CYP2D6 PHENOTYPES AMONG JAVANESE AND SUNDANESE SUBJECTS IN INDONESIA

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Received: 15 March 2019, Received and Accepted: 20 July 2019

ABSTRACT

Objective: The objective of this study was to determine CYP2D6 phenotype in a Javanese and Sundanese healthy subject in Indonesia.

Methods: Ninety unrelated healthy Indonesian subjects from Java and Sunda were studied. Metoprolol was used as phenotyping substrate. A 100 mg oral tablet of metoprolol was administered to all the subjects. Urinary metoprolol and α-hydroxymetoprolol were determined to calculate metoprolol metabolic ratio (MR). Determination of metoprolol and α-hydroxymetoprolol was carried out by high performance liquid chromatography method.

Results: Metoprolol MR varied widely (from 0.08 to 72.75). One subject (1.11%) in the study was classified as poor metabolizer (PM), one subject (1.11%) as ultrarapid metabolizer, and the remaining 88 subjects (97.78%) were classified as extensive metabolizers.

Conclusion: The frequencies of PM for the CYP2D6 phenotype (1.11%) in the Javanese and Sundanese population are in concordance with most results of oxidation metabolizers in other Asian populations.

Keywords: CYP2D6, Javanese and Sundanese, Indonesia, Metoprolol, Phenotype.
RESULTS AND DISCUSSION

Characteristics of the subjects who participated in this study can be shown in Table 1. In this study, factors that can change the absorption, distribution, metabolism, and excretion of the drug are controlled. These factors include age, pregnancy, ethnicity, pathological conditions, obesity, consumption of drugs or other compounds, and time of administration of the drug.

The MR value of the subjects had a very wide range (from 0.08 to 72.75). MR distribution patterns are displayed as a histogram in Fig. 1. As shown in the histogram, the distribution of MR showed the presence of three different phenotypes. A clear-cut point between 9.84 and 72.75 MR value was 12.6 (anti-mode). To determine metabolizer status to metoprolol, 12.6 is used as anti-mode [11]. Anti-mode for debrisoquine and metoprolol has proved equally on studies for the Turkish population and the other Caucasian population [12].

Based on the phenotyping study, there are differences in the hydroxylation capacity of metoprolol in the Javanese and Sundanese healthy subjects groups (Table 2). Metoprolol MR varied widely. The MR data are in the range from 0.1 to 74.9 with a median of 1.3. The LogMR value range is –1.1–1.9 with a median of 0.1. One subject from Sundanese women (1.11%) in the study was classified as PM, one subject from Javanese women (1.11%) as UM, and the remaining 88 subjects (97.78%) were classified as EM.

There is no evidence of significantly different between the subjects for the LogMR value between Javanese and Sundanese subjects based on the Mann-Whitney U-test (p>0.05). LogMR and MR values mostly are above the median value either for women test subjects or men. This illustrates that the metoprolol metabolism capacity of the women and men subject, in general, is similar.

The results of this study are different from the previous studies. Studies with CYP2D6 substrate, especially dextromethorphan, showed that in EM individuals, there was a shift in the value of dextromethorphan/dextrophan MR for female subjects compared to MR values in male subjects. The CYP2D6 activity in male subjects was higher than in female subjects [13]. The results of studies on other CYP2D6 substrates such as metoprolol, sertraline, mirtazapine, and propranolol showed that CYP2D6 activity was higher in male subjects than in female subjects [14].

Table 1: Characteristics of 90 subjects who participated in this study

<table>
<thead>
<tr>
<th>Subject characteristics</th>
<th>Number/ Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>19.58±1.47</td>
</tr>
<tr>
<td>Gender</td>
<td>34 (37.78)</td>
</tr>
<tr>
<td>Man</td>
<td>56 (62.22)</td>
</tr>
<tr>
<td>Female</td>
<td>80</td>
</tr>
<tr>
<td>Tribe</td>
<td>18 (20)</td>
</tr>
<tr>
<td>Javanese</td>
<td>72</td>
</tr>
<tr>
<td>Sundanese</td>
<td>57.9±7.36</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>54.9±7.36</td>
</tr>
<tr>
<td>Man</td>
<td>167.2±5.83</td>
</tr>
<tr>
<td>Female</td>
<td>156.18±5.50</td>
</tr>
</tbody>
</table>

