

Single-Isomer Drugs

True Therapeutic Advances

Tommy Andersson

Experimental Medicine, AstraZeneca LP, Wilmington, Delaware, USA

Abstract

Chirality is one of the main features of biology, and many of the processes essential for life are stereospecific, meaning that one out of two or more isomers may work best in a particular physiological situation. Could this be used in drug development and result in any clinical relevance and true therapeutic advance? There are occasions when the development of one of the isomers might be expected to be advantageous: for example, only one of the isomers may be active, only one of the isomers may cause adverse effects, or one of the isomers may have more advantageous pharmacological properties. As an example of the last, the successful development of esomeprazole will be described.

Before the introduction of esomeprazole, the proton pump inhibitor omeprazole was the standard treatment for gastric acid-related diseases, such as gastro-oesophageal reflux disease. A serious type of gastro-oesophageal reflux disease is erosive oesophagitis, an increasingly common condition that may lead to life-threatening complications. Doubling the standard dose of omeprazole from 20 to 40mg did not improve healing rates (74% versus 75%), and thus a substantial proportion of patients remained unhealed with standard treatment.

The (*S*)-isomer of omeprazole, esomeprazole, was shown to heal more patients than omeprazole as a result of unique metabolic properties that clearly differentiates esomeprazole from omeprazole, the racemate. At comparable doses, these properties lead to several clinical advantages: higher bioavailability in extensive metabolisers (the majority of patients), lower exposure in poor metabolisers, less interindividual variation and a steeper dose-response curve at steady state resulting in a more pronounced inhibition of gastric acid secretion. Esomeprazole has been studied clinically for a variety of acid-related conditions, showing that the compound is as well tolerated and more effective with regard to healing and symptom relief than the recommended treatment with omeprazole.

Thus, from this example it is clear that the exploration and development of single-isomer drugs may bring significant advances in treatment options.

The history of stereochemistry goes back more than 150 years to when Louis Pasteur demonstrated that a polarised beam of light passed through solutions of the tartar deposits found on old wine casks would be rotated to the right, to the left, or not at all. He found that natural tartaric acid but not racemic

tartaric acid, despite identical chemical and physical properties, rotated the light beam. Pasteur also observed that the racemic acid crystallised into two different shapes that were mirror images of each other. Solutions of the two separated crystal forms rotated polarised light to the left or to the right,

whereas a solution of the mixture of the two crystal forms was optically inactive. Therefore, mixtures of equal parts of left- and right-rotating compounds are called 'racemates'. Compounds containing an atom (e.g. sulfur or carbon) binding four different groups (for sulfoxides one of the groups is a free electron pair) are chiral molecules and can occur in two forms that are mirror images of each other. These are referred to as stereoisomers or simply isomers, and except for the ability to rotate plane polarised light their chemical structures and physicochemical properties are the same.

Chirality is one of the main features of biology, and many of the processes essential for life are stereospecific, meaning that only one of two or more isomers will work or will work the best in a physiological environment. The building blocks of nucleic acids, proteins and carbohydrates are single isomers, and pharmacological targets such as receptors, enzymes and ion channels are chirally distinctive (i.e. preferentially recognise one of the ligand isomers).

After decades of pharmaceutical research completely ignoring the stereospecific aspects of development, stereochemistry was rediscovered in the 1980s. This was a result of the emergence of chemical technologies allowing for production of pure isomers in quantity, research that actually resulted in the Nobel Prize in Chemistry in 2001, together with advances in stereoselective bioanalysis that shed light on the importance of stereospecificity in pharmacology. A prerequisite for the single isomer concept, though, is that the single isomer does not undergo racemisation, i.e. does not convert, spontaneously or via metabolism, to the other isomer. With the tools available and the knowledge of the relevance of stereochemistry for essential biological processes, national health authorities recommended in the early 1990s the development of single isomers rather than racemates. The importance and value of developing a single isomer instead of a racemate has previously been reviewed by several authors.^[1,2]

Independent of whether the development of a single-isomer drug instead of the racemate is done originally or after the racemate has been on the market for some time, there are at least four different

reasons why this should be done. All four emanate from a more or less clearly pronounced medical need to provide optimal treatment.

