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Study of warfarin reductive metabolism using chiral HPLC and SFC analysis

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Warfarin is the most commonly prescribed oral anticoagulant but its use is complicated by its narrow therapeutic index. The biotransformation of warfarin involves both oxidative and reductive processes. In contrast to oxidative pathways, the reductive metabolism of warfarin has not been yet investigated thoroughly. Reduction of warfarin generates warfarin alcohols of two diastereomers. Because warfarin alcohols retain pharmacological activity, the reductive metabolism of warfarin may have impact on treatment outcomes. Two HPLC and SFC methods have been developed and applied for analysis of warfarin alcohols formed after incubation with human liver subcellular fractions and purified recombinant enzymes. One of the methods was the UPLC method for detection of diastereomers of warfarin alcohol, i.e. RS/SR-warfarin alcohol (alcohol 1) and RR/SS-warfarin alcohol (alcohol 2). The second chiral HPLC method allowed analysing the formation of individual enantiomers of warfarin alcohols. Notably, this is the first chiral HPLC method developed so far for the detection of enantiomers of warfarin alcohols. The formation of warfarin alcohols in cytosol exceeded that in microsomes by 10-fold. From the tested enzymes, significant activity toward warfarin reduction has been exhibited by cytosolic enzyme AKR1C3. Another well-known cytosolic enzyme implicated in xenobiotic reductive metabolism, CBR1, formed only low amounts of warfarin alcohols. Even lower activity has been detected for AKR1C1 and AKR1C2. The predominant metabolite formed after incubation with AKR1C3 was RS-warfarin alcohol. This is in agreement with *in vivo* results from human patients. In conclusion, AKR1C3 was suggested to be the main enzyme responsible for warfarin reduction.

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