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Review

Caffeine as a marker substrate for testing cytochrome P450 activity in human and rat

Marta Kot, Władysława A. Daniel

Department of Pharmacokinetics and Drug Metabolism, Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, PL 31-343 Kraków, Poland

Correspondence: Marta Kot, e-mail: kot@if-pan.krakow.pl

Abstract:
The current knowledge on the involvement of cytochrome P450 (P450, CYP) isoforms in the metabolism of caffeine in rat and human liver is reviewed. Attention is also paid to species- and concentration-dependent metabolism of caffeine. Finally, we discuss the P450-mediated metabolism of caffeine in relation to coffee addiction and drug interactions.
Due to its safety, favorable pharmacokinetic properties, and P450 isoform-selective metabolism, caffeine has great potential as a metabolic marker substance in both humans and rats, and as a more universal metabolic tool in the latter species. However, the qualitative and relative quantitative contribution of P450 isoforms to the metabolism of caffeine is species- and concentration-dependent. While 3-N-demethylation is quantitatively the main oxidation pathway in human, 8-hydroxylation is the dominant metabolic pathway in rat. Both of these main reactions in the two species are specifically catalyzed by CYP1A2. Caffeine may be applied as a marker substance for assessing the activity of CYP1A2 in human and rat liver, but by using different reactions: 3-N-demethylation in humans and C-8-hydroxylation in rats. In addition, caffeine can be used to preliminarily and simultaneously estimate CYP2C activity in rat liver using 7-N-demethylation as a marker reaction. On the other hand, CYP3A4-catalyzed 8-hydroxylation in humans is not sufficiently isoform-specific to mark the activity of CYP3A4. Caffeine pharmacokinetics may be changed by drugs affecting the activity of CYP1A2 (human and rat) or CYP2C (rat), e.g. *via* autoinduction or by treatment with certain antidepressants or neuroleptics. Therefore, patients taking caffeine-containing medicine or coffee drinkers taking drugs that interact with CYP1A2 may require proper dosage adjustments upon caffeine ingestion and cessation.

Key words:
caffeine, pharmacokinetics, pharmacodynamics, cytochrome P450, N-demethylation, 8-hydroxylation, drug interactions, coffee addiction