Correlation of pharmacogenetic genotype in cytochrome P450 with steady-state metabolic profiles of tamoxifen: effect on active metabolite concentrations

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To test the hypothesis that polymorphisms in cytochrome P450 (CYP) might alter tamoxifen metabolism to active metabolites, we measured the drug and three metabolites in the subjects with chronic tamoxifen treatment.Twenty-nine women prescribed tamoxifen (20mg po qd) were recruited.

Genotypes for CYP2C9 (*2 and *3), CYP2C19 (*2 and *3), CYP2D6 (*3, *4, *6, *8, *10, and *17), and CYP3A5 (*3 and *6) were determined by PCR-RFLP (polymerase chain reaction-restriction fragment length polymorphism). Plasma concentrations of tamoxifen, N-desmethyltamoxifen, 4-hydroxytamoxifen, 4-hydroxy-N-desmethyl-tamoxifen after 4 months of tamoxifen treatment were determined by HPLC (high- performance liquid chromatography) with on-line postcolumn UV photocyclization and fluorescence detection.

The genotypes for CYP2C19 and CYP3A5 did not correlate separately, or in any combination with plasma concentrations of tamoxifen or its metabolites. CYP2D6 genotype did not cause a significant change in the concentrations of tamoxifen and N-desmethyltamoxifen. In contrast, the steady-state concentrations of 4-hydroxytamoxifen and 4-hydroxy-N-desmethyltamoxifen were significantly lower ($p<0.05$) in the subjects who have CYP2D6*1/*4 genotype (n=7) compared with those who have CYP2D6*1/*1 genotype (n=18). Accordingly, the plasma molar concentration ratios of 4-hydroxy-N-desmethyltamoxifen/N-desmethyltamoxifen and 4-hydroxy-N-desmethyltamoxifen/tamoxifen were lower in the subjects who have CYP2D6*1/*4 genotype compared with those who have CYP2D6*1/*1 genotype ($p=0.001$ and $p=0.004$, respectively).

In conclusion, the *4 variant of the CYP2D6 gene resulted in a marked decrease in metabolic conversion of N-desmethyltamoxifen to 4-hydroxy-N-desmethyltamoxifen in in vivo women, consistent with our in vitro data indicating that CYP2D6 is the primary enzyme in catalyzing the conversion of N-desmethyltamoxifen and 4-hydroxytamoxifen to 4-hydroxy-N-desmethylatmoxifen.

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