ROLE OF SEROTONIN 5-HT\textsubscript{2C} AND HISTAMINE H\textsubscript{1} RECEPTORS IN ANTIPSYCHOTIC-INDUCED DIABETES
A PHARMACOEPIDEMIOLOGICAL-PHARMACODYNAMIC STUDY IN VIGIBASE

François MONTASTRUC\textsuperscript{a,b,c}, Aurore PALMARO\textsuperscript{a,b}, Haleigh BAGHERI\textsuperscript{a,b}, Laurent SCHMITT\textsuperscript{c}, Jean-Louis MONTASTRUC\textsuperscript{a,b,c}, Maryse LAPEYRE-MESTRE\textsuperscript{a,b}

\textsuperscript{a}Service de Pharmacologie Médicale et Clinique, Faculté de Médecine de Toulouse, Centre Hospitalier Universitaire de Toulouse, France
\textsuperscript{b}INSERM UMR 1027, Pharmacopéïologie, Évaluation de l’utilisation et du risque médicamenteux, Université de Toulouse, France
\textsuperscript{c}Pharmacopôle Midi-Pyrénées, Centre Midi-Pyrénées de Pharmacovigilance, de Pharmacopéïologie et d’Informations sur le médicament, Toulouse, France

\textsuperscript{d}Service Hospitalo-Universitaire de Psychiatrie et Psychologie Médicale, Faculté de Médecine de Toulouse, Centre Hospitalier Universitaire de Toulouse, France

\begin{itemize}
  \item **Introduction**
  Pharmacodynamic mechanisms of diabetes induced by antipsychotic drugs remain discussed, while numerous receptors have been suspected to be involved in the genesis of this Adverse Drug Reaction (ADR).
  \item **Objectives**
  We investigated potential relationships between antipsychotics’ receptor occupancy (serotonin 5-HT\textsubscript{1A}, 5-HT\textsubscript{2A}, 5-HT\textsubscript{2C}, histamine H\textsubscript{1}, muscarinic M\textsubscript{3}, adrenergic \(\alpha\textsubscript{1}, \alpha\textsubscript{2}\) or dopaminergic D\textsubscript{1} \& D\textsubscript{2} occupancies) and reports of diabetes using VigiBase\textsuperscript{a}, the World Health Organization (WHO) global Individual Case Safety Report (ICSR) database.
  \item **Methods**
  All ADR reports from 15 first and second generation antipsychotic drugs recorded in VigiBase\textsuperscript{a} between 01/01/1994 (year of the first diabetes case-report of with clozapine) to 29/03/2013 were extracted. Logistic regression models, completed by disproportionality analysis, were used to determine the associations between antipsychotics’ receptor occupancy and ICSRs of diabetes on VigiBase\textsuperscript{a}.
  Degrees of receptor occupancy were considered calculated according to an equation derived from the pharmacological receptor theory’s model of Kenakin. Receptor occupancy theory is a useful approach to predict quantitatively the receptor-mediated pharmacological actions.
  \item **Results**
  During the study period, 94,460 reports involved at least one of the 15 antipsychotics of interest. Male/female sex ratio was 1.2 and mean age 43.7 years (±17.1). Diabetes was reported in 1,799 (1.9%) patients. Clozapine was the most frequently reported as suspected drug (n=953; 53.0%) followed by olanzapine (n=552; 30.7%) and risperidone (n=141; 7.8%). Since 1994, reports of diabetes increased with a maximum in 2011.
  The stepwise regression multivariable model including receptor binding values positively associated (i.e. serotonin 5-HT\textsubscript{1A}, 5-HT\textsubscript{2C}, histamine H\textsubscript{1}, muscarinic M\textsubscript{3} receptors (Table 1)) and adjusting for all potential confounders, showed that only serotonin 5-HT\textsubscript{2C} (AOR=2.13, CI 95% 1.72-2.64) and histamine H\textsubscript{1} (AOR=1.91, CI 95% 1.38-2.64) receptor occupancy predicted the risk for diabetes mellitus (p<0.001).

