A Population PK Model for Cariprazine and the Metabolites

INTRODUCTION

Cariprazine (CAR) is a potent dopamine D3/D2 receptor partial agonist with clinical trials in Japan. Forest Research Institute, Inc. (FRI) and Gedeon Richter Plc. for the treatment of schizophrenia. 

TABLE 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CAR</th>
<th>DCAR</th>
<th>DDCAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vc</td>
<td>6.55</td>
<td>14.5</td>
<td>14.5</td>
</tr>
<tr>
<td>CL/F</td>
<td>8.55</td>
<td>14.5</td>
<td>14.5</td>
</tr>
<tr>
<td>VD/F</td>
<td>18.5</td>
<td>37.0</td>
<td>37.0</td>
</tr>
<tr>
<td>Ctr</td>
<td>0.15</td>
<td>0.15</td>
<td>0.15</td>
</tr>
<tr>
<td>ASW</td>
<td>0.15</td>
<td>0.15</td>
<td>0.15</td>
</tr>
<tr>
<td>%CV</td>
<td>70.3</td>
<td>70.3</td>
<td>70.3</td>
</tr>
<tr>
<td>%SEM</td>
<td>6.66</td>
<td>6.66</td>
<td>6.66</td>
</tr>
</tbody>
</table>

RESULTS

A total of 14613 CAR measurable plasma concentrations from 2392 patients, 13.4% were black patients. All patients had measurable CAR plasma concentrations from 2392 patients were used in the development of the model. 

The PPK models showed the data adequately. Selected goodness of fit plots are shown in Figure 3. A total number of observations at higher concentrations were underestimated by the PPK models, the overall majority of the data were explained by the models well. A total of 100 bootstrap datasets were also generated by re-sampling with replacement (2000 draws each). Each parameter estimate of the final model was within the bootstraps 90% CI. VPCs were performed with selected covariates to assess the predictability of the model adequately (the results are not shown). 

The CL/F, V/F, Vc of each moiety were statistically dependent on a function of body weight. Race, gender, and age were also statistically significant predictors of the CL/F, V/F, Vc of each moiety. No significant covariates were found to be clinically relevant (their effect ranged between 2-32%).

All patients signed an informed consent for participation in the study. All the studies were conducted in accordance with the principles of Good Clinical Practice, the Declaration of Helsinki, and applicable regulatory requirements. 

All patients were from 18 years old. Patients were treated with 15 mg/day or 30 mg/day during the first two days of treatment, followed by dose adaptation during the next 13 days.

The influence of demographics and indices of hepatic and renal function were estimated on each PK parameter separately using a step-wise generalized linear modeling approach.

The dose-normalized observed plasma concentrations for all three moieties and model predictions are shown in Figure 4. All three PPK models described the data adequately. Selected goodness of fit plots are shown in Figure 3. 

The linear population PK models adequately described the PK profiles of CAR and its two major active metabolites in patients with schizophrenia or patients with manic or mixed episodes associated with bipolar I disorder after exposure to doses ranging from 1.5 to 10 mg/day.

The FL (plasma V/F, Vc) of each moiety were statistically dependent on a function of body weight. Race, gender, and age were also statistically significant predictors of the FL, V/F, Vc of each moiety. No significant covariates were found to be clinically relevant (their effect ranged between 2-32%).

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