Chiral Inversion of (R)-(−)-Fenoprofen in Guinea-pigs Pretreated with Clofibrate

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ABSTRACT

The influence of clofibrate on the stereoconversion of fenoprofen (FPF) was studied in guinea pigs. This hypolipidaemic agent has been related to some biochemical changes in the liver leading to an increase in the chiral inversion process. Two groups of animals (n = 6 per group) were pretreated with oral doses of clofibrate (280 mg/kg per day) for three days and were then given (R)- or (S)-FPF (5 mg/kg, IV). The FPF enantiomers were extracted from the guinea-pigs’ plasma using a solid phase procedure and analysed by HPLC with previous derivatization with 1-leucinamide. Pretreatment with clofibrate increased the chiral inversion of (R)-FPF in favour of the pharmacologically active (S)-FPF enantiomer. Before this metabolic interaction can be applied to therapy with fenoprofen, the toxic effects of (S)-(+)–FPF on the gastrointestinal and renal tracts and the interference by (R)-(−)-FPF with the metabolism of lipids should be thoroughly evaluated.

Keywords: arylpropionates, chiral inversion, clofibrate, lipid metabolism, profens

Abbreviations: AUC, area under the concentration–time curve; AUCp, area under the concentration–time curve of the S-enantiomer; AUCR, area under the concentration–time curve of the R-enantiomer; FPF, fenoprofen; IV, intravenous

INTRODUCTION

Fenoprofen (FPF) is a nonsteroidal anti-inflammatory drug belonging to the family of the 2-arylpropionic acids or profens. Although it is not licensed to be used in veterinary medicine, it represents very well other molecules of the group that undergo inversion. It has a chiral carbon atom (C-2) and it is marketed as a racemate (50:50, (R)-(S)-enantiomers) for clinical use in humans. Studies in vitro have shown that the (S)-enantiomer is the compound responsible for inhibition of prostaglandin synthesis (Rubin et al., 1985; Caldwell et al., 1988). The stereoselective disposition of FPF has been mainly attributed to a unidirectional metabolic chiral inversion of (R)-(−)-FPF to its antipode.

The molecular mechanism of chiral inversion of profens involves three steps: (i) stereoselective activation of (R)-(−)-profen by formation of the acyl-CoA thioester in the presence of co-enzyme A, ATP and Mg^{2+}; (ii) enzymatic epimerization of the
(R)-(−) thioester to the (S)-(+) thioester; (iii) release of the free active (S)-(+) enantiomer by hydrolysis of the thioester (Figure 1) (Wechter et al., 1974; Nakamura et al., 1981). Berry and Jamali (1991) have demonstrated that the liver is the most important organ in the development of this mechanism. Stereocconversion also takes place in the intestine, kidney, lung, muscle and fat (Cox et al., 1985; Mehvar and Jamali, 1988; Jeffrey et al., 1991; Hall et al., 1992). The chiral inversion of FPF has been studied in humans (Rubin et al., 1985), rabbits (Hayball and Meffin, 1987), rats (Berry and Jamali, 1991), sheep (Soraci et al., 1995), horses and dogs (Soraci et al., 1996) and cats (Castro et al., 1998). The results showed large interspecies variations in the magnitude of inversion related to the expression of long-chain acyl-CoA synthetase (EC 6.2.1.3).

![Diagram of chiral inversion process of aryl-2-propionic acids or profens]

Figure 1. Chiral inversion process of aryl-2-propionic acids or profens

The chiral inversion may be of toxicological significance because the intermediate acyl-CoA thioester can modulate lipid metabolism. In addition, the acyl-CoA thioester can inhibit mitochondrial β-oxidation of fatty acids, favouring the development of microvesicular steatosis (Freneau et al., 1990; Zhao et al., 1992), can be incorporated into triglycerides, altering plasma membranes and second messenger mechanisms (Williams et al., 1986; Sallustio et al., 1987), and can lower serum lipid levels (Fears et al., 1978; Kemal and Casida, 1992). In rat liver homogenates, the formation of (R)-ibuprofen-CoA is dependent on the concentrations of both CoA and (R)-ibuprofen