1. One of the isomers causes adverse effects, and in order to exclude the 'bad' component from the racemate the other ('good') enantiomer is developed as a drug.
2. One of the isomers has an antagonistic effect to the active isomer.
3. Only one of the isomers exhibits the desired effect, so by developing this single isomer only effective material will be administered to patients.
4. One of the isomers has more advantageous properties, pharmacokinetic or pharmacodynamic or both, than the other.

There may be other situations where the development of an isomer would be preferable, but the four mentioned above are the fundamental and most likely rationales, and there are examples of all four. The first situation is most easy to understand and most obvious. An example would be D-penicillamine, which is used as an antirheumatic drug; the other isomer, L-penicillamine, and the racemate are neurotoxic. The second situation can be exemplified by salbutamol (albuterol), a β_2 -adrenoceptor agonist used as a bronchodilator; (*S*)-salbutamol antagonises the effects of (*R*)-salbutamol, and therefore provided the basis to switch from the racemate to the (*R*)-isomer (levosalbutamol or levalbuterol). The third situation basically offers the patients only active drug and does not burden them with substance that will be ineffective for their disease. An example of this case would be the racemate α -methyldopa, in which only the L-isomer is active and accordingly was developed and used for treatment of hypertension. The fourth scenario will be exemplified below by the development of esomeprazole, the (*S*)-enantiomer of omeprazole.

1. Background/Medical Need

Examples of gastric acid-related diseases are peptic ulcer and gastro-oesophageal reflux disease (GORD). A complication of GORD is erosive oesophagitis, an increasingly common condition with a reported prevalence of about 2%.^[3,4] Erosive oeso-

phagitis is caused by reflux of acidic gastric contents into the distal part of the oesophagus. Acid and activated pepsin erode the oesophageal epithelium, which may lead to serious complications, such as stricture, deep ulcer and bleeding – a life-threatening condition. Effective treatment of erosive oesophagitis that leads to complete healing is generally considered the best way to avoid these serious complications. In addition, treatment that leads to healing of erosive oesophagitis also considerably improves the symptoms associated with acid gastro-oesophageal reflux.

Omeprazole is a gastric acid-reducing proton pump inhibitor (PPI) used for the treatment of gastric acid-related diseases, and indicated for healing of erosive oesophagitis at a dosage of 20mg once daily. Prior to making esomeprazole available on the market, no other PPI had shown higher healing rates at 8 weeks than omeprazole 20mg once daily.^[5-8] In addition, doubling the dosage of omeprazole to 40mg once daily did not demonstrate significantly better healing results (74% for 20mg versus 75% for 40mg).^[9] Thus, a substantial proportion of patients remained unhealed on a standard course of PPI treatment.

The rate of healing of erosive oesophagitis is closely related to the duration of gastric acid inhibition, usually described as time of intragastric pH above 4. Omeprazole 20mg once daily provides about 10 hours of pH >4 at steady state, but more prolonged acid inhibition would be needed to increase healing rates.^[10] In addition, omeprazole shows a significant interindividual variability in pharmacokinetics and pharmacodynamics. Thus, there was a need for a compound with a longer duration of gastric acid inhibition and less variability with the potential to provide significantly higher healing rates than omeprazole 20mg. A large number of substances were synthesised, screened and evaluated nonclinically by AstraZeneca and its predecessors. Of the compounds tested clinically, esomeprazole was determined to have the least variability, the most pronounced acid inhibition, and, thus, the highest potential to heal more patients than omeprazole, and still exhibit a similar safety profile.

2. Omeprazole Versus Esomeprazole

Omeprazole is a racemic mixture of two optical isomers, (*S*)-omeprazole (or esomeprazole) and (*R*)-omeprazole. Esomeprazole has been demonstrated *in vivo* in humans to be stable against racemisation and, thus, does not convert to the other isomer, which is crucial in this context.^[11] When (*R,S*)-omeprazole or esomeprazole reach the parietal cells in the gastric mucosa via the systemic circulation, they are protonated and converted in the acidic compartment of the parietal cell, forming the active inhibitor, the achiral sulfenamide. This compound is formed from both isomers and is identical for the two drugs, and consequently acts identically on the H⁺/K⁺-ATPase, the proton pump.^[12] This means that exposure to the active drug, expressed as area under the plasma concentration-time curve (AUC), irrespective of whether it originates from administered omeprazole or esomeprazole, is correlated with the acid inhibitory effects.^[13,14] However, several lines of evidence demonstrate that the metabolic profile of the two drugs is different, leading to different systemic exposure and thus different pharmacodynamic effects. This eventually results in different clinical effects.

2.1 Pharmacokinetic Differences

Omeprazole is mainly metabolised by cytochrome P450 (CYP) 2C19.^[15-17] This enzyme is polymorphically expressed, which means that some individuals do not express a functioning CYP2C19 enzyme. In these individuals, another CYP isoform (CYP3A4), which normally plays a less dominant role in the metabolism of omeprazole, takes over. The metabolism of omeprazole by CYP3A4 is slower than that by CYP2C19, and, therefore, these individuals may be considered poor metabolisers (3% of Caucasians and 15–20% of Asians) as opposed to the majority of the population, the so-called extensive metabolisers. Studies *in vitro* have shown that the drug-metabolising CYP enzymes in the liver exhibit a stereoselective metabolism of omeprazole.^[18] Although the same kind of metabolites are formed from the two isomers, there are quantitative differences, and the intrinsic clearance

of esomeprazole is three times lower than that of (*R*)-omeprazole in human liver microsomes (figure 1).

These *in vitro* findings have been confirmed *in vivo* in healthy volunteers.^[11] Thus, in extensive metabolisers receiving 15mg oral doses of esomeprazole, (*R*)-omeprazole and (*R,S*)-omeprazole, the average AUC of esomeprazole was higher, whereas that of (*R*)-omeprazole was lower, compared with (*R,S*)-omeprazole (figure 2). Since acid inhibitory effect is directly correlated to AUC,^[13,14] this pharmacokinetic parameter is most relevant. The difference in AUC was more pronounced with repeated administration than after a single dose, since the AUC of esomeprazole doubled with repeated once-daily administration and no change was seen for (*R*)-omeprazole. Consequently, for racemic omeprazole, the 1 : 1 mixture of the two isomers, the increase in AUC with repeated administration was less pronounced (increased by approximately 50%) than that for esomeprazole. The increase in AUC was seen over the first 4 days of treatment, with no subsequent changes.^[19] At steady state, the mean AUC of esomeprazole was twice as high as that of omeprazole and the mean AUC of (*R*)-omeprazole was less than half that of omeprazole.

Poor metabolisers, who normally exhibit a several-fold higher AUC of omeprazole compared with extensive metabolisers, received 60mg oral daily doses of omeprazole, esomeprazole and (*R*)-omeprazole. The average AUC of esomeprazole was 30% lower than that of omeprazole, whereas the plasma concentrations of (*R*)-omeprazole were more than 20% higher.^[11] The pattern in poor metabolisers was thus reversed compared with that seen in

extensive metabolisers; the exposure to drug in poor metabolisers, which already with omeprazole was higher than needed to obtain optimal inhibition of gastric acid secretion, was decreased with esomeprazole, and the exposure in extensive metabolisers, which with omeprazole was not enough to obtain optimal acid inhibition in all subjects, was increased with esomeprazole. This all resulted in less overall variability in the pharmacokinetics of esomeprazole than that of (*R*)-omeprazole and, consequently, the racemate omeprazole. This shows that the impact of polymorphic metabolism is less pronounced for esomeprazole than for the racemate omeprazole, and especially for (*R*)-omeprazole.

The differences in pharmacokinetic properties of esomeprazole and (*R*)-omeprazole can be summarised as follows: (i) a 3-fold difference in metabolic clearance as assessed *in vitro*;^[18] (ii) a significant difference in relative dependency on CYP2C19 and CYP3A4 as assessed *in vitro*;^[18] (iii) as a consequence, less impact of polymorphic metabolism *in vivo* for esomeprazole, resulting in overall less variability in pharmacokinetics;^[11] and (iv) time-dependent pharmacokinetics were observed *in vivo* only for esomeprazole.^[11]

These different properties of the two omeprazole isomers, demonstrated both *in vitro* and *in vivo*, result in the following pharmacokinetic differences in the clinical situation when comparing esomeprazole and the racemate omeprazole: (i) a given oral dose of esomeprazole appears to result in an approximately 2-fold higher AUC than the same dose of omeprazole;^[11,20,21] (ii) less difference in AUC between poor and extensive metabolisers, due to a lower AUC in poor metabolisers and a higher

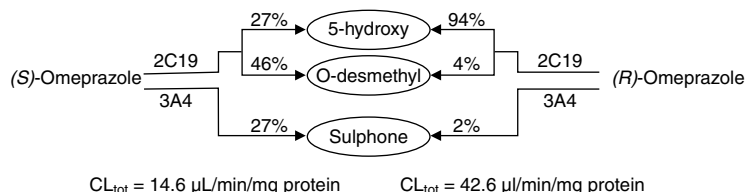


Fig. 1. Elimination pathways for (*S*)- and (*R*)-omeprazole via cytochrome P450 (CYP) enzymes, based on data from an *in vitro* study in human liver microsomes.^[18] CL_{tot} = total clearance.

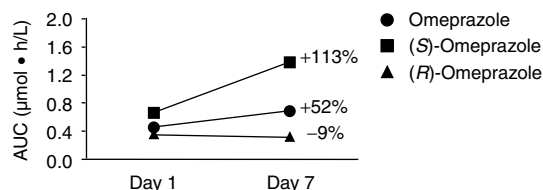


Fig. 2. Area under the plasma concentration-time curve (AUC) after single and repeated oral administration of 15mg doses of omeprazole, esomeprazole [(S)-omeprazole] and (R)-omeprazole in healthy subjects.^[11]

AUC in extensive metabolisers than with omeprazole at similar doses;^[11] (iii) more pronounced time-dependent pharmacokinetics for esomeprazole than for omeprazole, i.e. the increase in AUC from single to repeated administration is greater for esomeprazole (figure 2);^[11,20] and (iv) the interindividual variation in AUC is significantly less for esomeprazole than for the same dose of omeprazole (figure 3).^[20,21]

2.2 Pharmacodynamic Advantages

Various factors contribute to esomeprazole providing more pronounced acid inhibition than omeprazole. First, for a given oral dose of esomeprazole, a higher AUC is obtained than for the same dose of omeprazole in the majority of the population, the extensive metabolisers. Adding to this, the more pronounced nonlinearity in pharmacokinetics during repeated administration of esomeprazole results in an almost 2-fold higher AUC with esomeprazole 15 and 20mg (1.36 and 4.2 μmol • h/L) than with omeprazole 15 and 20mg (0.67 and 2.3 μmol • h/L).^[21,22]

The effect on gastric acid secretion, assessed as inhibition of pentagastrin-stimulated acid secretion or time with pH >4 during the 24 hours after administration, reflects the different pharmacokinetic profiles of esomeprazole and omeprazole. Esomeprazole 15mg resulted in a 91% reduction of stimulated gastric acid secretion whereas omeprazole 15mg resulted in a 65% reduction.^[22] The time with pH >4 was 10.8 hours for omeprazole 20mg and 12.8 hours for esomeprazole 20mg (figure 4).^[21] Doubling the dose of esomeprazole to 40mg increased the AUC 5-fold (12.6 μmol • h/L) compared

with that of omeprazole 20mg and resulted in 16.9 hours of time with pH >4.^[21] Doubling the dose of omeprazole did not result in such an effect, as shown by comparing omeprazole 40mg with esomeprazole 40mg in patients with GORD.^[23] The time with pH >4 was 1.9 hours longer on day 1 and 1.5 hours longer on day 5 for esomeprazole than for omeprazole.

Thus, the increased AUC and decreased inter-individual variability in AUC translate into significantly increased pharmacodynamic efficacy, assessed as inhibition of stimulated gastric acid secretion or increased time with intragastric pH >4, in patients with GORD, as well as decreased intersubject variability for these assessments.^[11,20-23]

2.3 Clinical Advantages

The results showing clear pharmacokinetic and consequently pharmacodynamic differences between omeprazole and esomeprazole led us to investigate esomeprazole in a clinical programme to determine if these differences also translate into clinical advantages in patients with erosive oesophagitis. The major comparator was the approved dosage regimen for this indication, omeprazole 20mg. This program included four well-controlled studies, one of which was also a dose-finding study, comparing esomeprazole 20mg and 40mg with omeprazole 20mg. The results of these studies showed higher rates for healing of erosive oesophagitis at week 8 with esomeprazole than with omeprazole.^[24-26] It was also demonstrated that symptom relief was more pronounced with esomeprazole than with omeprazole.

