Aim: The anti-estrogen tamoxifen (Tam) requires activation to endoxifen by cytochrome P450 (CYP) enzymes. The use of potent CYP2D6-inhibiting drugs can significantly disrupt endoxifen formation, which probably affects the efficacy of Tam. For this reason, the use of potent CYP2D6-inhibiting antidepressants (AD) along with Tam is discouraged. However, this combination is still frequently used (Binkhorst et al, BCRT 2013). We studied the feasibility of switching potent CYP2D6-inhibiting AD to the mild CYP2D6 inhibitor escitalopram.

Methods: Women receiving Tam in combination with a potent CYP2D6-inhibiting AD (paroxetine or fluoxetine), for at least 4 weeks, underwent blood sampling for pharmacokinetics (PK) during a 24h period. Patients were then switched to a mild CYP2D6-inhibiting AD by the psychiatrist. After 4 weeks, patients underwent a second PK sampling period. A validated LC-MS/MS method was used for quantification and PK parameters were calculated.

Results: All included patients were successfully switched (cross-tapering) from paroxetine or fluoxetine to escitalopram, without any adverse effects or psychiatric relapse. During escitalopram treatment, the area under the curves (AUC₀–2₄) of the active metabolites 4OH-Tam and endoxifen were significantly higher than during paroxetine/fluoxetine treatment. The median endoxifen AUC₀–2₄ increased by 324% (n = 7; 445 nM*h (range 175-637) vs 163 nM*h (range 70-210); p = 0.018; Wilcoxon signed-rank test) and that of 4OH-Tam by 39% (90.2 nM*h (range 51.1-148) vs 65.0 nM*h (range 27.4-98.2); p = 0.028). Ratios of endoxifen/ND-Tam and 4OH-Tam/Tam increased by ~3.4 and ~1.4-fold, respectively.

Conclusions: Switching from a potent CYP2D6-inhibiting AD to a weaker variant in women receiving Tam resulted in dramatic effects on endoxifen exposure. After switching, endoxifen concentrations were similar to that observed in our reference population of TAM-using women without CYP2D6-inhibiting co-treatment. The increase in metabolic ratios reflects higher CYP2D6 activity. No negative effects on the psychiatric treatment with AD were noticed. These data suggest that escitalopram, and probably other mild CYP2D6 inhibitors, is a safe and effective alternative in Tam-users.

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