Metabolism and therapeutic drug monitoring of quetiapine

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ABSTRACT

The dissertation concerns the development of an analytical method for the atypical antipsychotic quetiapine, application of the method for therapeutic drug monitoring (TDM), and in vitro studies on the metabolism of quetiapine. The dissertation is based on three published papers.

The analytical method was based on solid phase extraction of quetiapine from human serum followed by liquid chromatographic separation of the compound from other substances with ultra violet detection. The composition of the mobile phase and the total run time was optimised to reduce interference from other psychoactive drugs commonly used in our area. The method has been in use in our routine TDM laboratory for several years.

In the TDM study, sixty-two patients were enrolled. The 80% central interval of serum concentrations of patients receiving recommended doses of quetiapine was between 50 and 650 nM. Based on 13 patients with two to eight measurements available, the intra-individual variation was estimated to 49%, which is in the same order of magnitude as other drugs with short elimination half-lives. For patients receiving drugs, either inhibitors or substrates of CYP3A4/5, the median C/D was 70% higher than the median of patients in quetiapine monotherapy. The difference, however, was not significant. Two patients receiving carbamazepine displayed a several-fold lower C/D median value than that of the monotherapy group.

The involvement of CYP isozymes in the metabolism was investigated using cDNA-expressed CYP isozymes and human liver microsomal (HLM) preparations. By screening cDNA-expressed CYPs for metabolic activity in relation to quetiapine, we found that CYP3A4, CYP3A5, and CYP2D6 were able to transform quetiapine to more than 15 metabolites. The relative contributions of CYP3A4/5 and CYP2D6 were determined to 89% and 9%, respectively, using the specific inhibitors ketoconazole and quinidine in human liver microsomes. In vitro inhibitory studies of commonly co-medicated drugs that are known inhibitors of CYP3A4/5 or CYP2D6 substantiated that CYP3A4/5 are the isozymes mainly responsible for quetiapine metabolism. The antidepressant nefazodone displayed a high inhibitory effect as expected, but other commonly co-medicated drugs also exerted some inhibitory effect.

In conclusion, quetiapine is mainly metabolised by CYP3A4/5, and strong inhibitors and inducers of CYP3A4/5 are likely to exert a clinically relevant impact on quetiapine serum concentrations. Co-administration of this type of compounds with quetiapine should therefore be considered with care. In the context of TDM, serum concentrations between 50 and 650 nM quetiapine were chosen as an orientating interval for patients receiving recommended doses.