Original Paper

Pharmacokinetic considerations in the treatment of hypertension in risperidone-medicated patients – thinking of clinically relevant CYP2D6 interactions

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Michael Paulzen[1,2], Ekkehard Haen[3,4], Gerhard Gründer[1,2], Sarah E Lammertz[1,2], Benedikt Stegmann[3,4], Koen RJ Schruers[5], Sebastian Walther[6] and Georgios Schoretsanitis[1,2,6]

Abstract

Background: Treatment of arterial hypertension in patients with severe mental illnesses often results in polypharmacy, potentially leading to drug-drug interactions. The objective of the study was to analyse the in vivo inhibitory potential of two antihypertensive drugs, amlodipine and metoprolol on CYP2D6 catalysed 9-hydroxylation of risperidone (RIS).

Methods: A therapeutic drug monitoring database with plasma concentrations of RIS and 9-hydroxyrisperidone (9-OH-RIS) of 1584 patients was analysed. Three groups were considered; a group of patients receiving RIS without a potentially cytochrome influencing co-medication (control group, R_0, n=852), a group co-medicated with amlodipine (R_A, n=27) and a group, co-medicated with metoprolol (R_M, n=41). Plasma concentrations, concentration-to-dose ratios (C/Ds) of RIS, 9-OH-RIS and the active moiety (AM), as well as the metabolic ratios were computed and compared using the Kruskal-Wallis test, the Mann-Whitney U test and the Jonckheere-Terpstra test to determine the means and different patterns of distribution of plasma concentrations as well as the concentration-to-dose ratios.

Results: The median daily dosage of RIS did not differ between the groups (p=0.708). No differences were found in median plasma concentrations of RIS, 9-OH-RIS and AM. However, concentration-to-dose ratios for RIS, 9-OH-RIS and AM were significantly higher in the amlodipine group (p=0.025, p=0.048 and p=0.005). In the metoprolol group, the concentration-to-dose ratio for RIS was significantly higher than in the control group (p=0.017), while the C/D for 9-OH-RIS and AM was not.

Conclusions and limitations: Our data show a potential pharmacokinetic interaction, most likely via CYP3A4 between amlodipine and RIS, reflected in significantly different C/Ds for RIS, 9-OH-RIS and AM. Although the interaction did not result in significantly higher plasma levels, changes in C/Ds and their distribution with regard to the median concentrations were observed.

Keywords
Therapeutic drug monitoring, risperidone, amlodipine, metoprolol, CYP2D6, interaction, pharmacokinetics

Introduction

A marked prevalence of cardiovascular diseases including arterial hypertension has been frequently reported in patients with severe mental illnesses such as schizophrenia (Bresee et al., 2010; Liao et al., 2011; Nasrallah et al., 2015). The high prevalence is followed by a concomitant need for non-pharmacological interventions and pharmacological treatment to prevent the patients from negative consequences (Hennekens et al., 2005). Some researchers reported an association between arterial hypertension, metabolic syndrome conditions and negative symptoms of schizophrenia (Sicras-Mainar et al., 2015). A plausible interpretation attributes the underlying sedentary lifestyle and lack of physical exercise to the negative symptoms, a key element of schizophrenia (Fervaha et al., 2014; Rabinowitz et al., 2012). Furthermore, antipsychotic treatment is considered to contribute to the relative risk of developing cardiovascular disease in schizophrenia. In contrast to first-generation antipsychotic agents (FGAs), second-generation antipsychotics (SGAs) are regarded as less cardiotoxic, but a chronic dopamine D_2-receptor blockade by an SGA might lead to increased sympathetic tone and consequently to hypertension and an increased risk of cardiac arrhythmia by abolishing peripheral dopaminergic modulation

[1]Department of Psychiatry, Psychotherapy and Psychosomatics, RWTH Aachen University, Aachen, Germany
[2]Jülich Aachen Research Alliance, Translational Brain Medicine, Jülich/Aachen, Germany
[3]Department of Psychiatry and Psychotherapy, University of Regensburg, Regensburg, Germany
[4]Department of Pharmacology and Toxicology, University of Regensburg, Regensburg, Germany
[5]School for Mental Health and Neuroscience, Maastricht University, Maastricht, the Netherlands
[6]University Hospital of Psychiatry, Bern, Switzerland

