GUEST EDITORIAL

CHIRALITY AND THE ACTIONS OF ANTI-INFLAMMATORY DRUGS

The mirror images of a symmetrical object are identical to one another. Such is not the case, however, for an asymmetric object, that is one which cannot be divided into two identical halves. Thus, the right hand is a mirror-image of the left hand and both are structurally alike, but neither can be superimposed upon the other. To a left-handed person, with no alternative but to use asymmetric utensils designed by right-handed people, the complexities of this "handedness" can be a source of considerable frustration. Invariably, however, right-handed people fail to see what all the fuss is about. Handedness, or *chirality*, also exists in the structure of organic molecules, the most common source being a tetrahedral carbon atom covalently linked to four chemically different substituents. For a molecule containing one *chiral* carbon atom, two non-superimposable mirror-image forms, or *enantiomers*, are possible. For a chemical containing n chiral centres, there are 2^n optical isomers.

Although chirality is common in nature, life has evolved to be highly efficient and chiral molecules of biological importance, including proteins, enzymes, receptors, neurotransmitters, hormones and vitamins, are usually synthesized as single isomers (think of the mess otherwise—even a simple polypeptide containing 10 chiral amino acids could have 1024 optical isomers!). Indeed, higher order organisms can only utilize the "left-handed" forms of chiral amino acids and "right-handed" carbohydrates. It is not surprising that the enantiomers of a chiral drug, when introduced into the complex chiral world of the living organism, can exhibit strikingly different pharmacological and pharmacokinetic properties.

Chiral drugs obtained from natural sources, such as morphine, digoxin and penicillin, are produced as single isomers and are usually marketed as such. However, with few exceptions, chiral drugs obtained synthetically are produced and used as an equal mixture of the enantiomers, i.e. as a *racemate.* Indeed, about 25% of all drugs used in humans are racemates (Millership & Fitzpatrick, 1993). Often, only one enantiomer elicits the desired therapeutic action, while in other cases the enantiomers produce different pharmacological effects. For example, S(+)-ketamine is three to four times more potent as a surgical anaesthetic than its mirror-image form, R(−)-ketamine, which is more likely to produce postoperative CNS toxicity. Rarely do the enantiomers of chiral drugs have similar pharmacological properties. Hence, for one in every four drugs prescribed for human use, the patient actually receives a fixed combination of two "drugs". In the case of

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labetalol, which contains two chiral centres, a patient receives a fixed combination of four optical isomers with differing α- and β-adrenoceptor blocking activities.

Until 1984, the field of clinical pharmacology was, in many ways, comprised of chirally naive, "right-handed" scientists. It was in that year that Everhardus J. Ariens published a landmark article entitled "Stereochemistry, a basis for sophisticated nonsense in pharmacokinetics and clinical pharmacology", in which he questioned the ethics of administering drugs with 50% or more of "isomeric ballast" and the validity of performing pharmacokinetic studies by administering a racemic drug and measuring the concentration of drug in biological fluids using a method that does not distinguish between the individual enantiomers. Such a practice can lead to the generation of pharmacokinetic parameters that are at best meaningless and in some cases misleading (Evans *et al.*, 1988). The prevailing view in 1996 is that scientists wishing to use a non-enantioselective method for investigating the pharmacokinetics of a racemic drug must justify such action.

In this issue of the journal, Professor Peter Lees and his colleagues present the results of studies on the pharmacokinetics of carprofen in calves (Lees *et al.*, 1996). Carprofen belongs to a class of chiral non-steroidal anti-inflammatory drugs (NSAIDs) known as the profens, which have been used in humans over 20 years. The antipyretic, analgesic and anti-inflammatory actions of the profens appear to result, at least in part, from inhibition of the cyclo-oxygenase-mediated synthesis of prostaglandins, an action that resides almost exclusively with the enantiomers that have the S-configuration (Evans, 1992). In many ways, the mirror-image forms, the R-enantiomers, can be regarded as unnecessary contaminants. However, NSAIDs, including the profens, may act also *via* mechanisms that are independent of cyclo-oxygenase inhibition (Abramson & Weissmann, 1989). For example, NSAIDs are capable of inhibiting the stimulus–response coupling that transforms neutrophils into secretory cells capable of provoking tissue injury and inflammation. Although the clinical importance of this and other cyclo-oxygenase-independent properties of NSAIDs are far from completely understood, the possibility that the R-enantiomers of the profens may elicit such actions without the untoward effects of cyclo-oxygenase inhibition, such as gastrointestinal intolerance, provides a therapeutic opportunity that should not be ignored.