Table 1: Univariate and multivariate binary logistic regression for diabetes reports including receptor occupancies

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Diabetes Reports</th>
<th>Crude OR</th>
<th>CI 95%</th>
<th>AOR\textsuperscript{a}</th>
<th>CI 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenergic (\alpha\textsubscript{1})</td>
<td>1188 (66.1)</td>
<td>66071 (71.3)</td>
<td>0.78</td>
<td>0.71-0.87</td>
<td>0.51</td>
</tr>
<tr>
<td>Adrenergic (\alpha\textsubscript{2})</td>
<td>1111 (61.8)</td>
<td>59805 (64.5)</td>
<td>0.89</td>
<td>0.81-0.98</td>
<td>0.63</td>
</tr>
<tr>
<td>Dopamine D\textsubscript{1}</td>
<td>200 (11.1)</td>
<td>29816 (32.2)</td>
<td>0.26</td>
<td>0.23-0.31</td>
<td>0.33</td>
</tr>
<tr>
<td>Dopamine D\textsubscript{2}</td>
<td>197 (11.0)</td>
<td>25605 (27.6)</td>
<td>0.32</td>
<td>0.28-0.37</td>
<td>0.33</td>
</tr>
<tr>
<td>Histamine H\textsubscript{1}</td>
<td>1740 (96.8)</td>
<td>77843 (84.0)</td>
<td>5.71</td>
<td>4.40-7.42</td>
<td>3.63\textsuperscript{*}</td>
</tr>
<tr>
<td>Muscarinic M\textsubscript{3}</td>
<td>1611 (89.6)</td>
<td>65909 (71.1)</td>
<td>3.50</td>
<td>3.00-4.07</td>
<td>2.74\textsuperscript{*}</td>
</tr>
<tr>
<td>Serotonin 5-HT\textsubscript{1A}</td>
<td>1235 (68.7)</td>
<td>70274 (75.8)</td>
<td>0.70</td>
<td>0.63-0.77</td>
<td>0.44</td>
</tr>
<tr>
<td>Serotonin 5-HT\textsubscript{2A}</td>
<td>1740 (96.8)</td>
<td>78319 (84.5)</td>
<td>5.49</td>
<td>4.23-7.14</td>
<td>3.41\textsuperscript{*}</td>
</tr>
<tr>
<td>Serotonin 5-HT\textsubscript{2C}</td>
<td>1652 (91.9)</td>
<td>71270 (76.9)</td>
<td>3.40</td>
<td>2.87-4.02</td>
<td>2.81\textsuperscript{*}</td>
</tr>
</tbody>
</table>

\(\text{OR: Odds Ratio; AOR: Adjusted Odds Ratio; CI: Confidence Interval}\)

\(\text{\textsuperscript{*} Positively associated (p<0.001)}\)

\(\text{\textsuperscript{a} Where [Cr] represents the concentration of unbound antipsychotic. [Cr] were estimated according the “therapeutic reference ranges” reported in the “NHG Consensus Guidelines for Therapeutic Drug Monitoring in Psychiatry” and data of bound in plasma reported in pharmacological reference textbooks. Constant K characterizes affinity, defined as the ability of a drug to bind to a receptor, for antagonist drugs like antipsychotics. The K\textsubscript{d} refers to the equilibrium dissociation constant of a ligand determined in inhibition studies. We collected the different K\textsubscript{d} of the 15 studied antipsychotics for 9 different receptors potentially involved in diabetes pathophysiology and described above. These values were obtained through a search on the website IMACE (Integrative navigation in Pharmacological space)\).}

\begin{itemize}
  \item **Conclusion**
  Using an original pharmacoepidemiology-pharmacodynamic (P-E-PD) approach, our study supports that antipsychotic drugs blocking simultaneously histamine H\textsubscript{1} and serotonin 5-HT2C receptors are more frequently associated with diabetes reports in VigiBase\textsuperscript{a} than other antipsychotics. These findings should encourage investigation of histamine H\textsubscript{1} and serotonin 5-HT2C properties for predicting the risk of glycemic effects in candidate antipsychotics.
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