Pharmacokinetics of Tamoxifen and its major metabolites and the effect of the African ancestry specific CYP2D6*17 variant on the formation of the active metabolite, endoxifen.

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Tamoxifen is widely used in the treatment of hormone receptor-positive breast cancer. CYP2D6 is an enzyme that converts tamoxifen to its highly potent secondary metabolite, endoxifen. Studies have been conducted to determine the association between CYP2D6 genotype and endoxifen concentrations, but there is limited research on the association with reduced activity variants such as CYP2D6*17 which occur at high frequencies in people of African ancestry. We conducted a single-dose pharmacokinetic study in humans to investigate the effects of CYP2D6*17 variant, on the pharmacokinetics (PK) of tamoxifen and its active metabolites in 42 healthy black Zimbabweans. Subjects were grouped based on CYP2D6 genotypes as CYP2D6*1 or *2, CYP2D6*1/*17 or 2*/*17, and CYP2D6*17/*17. PK parameters for tamoxifen and its metabolites, N-desmethyl tamoxifen, 4-hydroxy-tamoxifen, and endoxifen, were determined. Metabolic ratios of endoxifen/ N-desmethyl tamoxifen were used to interpolate the predicted activity score. The non-parametric superposition tool in Phoenix WinNonlin was used to estimate tamoxifen dose increases to predict endoxifen steady-state plasma concentrations. The PK of endoxifen showed statistically significant differences among the three genotype groups. CYP2D6*17 gene carriers had significantly lower endoxifen exposure levels than CYP2D6*1 or *2 carriers, with the mean endoxifen $AUC_{0-\infty}$ in CYP2D6*17/*17 subjects being 452.01 (196.94) h*ng/mL, which was 5-fold lower than in CYP2D6*1 or *2 subjects. Individuals who were heterozygous or homozygous for CYP2D6*17 alleles showed a 2- and 5-fold decrease in Cmax, respectively, compared to the CYP2D6*1 or *2 genotype. Pharmacokinetic parameters of tamoxifen and the two primary metabolites, N-desmethyl tamoxifen and 4-hydroxy tamoxifen, did not show any significant difference in the three genotype groups. With observed differences in endoxifen exposure levels, we predicted an activity score value of 0.3 which is lower than the established activity score value of 0.5. Using single dose study and simulating to steady state we observed that CYP2D6*17/*17 patients failed to reach the 5.9 ng/ml endoxifen putative threshold, but further simulations showed that dose escalation to 40 mg per day resulted in all individuals homozygous for CYP2D6*17 having therapeutically effective endoxifen concentrations. The African-specific CYP2D6*17 variant showed reduced activity with a predicted activity score of 0.3, resulting in lower endoxifen exposure levels. CYP2D6-informed tamoxifen dosing could benefit IM patients who are homozygous for this variant.