# Efficacy on the other hand

Giving Ritalin, the attention deficit hyperactivity disorder (ADHD) drug, could be safer and more effective if it were used only in one handed form, according to chemists speaking at the Spring meeting of the American Chemical Society held in Dallas in March. Methylphenidate, marketed as Ritalin, is much more potent in one chiral form than in the other. Using the more active form could allow a much smaller dose to be given with the same beneficial effects but potentially with much reduced side-effects.

Chirality has really only been a major issue for medicinal chemists since the thalidomide tragedy and the realization that using mixtures of mixed enantiomeric forms of a drug can have dire consequences. Even though using one chiral form only could not have blocked the effects of thalidomide – the two are interconverted under physiological conditions – some drugs are proving to be better and safer if given in just one form.

## Ten times more potent

Ritalin is considered the treatment of choice for more than two million children suffering from ADHD with US sales topping $350 million in 1997. The drug is usually given as the racemate – the formulation of methylphenidate contains both the D-threo and L-threo forms. According to Yu-Shin Ding of the Brookhaven National Laboratory (Upton, NY, USA), some evidence now suggests that the therapeutic effects of the drug are attributed to the D-threo enantiomer only, which she adds is about ten times more potent than its chiral counterpart. 'If the beneficial effects of the drug reside only in the D-threo form,' she explained, 'then 50% of the weight of the administered drug may not contribute to its therapeutic effects.' This not only wastes resources in manufacture but also means that ADHD patients are receiving unnecessary amounts of the drug.

Ding, working with colleagues Joanna S. Fowler and Nora Volkow, has studied the effects of the individual D-threo and L-threo isomers on the CNS. They used a short-lived radioactive tracer chemical containing $^{11}C$ to tag each enantiomer of Ritalin and positron emission tomography (PET) to compare the effects of the enantiomers in the brains of baboons and humans.

The researchers found that the D-threo enantiomer bound to the dopamine targets specifically in the brain, while the binding of L-threo was not nearly so well targeted. 'The L-threo enantiomer may have some unwanted influence on the active enantiomer or may contribute unwanted side-effects, although long-term human studies would be needed to confirm this', adds Ding. 'This leads to the very important issue of whether we should use a racemic drug or a single enantiomer', she says.

## Chirality and pharmacokinetics

Ding and her colleagues say their results illustrate how PET can be used to study the pharmacokinetic properties of chiral drugs. In addition, they say, because of its high-specificity binding of dopamine receptors, D-threo tagged with $^{11}C$ has proved to be useful as a PET radiotracer to probe the neuronal loss that occurs in normal aging and in neurodegenerative conditions such as Parkinson's disease.

Many drugs exist in chiral forms. The painkiller ibuprofen, for instance, is three times more effective in one form than the other. Using radioactive tagged versions of chiral drugs with PET could allow scientists to determine whether resolution or synthesis of just one enantiomer for drug formulation would be sensible, given the added time and cost required. Legislation, however, will probably overtake such decisions as mixed enantiomer drugs become outlawed.

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