ANTIHISTAMINIC DIFFERENCES BETWEEN THE ENANTIOMERS OF DIMETHINDENE

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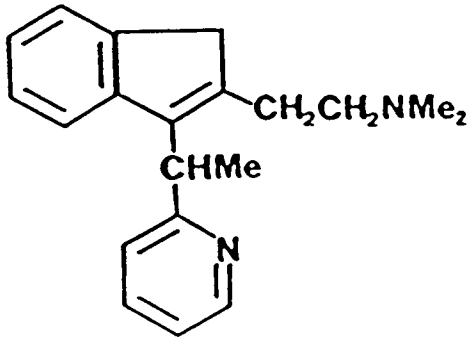
Differential in-vitro activity has been reported for the enantiomers of a variety of chiral antihistamines (Casy 1978). We report here in-vitro differences in H_1 receptor blockade found for the two enantiomers of dimethindene using guinea pig ileum assay and cerebellum binding study data. This has been extended to in-vivo evaluation of the enantiomers in humans with particular reference to the sedative side effects and impaired performance often associated with these compounds. The ultimate aim of this work was to evaluate if the sedative side effects of this drug lay solely with one of the enantiomers.

Racemic dimethindene was resolved by fractional crystallisation of the tartrate salts. Optical purity of the enantiomers was measured using optical rotation and ^{1}H-NMR techniques involving cyclodextrin inclusion complexes (Casy and Mercer 1988). In-vitro studies of the two enantiomeric tartrates of dimethindene, using guinea pig ileum assay, showed pA_2 results of *dextro* (+) 7.86 and *levo* (-) 9.54, indicating a potency ratio of greater than 50. Binding studies on guinea pig cerebellum using ^{3}[H] mepyramine and ^{125}[I] iodobolpyramine showed a 200 fold increase in the potency ratio of *levo* against *dextro* dimethindene at brain receptors.



Dimethindene

After conversion from the tartrate salts, the individual enantiomeric maleates, encapsulated with lactose, were administered to six healthy human volunteers as a double-blind study. The CNS effects were studied before and after ingestion of the individual enantiomers and by comparison with placebo and an active control (triprolidine) using a number of behavioural studies including sleep latency, subjective sleepiness and digit symbol substitution. Changes in measurements for (+) dimethindene were not different from those found for placebo. With (-) dimethindene there was a more marked reduction in sleep latency than with the (+) isomer or placebo. Increased subjective sleepiness was greater with (-) dimethindene than with the (+) isomer. Unlike sedation, changes in performance (measured by Digit Symbol Substitution) did not differ between the two enantiomers.

The in- vitro work illustrates the high stereospecificity of dimethindene as an H_1 antagonist and since it is only (-) dimethindene, the active enantiomer, that causes drowsiness in in-vivo studies it is reasonable to conclude that the sedation often seen with this antihistaminic drug may be due to blockade of brain H_1 receptors.

Casy, AF (1978), Handbook of Experimental Pharmacology, Vol XVIII/2
Casy, AF and Mercer, AD (1988), Magn. Res. Chem. 26: 765-774