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Enantiomeric disposition of ibuprofen in young and elderly volunteers

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Non-steroidal anti-inflammatory drugs (NSAIDs) are known to be the major class of agents responsible for adverse drug reactions in the elderly population (Cunningham et al 1997). Age associated alterations in drug disposition are well established and are probably a contributory factor to adverse reactions in the elderly. A number of the NSAIDs are used as racemic mixtures and only relatively recently has the significance of the pharmacodynamic and pharmacokinetic properties of the individual drug enantiomers present in such mixtures been appreciated. However, little is known concerning the influence of ageing on the stereochemical aspects of drug disposition. (*R,S*)-Ibuprofen is an important NSAID widely used for the treatment of pain and inflammation associated with rheumatic disorders. Ibuprofen shows stereoselectivity in both disposition and action, and undergoes metabolic chiral inversion from the relatively inactive *R*-enantiomer to its active *S*-antipode. In addition to chiral inversion, the metabolism of ibuprofen involves conjugation with glucuronic acid and oxidation to yield two major products, hydroxy- and carboxyibuprofen. Although the enantiomeric disposition of ibuprofen in man has been extensively investigated, few studies have presented a comprehensive picture of drug disposition following administration of the racemate as a result of methodological difficulties associated with the determination of the stereochemical composition of its two major metabolites.

In order to investigate potential age associated differences in the stereochemical disposition of ibuprofen, we have examined the pharmacokinetics and metabolism of the racemic drug following single dose oral administration (400mg) to both young (**Y**, mean age 25 years) and elderly (**E**, mean age 71 years) volunteers (n = 16 in each group). Enantiospecific analysis of ibuprofen in serum and urine was based on the indirect approach to chiral chromatography, involving derivatization with (*R*)-1-(naphthen-1-yl)ethylamine to yield diastereomeric amides followed by reverse phase HPLC (Tan et al 1997a). Protein binding of the individual enantiomers was carried out by equilibrium dialysis followed by stereospecific HPLC analysis (Tan et al 1997a). Determination of the stereochemical composition of hydroxy- and carboxyibuprofen in urine was performed by sequential achiral-chiral chromatography using a derivatized amylose CSP (Tan et al 1997b).

The serum kinetics of the enantiomers showed statistically significant differences ($p<0.05$) with (*S*)-ibuprofen showing greater values for CL, V_d, $t_{1/2z}$ and fraction unbound in comparison to the *R*-enantiomer in both age groups. Similarly examination of the urinary composition of the drug and metabolites showed preferential elimination of products with the *S*-configuration in both age groups. Comparison between the two age groups indicated age associated stereoselectivity with respect to the pharmacokinetics of (*S*)-ibuprofen with the elderly showing a reduced t_{max} (**Y**, 2.4 ± 1.3h; **E**, 1.7 ± 0.5 h) and increased apparent $t_{1/2z}$ (**Y**, 2.3 ± 0.5 h ; **E**, 3.0 ± 0.7 h). In contrast, there were no significant differences in the pharmacokinetics of (*R*)-ibuprofen or in the urinary recoveries of the drug or individual metabolites between the two age groups. Examination of the fraction unbound indicated an increase in the free fraction (**Y**, 0.48 ± 0.10 %; **E**, 0.64 ± 0.20 %) and reduced unbound clearance (**Y**, 15.8 ± 2.0 L min^{-1}; **E**, 11.6 ± 4.0 L min^{-1}) of the *S*-enantiomer in the elderly. However, the *R*-enantiomer showed no age associated changes in either fraction unbound, or unbound clearance via either inversion or non-inversion mechanisms.

The stereoselective increase in the exposure of the elderly to free levels of the active enantiomer of ibuprofen may contribute to the adverse reactions in this population sub-group.

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