Background

The prevalence of cardiovascular diseases including arterial hypertension in patients with severe mental illnesses such as schizophrenia has been consistently reported to be pronounced compared to the general population [1,2]. Despite the lack of a widely accepted underlying pathophysiological mechanism, the need for effective treatment of these comorbidities remains unmet, often ending up in polypharmacy. Hence, the risk of adverse drug-reactions mediated by alterations in cytochrome P450 (CYP) enzymes’ activity can increase remarkably. Knowledge about drug-drug interactions is essential to enhance tolerability in the treatment of the psychiatric disease as well as in the treatment of the somatic disease.

Risperidone (RIS) is a second generation antipsychotic, a cytochrome (CYP) 2D6-catalyzed 9-hydroxylation leads to the major active metabolite, 9-hydroxyrisperidone (9-OH-RIS). Increasing in vitro and in vivo findings support an involvement of CYP3A4 and CYSP35 in the RIS metabolism. Amlodipine is a dihydropyridine calcium channel blocker (CCB), mainly metabolized in the liver, mainly by CYP3A4. Ramipril, on the other hand, belongs to angiotensin-converting enzyme (ACE) inhibitors and its elimination follows a rapid hepatic hydrolysis producing a major metabolite, ramiprilate.

The aim of the study was to analyze the in vivo pharmacokinetic interaction potential between RIS and first-line antihypertensive agents such as amlodipine and ramipril based upon therapeutic drug monitoring (TDM) under naturalistic conditions.

Methods

The present study is a retrospective analysis of data that were collected as part of a cooperation between the Department of Psychiatry, Psychotherapy and Psychosomatics of RWTH Aachen University Hospital, Aachen, Germany, and the Department of Psychiatry and Psychotherapy at the University of Regensburg, Germany between 2005 and 2015 as part of the clinical routine in both institutions and as part of the AGATE, (Arbeitsgemeinschaft Arzneimittelsicherheit bei psychischen Erkrankungen) (www.amuep-agate.de). The TDM database contained plasma concentrations of RIS and 9-OH-RIS of 2,293 adult risperidone medicated patients. Out of the initial sample we considered a group under concomitant medication with amlodipine (R0, n=26), a group of patients under concomitant medication with Ramipril (R1, n=25) and a risperidone monotherapy group (R2, control group, n=842). Histograms yielded evidence of non-normal distributions, so that plasma concentrations, dose-adjusted plasma concentrations (C/D) of RIS, 9-OH-RIS and active moiety (RIS+9-OH-RIS; AM) as well as the metabolic ratios (MR) were compared pairwise between the groups by conducting a non-parametrical Mann Whitney U-test (MWU) with a significance level of 0.05. The demographic data of the two groups are presented in table 1.

Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>number</th>
<th>age (years, ±S)</th>
<th>gender (females %)</th>
<th>Dosage RIS (mg/day) (median, range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0</td>
<td>26</td>
<td>61.5 ± 14.6</td>
<td>76.9</td>
<td>4.0 (1.0-8.0)</td>
</tr>
<tr>
<td>R1</td>
<td>25</td>
<td>55.9 ± 13.7</td>
<td>64.0</td>
<td>6.0 (2.0-9.0)</td>
</tr>
<tr>
<td>R2</td>
<td>821</td>
<td>40.8 ± 14.6</td>
<td>43.6</td>
<td>4.0 (1.0-10.0)</td>
</tr>
</tbody>
</table>

Discussion

Clinical guidelines for the treatment of hypertension barely consider patients with SMI including schizophrenia and often neglect the potential of pharmacokinetic interactions. CCB and ACE inhibitors are considered as first-line antihypertensive agents [3]. Patients under a combination of RIS and amlodipine had higher C/D levels of RIS, 9-OH-RIS and AM compared to patients under risperidone monotherapy. Findings imply a potential inhibiting effect of amlodipine on RIS metabolism; this effect might be mediated by CYP 2D6. Contrastingly, pharmacokinetic parameters in patients under concomitant medication with ramipril didn’t differ from the control group, implying a comparable advantage in treatment of hypertension in RIS medicated patients; further research must validate this evidence.

References: