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# Identification of the Human Cytochrome P450 Enzymes Involved in the Two Oxidative Steps in the Bioactivation of Clopidogrel to Its Pharmacologically Active Metabolite

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## Abstract

The aim of the current study is to identify the human cytochrome P450 (P450) isoforms involved in the two oxidative steps in the bioactivation of clopidogrel to its pharmacologically active metabolite. In the *in vitro* experiments using cDNA-expressed human P450 isoforms, clopidogrel was metabolized to 2-oxo-clopidogrel, the immediate precursor of its pharmacologically active metabolite. CYP1A2, CYP2B6, and CYP2C19 catalyzed this reaction. In the same system using 2-oxo-clopidogrel as the substrate, detection of the active metabolite of clopidogrel required the addition of glutathione to the system. CYP2B6, CYP2C9, CYP2C19, and CYP3A4 contributed to the production of the active metabolite. Secondly, the contribution of each P450 involved in both oxidative steps was estimated by using enzyme kinetic parameters. The contribution of CYP1A2, CYP2B6, and CYP2C19 to the formation of 2-oxo-clopidogrel was 35.8, 19.4, and 44.9%, respectively. The contribution of CYP2B6, CYP2C9, CYP2C19, and

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CYP3A4 contributed substantially to the second oxidative step. These results help explain the role of genetic polymorphism of CYP2C19 and also the effect of potent CYP3A inhibitors on the pharmacokinetics and pharmacodynamics of clopidogrel in humans and on clinical outcomes.

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## Footnotes

- Article, publication date, and citation information can be found at <http://dmd.aspetjournals.org>.

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- P450

*cytochrome P450*

LC/MS/MS

*liquid chromatography/tandem mass spectrometry*

HPLC

*high-performance liquid chromatography*

$\beta$ -NADP

*$\beta$ -nicotinamide adenine dinucleotide phosphate sodium salt*

$CL_{int}$

*intrinsic clearance.*

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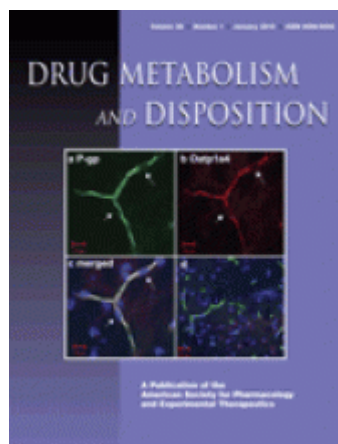
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