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Phenoconversion and therapeutic drug monitoring

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\textbf{Keywords:} clobazam; clozapine; genotype–phenotype mismatch; personalized medicine; pharmacogenetics; risperidone; therapeutic drug monitoring; venlafaxine.

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I would like to congratulate Shah and Smith for their excellent comprehensive review of phenoconversion [1]. They used a narrow definition of personalized medicine restricted to pharmacogenetics as they described phenoconversion as its Achilles’ heel. A more comprehensive view of personalized medicine and its application for prescribing medication, personalized prescription, considers not only genetic factors but environmental and personal factors [2]. Inhibitors, among environmental factors, and inflammation, among personal factors, can cause phenoconversion to a poor metabolizer (PM) phenotype. Personalized prescription can be implemented as personalized drug selection and personalized dosing [2]. Combining pharmacogenetics and therapeutic drug monitoring (TDM) is the best way for implementing personalized dosing [3]. Moreover, with TDM, phenoconversion is no longer a problem but a helpful piece of additional information.

Venlafaxine and risperidone TDM and CYP2D6 genotyping are described as examples. A plasma O-desmethylvenlafaxine/venlafaxine concentration ratio <1 signals the absence of CYP2D6 activity, explained by 1) genetic PM status, or 2) phenoconversion after taking a powerful CYP2D6 inhibitor, or from competitive inhibition after the use of venlafaxine itself [4]. Shah and Smith described them, respectively, as gPM and pPM [1]. Preskorn et al. [4], using this ratio, found that venlafaxine had mild CYP2D6 inhibitory properties and that 21% (159/748) of CYP2D6 extensive metabolizers (EMs) experienced phenoconversion to pPM status. Not unexpectedly, nine subjects with a genotype of CYP2D6 *4/*10 (a null allele and an allele with very low activity) had a median ratio of 1.2, since venlafaxine competitively inhibited the very limited CYP2D6 activity they had.

A risperidone TDM ratio was first used in psychiatry to detect phenoconversion during a risperidone North American randomized clinical trial (RCT) [5]. CYP2D6 EMs had higher plasma 9-hydroxyrisperidone concentrations than risperidone concentrations. If we then calculate a risperidone/9-hydroxyrisperidone ratio for CYP2D6 EMs, the ratio is <1 [6]. An inverted ratio, with higher concentrations of risperidone than 9-hydroxyrisperidone, occurred in CYP2D6 PMs and was expected in 50% of CYP2D6 EMs taking paroxetine or fluoxetine [5]. Unfortunately, the RCT risperidone TDM data
was never published by the company in a peer-review journal but was only presented in a poster. In a review article [7], graphics summarized the TDM data from the RCT by focusing on the mean values of the risperidone/9-hydroxyrisperidone ratio and the total concentration-to-dose ratio (C/D ratio), a measure of risperidone clearance from the body. The total concentration is calculated by adding the risperidone and 9-hydroxyrisperidone plasma concentrations [7].

In a naturalistic study of risperidone pharmacogenetics, 277 patients provided risperidone TDM data [8]. Table 1 shows that an inverted ratio (risperidone/9-hydroxyrisperidone ratio >1) was present in almost every CYP2D6 gPM, 95% (19/20) versus 15% (39/257) for the rest of the patients. Phenoconversion was particularly frequent, 83% (5/6), in the intermediate metabolizers [IMs] taking CYP2D6 inhibitors.

A clobazam TDM ratio may also be used to establish phenoconversion. After reviewing the clobazam literature, we have proposed that a steady-state plasma N-desmethylclobazam/clobazam ratio >25 will identify a CYP2C19 gPM as long as CYP2C19 inhibitors are absent [9]. Interpreting clozapine TDM is more complex, requiring stratification by smoking and gender because they influence CYP1A2 activity. A clozapine concentration/dose ratio of >1.20 in a US female non-smoker is suggestive of poor clozapine metabolism [10].

References


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<table>
<thead>
<tr>
<th>CYP2D6 genotyping</th>
<th>Total sample</th>
<th>On inhibitors</th>
<th>No inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>gPMs</td>
<td>95% (19/20)</td>
<td>63% (27/43)</td>
<td>6% (12/214)</td>
</tr>
<tr>
<td>Non gPMs</td>
<td>15% (39/257)</td>
<td>63% (27/43)</td>
<td>6% (12/214)</td>
</tr>
<tr>
<td>gIMs</td>
<td>43% (13/30)</td>
<td>83% (5/6)</td>
<td>33% (8/24)</td>
</tr>
<tr>
<td>gEMs</td>
<td>12% (26/219)</td>
<td>61% (22/36)</td>
<td>2% (4/183)</td>
</tr>
<tr>
<td>gUMs</td>
<td>0% (0/8)</td>
<td>0% (0/1)</td>
<td>0% (0/7)</td>
</tr>
</tbody>
</table>

Another factor influencing an inverted ratio was body weight. After excluding the CYP2D6 gPMs, a logistic regression analysis of R/9-OHR > 1 was performed. The significant variables were the number of CYP2D6 active alleles (odds ratio OR=0.18, 99% confidence interval, 0.08, 0.43), use of CYP inhibitors (OR=16.7; 6.2, 44.9), and body weight higher than the sample mean (OR=0.27, 0.10, 0.69).

Bupropion, fluoxetine or paroxetine. Bupropion is a moderate CYP2D6 inhibitor; paroxetine and fluoxetine are potent CYP2D6 inhibitors.

g refers to genetic. This is the terminology proposed by Shah and Smith [1].

Any patient who is not a gPM and has an inverted ratio would be a pPM according to the terminology proposed by Shah and Smith [1].

Phenoconversion is influenced by CYP2D6 genotype. In the 36 gEMs on inhibitors, the frequency of inverted ratios was 61%, but the prevalence varied according to the number of active alleles: 80% (12/15) in those with 1.0 active allele, 71% (5/7) in those with 1.4 active alleles, and 36% (5/14) in those with 2.0 active alleles.