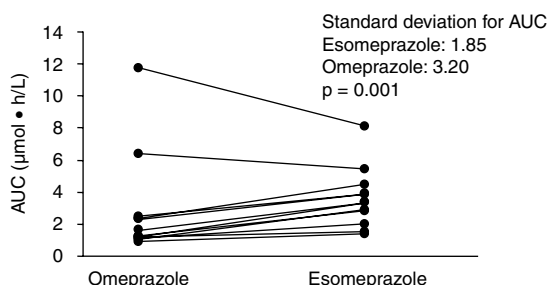


Fig. 3. Interindividual variation in AUC after repeated 20mg doses of esomeprazole or omeprazole.^[20]

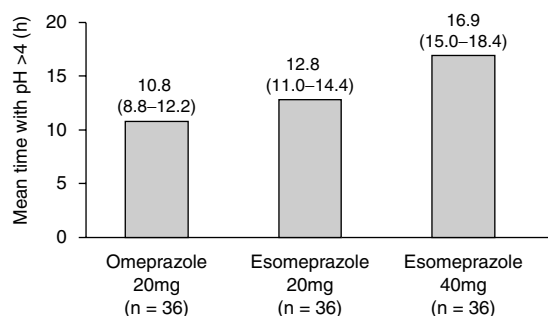


Fig. 4. Mean (95% CI) time with pH >4 after repeated doses of omeprazole 20mg, esomeprazole 20mg and esomeprazole 40mg in 36 patients with gastro-oesophageal reflux disease.^[21]

2.4 Similar Safety

Importantly, all four studies of 8-week healing of erosive oesophagitis showed no differences in safety among esomeprazole 40mg, esomeprazole 20mg and omeprazole 20mg. When pooled, these studies included 2434 patients on esomeprazole 40mg, 1240 patients on esomeprazole 20mg and 3008 patients on omeprazole 20mg. The most frequently occurring adverse events ($\geq 1\%$) in all three groups were headache (5.0%, 5.5% and 3.8%, respectively) and diarrhoea (no difference among the three groups). Nausea, flatulence, abdominal pain, constipation, and dry mouth occurred at similar rates among patients taking esomeprazole and among patients taking omeprazole.

In addition, two 6-month studies of esomeprazole 40 and 20mg in the maintenance of erosive oesophagitis, and one 12-month study of esomeprazole 40mg for safety, showed no adverse events or safety trends emergent with longer term treatment, and there did not seem to be any differences when compared with previous studies on the long-term safety of omeprazole.^[9,27,28] With no new or increased safety concerns, any improvement in efficacy with esomeprazole would be of benefit to patients.

3. Conclusion

As an example of clinical development of one isomer that has more advantageous pharmacological properties than the other, the rationale behind the development of esomeprazole, one of the two isomers of omeprazole, has been described.

Erosive oesophagitis is a common disease that can lead to serious complications. Treatment with PPIs was a major advance over H₂ receptor antagonists, but there was still a large number of patients who were not completely healed or did not get sufficient symptom relief on omeprazole. Esomeprazole has unique metabolic properties that clearly differentiate it from omeprazole, the racemate. At comparable doses, these unique properties led to several clinical advantages – higher bioavailability in the majority of patients (extensive metabolisers), lower exposure in poor metabolisers, less interindividual variation and a steeper dose-response curve at steady state resulting in a more pronounced inhibition of gastric acid secretion – that translated into better therapeutic effect and less risk of treatment failures in the majority of patients. Esomeprazole has been documented clinically for a variety of acid-related conditions, and clinical studies have proven that the compound is as well tolerated and more effective with regard to healing and symptom relief than the recommended treatment with omeprazole. For many patients, a treatment providing an increased possibility for complete healing of erosive oesophagitis, and therefore decreased potential for serious complications, as well as providing better symptom relief is an important addition to their treatment options. Thus, from this example, it is clear that the exploration and development of single-isomer drugs may bring significant advances in treatment options.

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Correspondence and offprints: Dr Tommy Andersson, Experimental Medicine, AstraZeneca LP, PO Box 15437, 1800 Concord Pike, Wilmington, DE 19850-5437, USA.
E-mail: tommy.andersson@astrazeneca.com

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