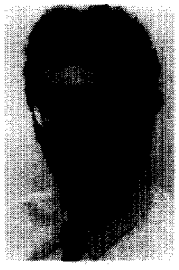
Stereochemistry: handling interactions



Is there a case for evaluating enantiomeric interactions and considering the use of non-racemic mixtures?

The importance of stereochemical considerations in the pharmaceutical industry has impacted on all areas of drug discovery and development over recent years. In this issue of *Drug Discovery Today* Dr David Triggle has reviewed the stereoselectivity of drug action and highlights the differences that may be observed in the pharmacodynamic and pharmacokinetic profiles of different enantiomers.

It has long been accepted that in many cases the administration of a pure enantiomer offers a therapeutic advantage over the use of the racemate. The introduction of formal guidelines by the FDA and the European Union Committee on Proprietary Medicinal Products in 1992 and 1993 has encouraged drug companies to focus on the development of pure enantiomers rather than racemates if there is a therapeutic benefit in administering the single enantiomer. In many cases companies have to consider whether the increased development and production costs of producing pure enantiomers outweigh the benefits offered in terms of efficacy and tolerability[1]. In particular, careful consideration must be given to the development of pure enantiomers that undergo racemization following administration. As technologies for the synthesis and isolation of single enantiomers improve, developing and producing single enantiomers should become more commercially viable. This is evidenced by the growth of companies such as Chiroscience, which specialize in chiral technology and are championing 'racemic switches' from previously marketed racemic drugs to the active enantiomer.

Although the 'racemate versus enantiomer' debate has had widespread attention, there has been little consideration of enantiomeric interactions and the potential therapeutic benefits of administering drugs as non-racemic mixtures of enantiomers. As illustrated in Triggle's review, stereoisomers may have different therapeutic and toxic effects, distribution, metabolism and rates of clearance. Given that co-administration of different drug substances can overcome potential side effects or improve therapeutic efficacy, should more consideration be given to interactions between different enantiomers and the potential benefits of co-administration of non-racemic mixtures where appropriate?

The strongest therapeutic argument for investigating enantiomeric mixtures applies in cases where the enantiomers have complementary actions resulting in an improved therapeutic profile on administration of the mixture rather than the pure enantiomers. For example, (+)-indacrinone is a diuretic and consequently causes uric acid retention, whereas (–)-indacrinone antagonizes this side effect through its action as a uricosuric agent. Clearly the administration of an enantiomeric mixture is fully justified in such a case and indeed studies have shown that the optimal therapeutic profile is obtained with a 1:4 or 1:8 ratio of (+)-isomer to (–)-isomer[2]. In other cases the co-administration of the distomer may increase the free plasma concentration of the eutomer by reducing plasma binding, metabolism or clearance of the eutomer.

It is well known that the interactions between different enantiomers may be complex. For example, in the case of ibuprofen it has been suggested that administration of the inactive (*R*)-isomer enhances the protein binding of the active (*S*)-isomer, thereby further reducing the level of free drug. Although some predictions may be possible, it is likely that the therapeutic effects of various enantiomeric mixtures can only be determined experimentally and therefore at some cost to the industry. However, because companies developing racemates are required to show that there is no therapeutic advantage in using a pure enantiomer over a racemate, should we not also expect them to evaluate the potential of at least a few non-racemic mixtures?

It may also be argued that the consideration of non-racemic mixtures is not commercially viable given the need to produce unequal quantities of each enantiomer. However, enzyme systems such as lipases, already used in the production of pure enantiomers, may be readily used to obtain non-racemic mixtures. Also, more recent studies have demonstrated that microbial systems can be used to rapidly generate a range of racemic mixtures of profens from a racemate without loss of substrate[3].

It is unlikely that the use of non-racemic mixtures will offer a potential benefit in cases where the pure enantiomer has been selected on the basis of the toxicity of the distomer. However, if there is no potential therapeutic benefit from administering a pure enantiomer the use of non-racemic mixtures may offer a means of improving the therapeutic index. Perhaps each individual enantiomer should now be considered as a separate drug and the enantiomer–enantiomer interactions given more consideration to obtain mixtures with optimal therapeutic profiles.

Andrew W. Lloyd

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Andrew W. Lloyd, Department of Pharmacy, University of Brighton, Moulsecoomb, Brighton, UK BN2 4GJ. tel: +44 1273 642049, fax: +44 1273 679333, e-mail: a.w.lloyd@brighton.ac.uk

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