Take a close look at citalopram and you can predict its contraindications

In this science article, Timothy J. Snape and Alison M. Astles go back to basics with some revision of fundamental chemistry principles and look at how they are directly applicable to current pharmacy practice, using citalopram as an example.
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contact with its target protein, one enantiomer will experience superior binding to the protein’s chiral active site because the shape of the two molecules will be complementary to each other. The other enantiomer, on the other hand, which does not have the same 3D shape, cannot bind in the same manner and thus cannot elicit the same response from the protein because the molecular shapes are no longer as complementary.

Enantiomers and patents

Lundbeck’s patent for citalopram expired in 2003. This allowed other companies to produce generic versions. The general trend in pharmaceutical research in recent years has seen a move towards the preparation and marketing of single enantiomers of chiral drugs since it has been demonstrated that most enantiomers have different pharmacological activity, and pharmacokinetic and pharmacodynamic properties to each other. Accordingly, it is better to market a single enantiomer than a racemic mixture. For racemic drugs that have been on the market for several years and are approaching the end of their patent life, switching to a single, more effective enantiomer can be financially rewarding. Arguably, a single enantiomer can be considered as a new invention and thus a new patent can be filed. Nevertheless, pharmaceutical companies do have to prove that the new single enantiomer formulation is a better alternative to the original racemic mixture and that they did not know this at the time of the original patent application.

Consequently, Lundbeck was able to capitalise on the practice of chiral switching and released an updated formulation, escitalopram. It is called escitalopram because it is the S-enantiomer of citalopram and thus Lundbeck acquired a new patent for it. Other drugs that have been the subject of chiral switching are the proton-pump inhibitor omeprazole (racemic) to esomeprazole (S-enantiomer), the non-steroidal anti-inflammatory drug ibuprofen (racemic) to dexibuprofen (S-enantiomer) and the antibiotic ofloxacin (racemic) to levofloxacin (S-enantiomer) among others. However, it is no longer possible to patent a new drug in its racemic form today, since the issue relating enantiomers and their potentially differing biological activity is now an established fact.

The dose of citalopram required for the treatment of depression is 20mg once daily and, for escitalopram, is 10mg once daily. As can be seen, the daily recommended dose of citalopram is half that of citalopram, a direct consequence of using a single enantiomer in the case of escitalopram as compared with a racemic mixture with citalopram whereby half of the mixture (ie, one enantiomer) is pharmacologically inactive.

Citalopram and MAOIs

Citalopram (and the other SSRIs, which include escitalopram) is contraindicated with monoamine-oxidase inhibitors (MAOIs). For an explanation of this adverse interaction, we need to understand a little more about the chemical role of monoamine oxidases. Monoamine oxidases (MAOs) are natural enzymes that catalyse the oxidation of amines and contain flavin adenine dinucleotide as an essential “helper molecule”.

There are two forms of MAO in humans: MAO-A and MAO-B. The natural function of these monoamine oxidases is to catalyse the removal of an amine (deamination) from a molecule as part of the metabolism of these compounds, the product of the reaction being the corresponding aldehyde and amine, which can be subsequently acted on by other enzymes.

The significance of MAO-catalysed serotonin deamination is that its levels in the body are reduced. Consequently, if the MAO enzyme is inhibited (eg, by MAOIs), the levels of serotonin will subsequently increase. These increased levels, in combination with the increased levels due to the inhibition of serotonin uptake proteins, lead to the potentially life-threatening condition known as serotonin toxicity.

As a result, SSRIs and MAOIs should not be given together. Moreover, it is recommended that an SSRI should not be started until two weeks after stopping an MAOI, while an MAOI should not be started until at least one week after an SSRI has been stopped to enable to body to rid itself of the contraindicated drug.

Conclusion

It has been the intention of this article to demonstrate the close link between the science of chemistry, which underpins pharmacy, and pharmacy practice. With regard to the example used here, a prior understanding of the chemical structure of citalopram, alongside knowledge of its mechanism of action, should have enabled the prediction of such contraindications as seen between SSRIs and MAOIs, a feature that further highlights the link between chemistry and pharmacy practice.

GLOSSARY

• Enantiomer One pair of molecular species that are mirror images of each other and are not superimposable (Figure 2)
• Chiral centre A carbon atom to which four different groups are attached
• Racemic mixture A mixture containing equal amounts of two enantiomeric species
• Chiral switching Replacing a racemic drug with a more effective single enantiomer
• Deamination The removal of nitrogen from a molecule