Study of Antidepressant Molecular Structure Leading to Safer Dosing

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The structure of drugs influences their metabolism and efficacy when they bind to CYP enzymes in the body. This study was conducted using QSAR (quantitative structure-activity relationship) with the MOE (Molecular Operating Environment) program to predict the binding inhibition of antidepressants with CYP2D6. Many antidepressants are both inhibitors of CYP2D6, a cytochrome P450 enzyme, and are also metabolized by 2D6. Because the CYP enzymes are involved with the metabolism of most drugs, inhibiting CYP enzymes can cause drug-drug interactions, as the enzymes' inhibition affects the metabolism of other molecules present in the body. After identifying SSRIs and SNRIs, classes of drugs that are known potent inhibitors of CYP2D6, a list of molecules in these classes, as well as other molecularly similar compounds, was compiled. A chart of these molecules that have known pKi data for inhibition of 2D6 was formed, and a list was compiled for molecules with no available pKi data for 2D6 inhibition. The structures of 16 molecules with known pKi values for CYP2D6 inhibition were evaluated in silico and quantified using molecular descriptors. This was done using a mathematical model that established a linear relationship between a drug's predicted pKi values and the drug's molecular structure.

After measuring the effect that different molecular descriptors had on the accuracy of the predicted pKi values, the math model was limited to 4 descriptors that provided reasonably good fit to predict a drug's pKi inhibition. Using this model, the predicted pKi values for the 16 molecules in the test set were calculated, and they were cross-validated against the known pKi values for each of the molecules. The model was then used to predict the pKi values for 3 antidepressants whose pKi values for inhibiting 2D6 were unknown. By deriving an equation to calculate the predicted pKi value for a drug based on its structural characteristics, it was proved that the binding inhibition of drugs including SSRIs, SNRIs, and other similar drugs can be predicted using their molecular structure, which was quantified using various molecular descriptors. This study was conducted because the derived equation allows researchers to calculate the predicted inhibition of drugs in this class with the CYP2D6 enzyme. This knowledge is essential as incorrectly prescribed doses of medications could result in adverse side effects. Physicians like to know this information, to avoid deadly synergy between various drugs (drug-drug interactions).