Table 2: CYP2D6 phenotype data

<table>
<thead>
<tr>
<th>Metabolic ratio metoprolol/α-hydroxymetoprolol</th>
<th>Phenotype</th>
<th>Number of subjects</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR&lt;0.1</td>
<td>Ultra rapid metabolizer</td>
<td>1</td>
<td>1.1</td>
</tr>
<tr>
<td>0.1&lt;MR&lt;12.6</td>
<td>Extensive metabolizer</td>
<td>88</td>
<td>97.78</td>
</tr>
<tr>
<td>MR&gt;12.6</td>
<td>Poor metabolizer</td>
<td>1</td>
<td>1.1</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>90</td>
<td>100</td>
</tr>
</tbody>
</table>

MR: Metabolic ratio

Figure 1: Histogram of metoprolol/α-hydroxymetoprolol metabolic ratio from Javanese and Sundanese healthy subjects (n=90)
The frequencies of PM for the CYP2D6 phenotype (1.11%) in this study are in concordance with most results of oxidation metabolizers in other Asian populations. The prevalence of PM in the Japanese population range from 0.3 to 0.5% in the Malaysian subjects amounted to 3.9% [15], in the Iran subject of at 2.5%. CYP2D6 phenotyping study has been reported using metoprolol substrate or other substrates such as dextromethorphan, debrisoquine, and sparteine with consistent results that the presence of PM is low in Asian populations such as Japan, China, Korea, Malaysia, and Iran. Using debrisoquine as a substrate, PM on Malaysia’s population is 3.9% [15]. Using metoprolol as the substrate, the frequency of PM population in Korea, Japan, and China was 0.5%, 0.7%, and 0%, respectively [16]. The existence of PMs individual in Indonesian subjects (1.11%) is lower than PMs in European and American countries (Gaussian individuals) such as the population of Britain (8.4%) [17], Czech (8.7%), and German (8.7%) [18]. Uruguay (7.3%) [19], and Mexico (10%) [20] and African countries such as Zimbabwe (5%) [11] and Nigeria (3.5%) [21].

The probit plot (Fig. 2) of the LogMR of all subjects shows a multimodal distribution profile. The plot also clarifies the existence of three phenotypes of the hydroxylation capacity of metoprolol. Fig 1 shows that the mode value of the LogMR is −0.1. The mode values in this Indonesian subjects are shifted to the right when compared to Japanese subjects (mode: 0.7) [22]. This shows that the hydroxylation capacity of Indonesian subjects is stronger than Japanese subjects but is weaker than Chinese subjects.

This polymorphism of CYP2D6 among Javanese had similarity with the polymorphism of CYP2A6 among the same genetic ethnic of Javanese [23]. Genetically, CYP2A6*4 was found higher compared to the occurrence of CYP2A6*1 among smoking and non-smoking subject. The distribution of these allele frequencies was different among those two types of subjects.

The MR data in the CYP2D6 phenotyping study using dextromethorphan as the substrate in the Chinese population (120 people) showed a bimodal distribution and about 36% of subjects were classified as IM [24]. However, the MR value in this phenotyping study involving 90 subjects has not been able to distinguish the extensive and IM.

CONCLUSION
Indonesian healthy subjects have different capacities to metabolize metoprolol through CYP2D6. The frequency of PM of CYP2D6 phenotype (1.11%) in the Javanese and Sundanese is in conformity and comparable to other Asian populations. This study has not been able to identify IM. It needs the additional study using more subjects. Further study was needed to determine the CYP2D6 genotype in Javanese and Sundanese populations. The results of this study might be helpful in patient dose adjusting to achieve the therapeutic goals.

ACKNOWLEDGMENTS
The authors thank the Directorate General of Higher Education Ministry of Research and Higher Education of the Republic of Indonesia and all the participants who have been involved in this study.

CONFLICTS OF INTEREST
All authors have none to declare.

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