The combination of pharmacogenetic and pharmacokinetic analyses to optimise clomipiramine dosing: a case report

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Clomipramine is a major tricyclic antidepressant successfully used in Europe for depression and other psychiatric conditions. However, its use is affected by interindividual pharmacokinetic variability that may lead to adverse drug reactions and/or to a reduced efficacy. Clomipramine is extensively metabolized in the liver into the main active metabolite desmethylclomipramine, via CYP450 enzymes *N*-demethylation (Balant-Gorgia et al. 1999; Nielsen et al. 1996). The parental drug and its metabolite are then hydroxylated by CYP2D6. Single nucleotide polymorphisms (SNPs) in genes encoding CYPs enzymes may affect their expression or function. Guidelines for CYP2C19 and CYP2D6 genotypes-based dosing of tricyclic antidepressants have been published by the Clinical Pharmacogenetics Implementation Consortium (CPIC). Therefore, an alternative drug is recommended for CYP2D6 or CYP2C19 ultrarapid metabolizers and for CYP2D6 poor metabolizers; 50% or 25% of dose reduction is suggested for CYP2C19 poor metabolizers and for CYP2D6 intermediate metabolizers, respectively (Hicks et al. 2013). Moreover, therapeutic drug monitoring (TDM) associated to an extensive pharmacogenetic analysis, may be useful to optimize clomipramine dosage. Here, we report on a 47-years-old woman, affected by recurrent Major depression requiring high clomipramine doses. The patient required a faster than standard upscale in the dosing of clomipramine (achieving in few days the maximum permitted intravenous daily dose of 75 mg). Subsequently, due to the difficulty to find a venous access, the administration route was changed: the maximum starting intramuscular dose (50 mg daily) was administered, in addition to 75 mg daily *per os*. A complete remission was not achieved and TDM revealed a sub-therapeutic plasma concentration. After several days, an improvement of symptoms permitted the switch to an only oral administration, although requiring a dose (225 mg daily) higher than the usual (100 mg daily). Under these conditions drug dosages were in therapeutic range and no adverse events were detected. In this scenario, pharmacogenetic analyses may be used to optimize dosing. Patient's DNA was isolated from peripheral blood cells. Genotypes were determined by Real-Time PCR using LightSNiP (TIB-MolBiol). The pharmacogenetics analysis revealed that the patient was an ultrarapid metabolizer for both genes involved in clomipramine metabolism. Indeed, she presented a CYP2C19*17 allele associated to an enhanced gene transcription and an increased metabolic activity and a CYP2D6 promoter variant (rs1080985), which has been identified recently as a major factor for the increase of gene expression and function (Llerena A et al. 2013). Based on genotypes identified in our patient it may be possible that the simultaneous presence of gain-of-function alleles in both genes involved in the clomipramine metabolic pathway resulted in a reduction of clomipramine and afterwards of its more active metabolite. These findings could explain also why after dose augmentation, the total plasma concentrations (clomipramine plus norclomipramine) and the norclomipramine levels were increased, while the clomipramine plasma concentrations were not altered. In conclusion, we propose the introduction into the clinical practice of pharmacogenetic analysis, alongside TDM, as a good tool to aid physicians in their decision-making processes.

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