Tamoxifen and Potent CYP2D6 Inhibitors: A Potentially Lethal Interaction

Abstract:
Sir
Tamoxifen has a well-established role in the management of oestrogen-receptor positive breast cancer halving the 5-year recurrence risk of early stage breast cancer, reducing mortality and controlling metastasis. It is an inactive pro-drug which is activated by the hepatic cytochrome P450 system.

The most important of metabolites are 4-hydroxytamoxifen and 4-hydroxy-N-desmethyltamoxifen (endoxifen). Both metabolites have a 100-fold greater affinity for the oestrogen receptor compared to tamoxifen. Endoxifen is the most pharmacologically active metabolite. This conversion is by cytochrome P450 isozyme 2D6 (CYP2D6). The CYP2D6 gene located on chromosome 22 is highly polymorphic with more than 80 different major alleles identified. Many alleles confer decreased or absent CYP2D6 activity. Reduced activity leads to lower endoxifen concentrations, increased risk of breast cancer recurrence and a shorter time to cancer relapse. Although conflicting data exist, these studies suggest an important role for CYP2D6 activity in tamoxifen metabolism. Co-administration of tamoxifen with medications that inhibit the activity of CYP2D6 can reduce endoxifen formation reducing tamoxifen effectiveness. This has major implications for clinical practice. Up to 25% of breast cancer patients experience clinically significant depression. CYP2D6 inhibitors selective serotonin reuptake inhibitor (SSRI) and norepinephrine reuptake inhibitor (SNRI) antidepressants are used as initial therapies. They are also used to treat tamoxifen-associated hot flushes. The potent SSRIs paroxetine and fluoxetine have a significant effect on tamoxifen metabolism. Paroxetine is the only SSRI that exhibits “suicide” inhibition with irreversible loss of enzyme function. Sertraline and citalopram are moderate inhibitors of CYP2D6. Venlafaxine escitalopram and mirtazapine are considered to have little or no inhibition of CYP2D6.

A retrospective investigation of the long-term impact of CYP2D6 inhibitors on clinical outcomes in 24,430 women treated for breast cancer with tamoxifen over a 13-year period, reported that 30% received at least one concomitant antidepressant. Paroxetine was most commonly prescribed (25%). Breast cancer related death rates were significantly higher in women in this cohort. This risk was directly proportional to the duration of co-prescribing. Such studies have resulted in recommendations to avoid potent CYP2D6-inhibiting antidepressants in patients receiving tamoxifen. Despite this, records from a community pharmacy database of three million people in the Netherlands demonstrated that paroxetine remains one of the most frequently prescribed antidepressants in women receiving tamoxifen. Prescribing trends matched those of the general population. An Irish study utilising the Primary Care Reimbursement Services pharmacy database, identified 4528 women commenced on tamoxifen between 2001 and 2006. Thirteen percent (n=599) were co-prescribed tamoxifen with moderate (6.9%) or potent (7.6%) CYP2D6 inhibitors. In 5.8% of patients, the CYP2D6 inhibitor was started after tamoxifen.

While more recent co-prescription rates have fallen, we remain concerned about the lack of awareness of this interaction. Paroxetine and fluoxetine co-administration with tamoxifen should be avoided. Preference should be given to antidepressants that show little or no inhibition of CYP2D6 such as venlafaxine and escitalopram. When the use of a potent CYP2D6 inhibitor is considered necessary, co-administration should be limited to the shortest possible duration.

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References

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