nucleic acids contain only D-glucose and proteins are derived from L-amino acids. L forms of thyroxine and adrenaline (epinephrine) are the more effective hormones, and D-penicillamine is the only safe form of the drug.

## ESOMEPRAZOLE

Omeprazole is a racemate with a central sulphur atom, which acts as a chiral centre; it contains two isomers, S and R, as shown in Figure 2. The pharmacokinetics and pharmacodynamics of the two isomers have been carefully studied.[1–4] At the cellular level, both isomers are protonated and converted in the acidic compartment of the parietal cell in exactly the same way to form the active inhibitor of $H^+$,$K^+$-ATPase, the achiral sulphenamide. The two isomers are therefore equally effective as acid suppressors at the cellular level, but their impact is determined by the concentration attained in the acid-producing parietal cell in the mucosa.

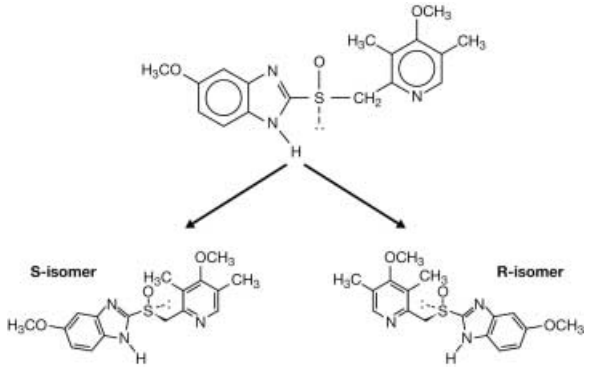


Figure 2. Omeprazole and its two isomers.

The major differences between the R and S forms of omeprazole relate to their metabolism.[1, 2] Omeprazole, its isomers and other proton pump inhibitors are metabolized by the cytochrome P450 enzymes CYP2C19 and CYP3A4. These convert the isomers to the 5-hydroxy and 5-O-desmethyl metabolites (2C19) and sulphone (3A4). The sum of the intrinsic clearances of all three metabolites for S-omeprazole (esomeprazole) is one-third of the rate for R-omeprazole. The metabolism of esomeprazole is not only slower but more reproducible. Furthermore, as the metabolites are inactive, the end result in humans, given comparable doses, is for esomeprazole to produce an area under the plasma concentration curve (AUC) for the active substance that is three–four times greater than for R-omeprazole. Andersson *et al.* have demonstrated this in healthy subjects,[3] as shown in Figure 3. The impact on stimulated gastric acid secretion is closely related to the AUC, as can be seen from the results in Figure 4.

About 3% of Caucasians and 15% of Asians are poor metabolizers by the cytochrome P450 system. However, esomeprazole metabolism is affected to a much lesser

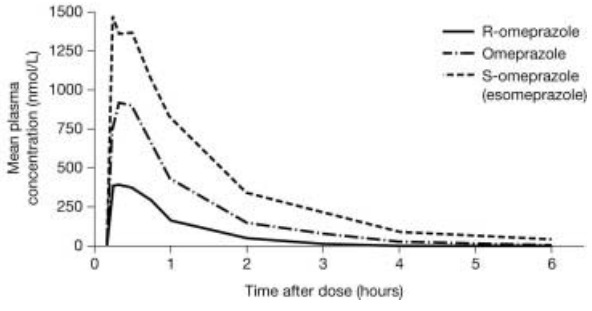


Figure 3. Plasma concentration vs. time after giving esomeprazole, 15 mg orally, to healthy subjects ($n = 4$; Day 7).[3]

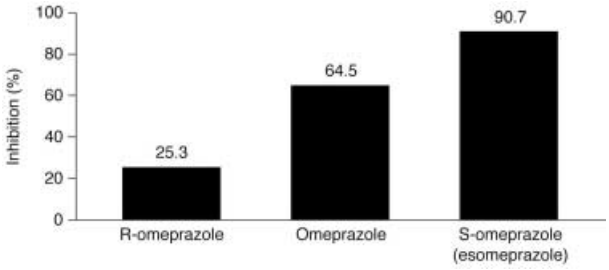


Figure 4. Effect on stimulated gastric acid secretion after giving esomeprazole, 15 mg orally, to healthy subjects ($n = 4$; Day 7).[3]

extent and, as a consequence, there is less difference between normal and poor metabolizers, and less variability in the plasma concentrations attained by different subjects.[2] Studies in patients with mild-to-moderately severe liver disease have shown that they are capable of metabolizing esomeprazole satisfactorily, making dose adjustments unnecessary. Patients with severe liver disease should begin therapy at a lower dose. As elimination is almost totally by hepatic metabolism, dose adjustments for patients with renal disease are not required.

The increased plasma concentrations and greater efficacy of esomeprazole have not been associated with any increase in unwanted effects. In studies involving large numbers of patients, the adverse event rates have been similar to those recorded for omeprazole and placebo.[5, 6] Gastrin levels are increased, but no serious abnormalities have been found in the gastric mucosa.[6, 7]

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