Metabolic characterization of the opioid analgesic meperidine and pharmacogenetic implications for generation of the neurotoxic metabolite normeperidine

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Background: Meperidine is an opioid analgesic which undergoes N-demethylation by hepatic cytochrome P450 (CYP) enzymes to generate normeperidine. Normeperidine is neurotoxic and can accumulate to cause agitation, tremors, and seizures, especially in patients with renal impairment or altered hepatic metabolism. Previous studies have indicated that meperidine N-demethylation is performed primarily by CYP2B6, CYP3A4, and CYP2C19; however, the relative enzyme contribution is not well established. Since CYP2B6 and CYP2C19 possess a high degree of genetic variation, P450 genetic polymorphisms may lead to variations in normeperidine formation and thus alter the potential for neurotoxicity among diverse patient populations.

Methods: Reaction phenotyping methods were used to determine the relative contributions of each P450 enzyme to meperidine N-demethylation in pooled human liver microsomes (HLM). Enzyme kinetics studies were performed to determine the Kₘ and Vₘₐₙ of normeperidine formation by individual recombinant P450 enzymes and HLM. Normeperidine generation was also assessed in a panel of 18 individual CYP2C19-genotyped HLM. Normeperidine was quantified by liquid chromatography-tandem mass spectrometry (LC-MS/MS).

Results: Meperidine was incubated with a panel of individual recombinant P450 enzymes, which generated normeperidine in the following order: CYP2B6 = CYP2C19 > CYP2D6 > CYP1A2 > CYP3A4. P450-selective inhibition of meperidine N-demethylation in HLM yielded the following results: ketoconazole reduced normeperidine formation by 39.0 ± 6.0% (p<0.01), ticlopidine reduced normeperidine formation by 30.2 ± 2.9% (p<0.001), and 2-phenyl-2-(1-piperidinyl) propane (PPP) reduced normeperidine formation by 24.7 ± 7.8% (p<0.05) compared to control. Kinetic analysis of meperidine N-demethylation with recombinant CYP2B6 and CYP2C19 revealed that CYP2C19 had 2.8-fold higher substrate affinity compared to CYP2B6, as measured by apparent Kₘ (CYP2B6 Kₘ = 423.1 ± 177.5 µM; CYP2C19 Kₘ = 153.4 ± 38.7 µM). The overall catalytic efficiency for meperidine N-demethylation was similar between CYP2B6 and CYP2C19, as measured by Vₘₐₙ/Kₘ (CYP2B6 Vₘₐₙ/Kₘ = 0.172 µL/min/pmol P450; CYP2C19 Vₘₐₙ/Kₘ = 0.191 µL/min/pmol P450). The metabolic clearance by recombinant CYP3A4 was markedly lower.

Conclusion: Collectively, these findings suggest that CYP2C19, CYP2B6, and CYP3A4 are important contributors to meperidine metabolism. Future studies are needed to examine the contribution of variable P450 expression and activity on normeperidine formation.