Phenoconversion of Cytochrome P450 2D6: The Need for Identifying the Intermediate Metabolizer Genotype

To the Editor: Preskorn and colleagues[1] reported on an impressively large population-based study among 900 patients who recently started venlafaxine treatment and who were both genotyped and phenotyped for cytochrome P450 (CYP) 2D6 metabolism. Among these patients, 3.9% and 27.0%, respectively, were genotyped and phenotyped as a poor metabolizer. The investigators inferred that "personalized medicine solely based on genetics can be misleading."(p614) Although we agree with this statement, some issues could have been addressed more extensively to underscore the need for pharmacogenetics.

Firstly, certain comedication can cause a patient to switch from a genetically classified extensive metabolizer or intermediate metabolizer to a poor metabolizer phenotype.[2] Dose adaptation guidelines based on CYP2D6 genotype concerning, for example, codeine or tricyclic antidepressants already emphasize the important influence of such comedication on interpretation of genotype data.[3,4] Importantly, CYP-inhibiting comedication is even an experimental clinical option to obtain adequate therapeutic blood levels in ultrarapid metabolizers of CYP2D6.[5]

Secondly, the intermediate metabolizers were excluded from analyses of the effect of comedication on phenoconversion rates. This seems reasonable since their reference method for phenotyping (ratio of venlafaxine to *O*-desmethylvenlafaxine) was not able to distinguish between the poor metabolizer and intermediate metabolizer genotype.[6] To this point, we looked at the definition of intermediate metabolizers according to Preskorn et al, because there is a lot of inconsistency in the literature about this definition.[3] According to the last 2 columns of Table 2, Preskorn et al classified patients genotyped as **1*3*, **1*4*, **1*5*, or **1*6* as extensive metabolizers. According to the definitions of the Dutch pharmacogenetics working group,[7] but also by other groups,[8] these patients (n = 222 of n = 740 patients classified as extensive metabolizers according to Preskorn et al) could be classified as intermediate metabolizers,[7] or heterozygote extensive metabolizers.[8] The lower activity of the CYP2D6 enzyme in the mentioned group of 222 patients is generally accepted.[9–11] According to Table 2, the results of Preskorn et al seem to be in agreement with the lower activity of extensive metabolizers with a **3, *4, *5, or *6* mutation. Moreover, it seems that this group of intermediate metabolizer (heterozygote extensive metabolizer) patients in particular were phenotyped as poor metabolizers when comedication that influences CYP2D6 was used. We would therefore be interested in an analysis that excludes this group of intermediate metabolizers (heterozygote extensive metabolizers) or, even better, an analysis of all the intermediate metabolizer (heterozygote extensive metabolizers) genotyped patients as a different subgroup.

Finally, it would be very interesting to see how many of the 209 patients noted in Figure 1 who were genotyped as non–poor metabolizers and phenotyped as poor metabolizers have an intermediate metabolizer (including the heterozygote extensive metabolizer) genotype.

In conclusion, according to the limited information about the intermediate metabolizers displayed in Table 2, we would infer that genotyping is a powerful method of identifying intermediate metabolizers (heterozygote extensive metabolizers) who will be at risk for a poor metabolizer phenoconversion, especially if they use CYP2D6 inhibitors. Therefore, genotyping can be used as the starting point of personalized medicine together with therapeutic drug monitoring. Genotyping and therapeutic drug monitoring should not be seen separately but as a combined pharmacologic tool to predict the risk for unsatisfactory response in patients.

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