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# Identification of Human Liver Cytochrome P450s Involved in the Microsomal Metabolism of the Antihistaminic Drug Loratadine

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**Key Words**

Cytochrome P450  
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Descarboethoxyloratadine  
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The purpose of this study was to determine which cytochrome P450 (CYP) enzymes metabolize loratadine, a non-sedating antihistamine, in humans. <sup>3</sup>H-Loratadine was incubated with pooled human liver microsomes and the rate of formation of SCH 34117, descarboethoxyloratadine (DCL), the major active circulating metabolite of loratadine, was determined. Control incubations without NADPH and incubations with a specific esterase inhibitor (phenylmethylsulfonyl fluoride) indicated that the formation of DCL was CYP dependent. A high correlation ( $r^2 = 0.96$ ) between the rate of formation of DCL, measured in 10 human liver microsomal samples, and testosterone 6- $\beta$ -hydroxylation, a CYP3A mediated reaction, was noted. With the addition of ketoconazole (an inhibitor of the CYP3A4 enzyme) to the incubation mixtures, the rate of DCL formation corre-

lated with that for the O-demethylation of dextromethorphan ( $r^2 = 0.81$ ), a CYP2D reaction. The formation of DCL by human liver microsomes was inhibited by the addition of selective chemical inhibitors of the CYP3A4 (troleandomycin) and CYP2D6 (quinidine) enzymes to the incubation mixtures. Addition of rabbit polyclonal antibodies raised against the rat CYP3A1 (similar homology to human CYP3A4) enzyme also inhibited the formation of DCL. Cell-line-derived human CYP3A4 and CYP2D6 microsomes were shown to metabolize loratadine to DCL. The results indicate that loratadine is metabolized to DCL principally by the CYP3A4 enzyme in human liver microsomes. In the presence of a CYP3A4 inhibitor, loratadine is metabolized to DCL principally by the CYP2D6 enzyme.