Enantioselectivity is also a feature of the metabolism, plasma protein binding and tissue distribution of the profens (Evans, 1992). The most intriguing aspect of this enantioselective disposition is the ability of the R-enantiomers of some profens, including ibuprofen, to be converted *in vivo* to the S-enantiomer. This inversion process is enantiospecific, proceeding in one direction only, and exhibits wide substrate and inter-species variability. Because it results in the formation of a "biologically active metabolite" it is also clinically important. Thus, R(−)-ibuprofen is an effective analgesic and anti-inflammatory agent *in vivo* despite being an ineffective inhibitor of prostaglandin synthesis *in vitro* (Adams *et al.*, 1976). In contrast, the efficacy of R(−)-carprofen in traditional models of inflammation is substantially less than that of S(+)-carprofen (Gaut *et al.*, 1975), which is consistent with the fact that R(−)-carprofen is a weak inhibitor of cyclo-oxygenase and a poor substrate for inversion.

Because carprofen is used as a racemate, and because the biological properties of the enantiomers are different, Lees and colleagues utilized an enantioselective

method to measure drug in plasma and inflammatory exudates. The pharmacokinetic analysis was then applied to each individual enantiomer. The observed change in the enantiomeric composition of carprofen in plasma, over several half-lives, is likely to be due to differences between enantiomers in metabolic clearance by the liver and/or extent of binding to plasma proteins.

Lees and colleagues also attempted to follow the time-course of the effects of carprofen on intermediate measures of NSAID effect, such as inhibition of thromboxane-B_2 synthesis, and semi-clinical end-points such as inhibition of chemical-induced inflammation. In the past, a number of studies have successfully established relationships between the concentrations of NSAIDs in plasma and inhibition of cyclo-oxygenase. For racemic NSAIDs, such relationships are meaningful only when plasma concentrations are expressed with reference to the active enantiomer (Evans, 1992). However, relating drug concentration to clinical end-points is a more significant challenge, and previous attempts to establish such relationships have generally failed, not because of problems in measuring drug concentrations, but because of variability in the response measurement (Day *et al.*, 1987). It may be for the same reason that in the small groups of calves studies by Professor Lees and his colleagues no clear pattern emerged between inhibition of prostaglandin synthesis and anti-inflammatory effect. It follows that it is difficult to reach a conclusion from this work regarding the mechanism of action of carprofen.

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REFERENCES

ABRAMSON, S. B. & WEISSMANN, G. (1989). The mechanism of action of non-steroidal anti-inflammatory drugs. *Arthritis and Rheumatism* **32,** 1–9.

ADAMS, S. S., BRESLOFF, P. & MASON, C. G. (1976). Pharmacological differences between the optical isomers of ibuprofen: evidence for metabolic inversion of the (−)-isomer. *Journal of Pharmacy and Pharmacology* **28,** 256–7.

ARIENS, E. J. (1984). Stereochemistry, a basis for sophisticated nonsense in pharmacokinetics and clinical pharmacology. *European Journal of Clinical Pharmacology* **26,** 663–8.

DAY, R. O., GRAHAM, G. G., WILLIAMS, K. M., CHAMPION, G. D. & DE JAGER, J. (1987). Clinical pharmacology of non-steroidal anti-inflammatory drugs. *Pharmacology and Therapeutics* **33,** 383–433.

EVANS, A. M. (1992). Enantioselective pharmacodynamics and pharmacokinetics of chiral non-steroidal anti-inflammatory agents. *European Journal of Clinical Pharmacology* **42,** 237–56.

EVANS, A. M., NATION, R. L., SANSOM, L. N., BOCHNER, F. & SOMOGYI, A. A. (1988). Stereoselective drug disposition: potential for misinterpretation of drug disposition data. *British Journal of Clinical Pharmacology* **26,** 771–80.

GAUT, Z. N., BARUTH, H., RANDALL, L. O., ASHLEY, C. & PAULSRUD, J. R. (1975). Stereoisomeric relationships among anti-inflammatory activity, inhibition of platelet aggregation, and inhibition of prostaglandin synthetase. *Prostaglandins* **10,** 59–66.

LEES, P., DELATOUR, P., FOSTER, A. P., FOOT, R. & BAGGOT, D. (1996). Evaluation of carprofen in calves using a tissue cage model of inflammation. *British Veterinary Journal* **152,** 199–211.

MILLERSHIP, J. S. & FITZPATRICK, A. (1993). Commonly used chiral drugs: a survey. *Chirality* **5,** 573–6.