Corresponding author:
Michael Paulzen, Department of Psychiatry, Psychotherapy and Psychosomatics and JARA – Translational Brain Medicine, RWTH Aachen University, Pauwelsstr. 30, 52074 Aachen, Germany.
Email: mpaulzen@ukaachen.de

(Scigliano and Ronchetti, 2013). An indirect mechanism may be based upon a drug-induced alteration of metabolic homeostasis (Correll et al., 2011) and weight gain may play a mediator role in schizophrenia-related hypertension (Goff et al., 2005; Nasrallah et al., 2006). Non-pharmacological interventions as well as pharmacological treatment of metabolic syndrome conditions and especially hypertension in patients with schizophrenia may be essential in eliminating the excess mortality rate and improvement of life expectancy.

However, the pharmacological treatment of hypertension in patients with severe mental illnesses often results in multiple drug therapy. Hence, the risk of adverse drug reactions (ADRs) and the potential for drug–drug interactions (DDIs) increases exponentially (Cadieux, 1989) with an increasing number of applied drugs. Therefore predicting a potential DDI is important for the safety and tolerability of pharmacotherapy in the clinical setting. Inhibition of cytochrome (CYP) metabolism is recognized as one of the most important mechanisms of clinical DDIs and may result in serious toxicological consequences, if dosage of the substrate is not adjusted (Hiemke et al., 2011). Most of the psychotropic drugs are metabolized extensively via CYP enzymes (Stingl et al., 2013) and some somatic drugs including quinidine, terbinafine or amiodarone, which are classified as strong, moderate or weak inhibitors of CYP2D6 according to the US Food and Drug Administration classification of in vivo inhibitors of CYP2D6 (US Food and Drug Administration, 2014) have the potential to cause clinically relevant DDIs. Recently, CYP-mediated DDI and the understanding of pharmacokinetic DDI involving CYP isoenzymes have been acknowledged and several tables of drugs as substrates, inhibitors and inducers of drug-metabolizing CYP enzymes have been published (Hiemke et al., 2011; US Food and Drug Administration, 2014). However, any assessment regarding potential DDIs remains provisional considering the great number of drugs that have not been investigated yet with regard to cytochrome blocking or inducing properties.

Therapeutic drug monitoring (TDM) databases are a valuable source for a better understanding of potential pharmacokinetic interactions. Here, we investigated whether the antihypertensive drugs amlodipine or metoprolol have potential interactions with the CYP2D6-mediated risperidone (RIS) metabolism.

RIS, a benzisoxazole derivative, is a second generation antipsychotic (SGA) with selective antagonistic properties at receptors serotonin/hydroxytryptamine, HT, 5-HT_2 and dopamine (D_2) (Janssen et al., 1988). RIS has been used effectively in the treatment of schizophrenia and a broad spectrum of other psychiatric diseases over the past two decades with a low incidence of extrapyramidal symptoms (EPSs) and a lack of anticholinergic effects (Chouinard and Arnott, 1993; Leucht et al., 1999; Marder et al., 1997). The primary pathway of RIS metabolism is a CYP2D6-catalysed 9-hydroxylation and the main active metabolite is 9-hydroxyrisperidone (9-OH-RIS). Minor metabolic pathways include an oxidative N-dealkylation and 7-hydroxylation. RIS and its metabolites are eliminated via the urine and, to a much lesser extent, via the faeces. In vitro findings have revealed that CYP3A4 and CYP3A5 might also be involved in the 9-hydoxylation of RIS (Fang et al., 1999; Xiang et al., 2010; Yasui-Furukori et al., 2001). As 9-OH-RIS is pharmacologically active, clinicians consider the combined concentration of RIS and 9-OH-RIS (active moiety (AM)) as the most relevant measure. According to the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) consensus guidelines, a so-called therapeutic reference range of 20–60 ng/mL is suggested for the AM (Hiemke et al., 2011).

Amlodipine is a long-acting dihydropyridine calcium-channel blocker (CCB) acting primarily as a peripheral vasodilator (Faulkner et al., 1986). It is slowly absorbed and extensively metabolized in the liver, mainly by CYP3A4 (Kim et al., 2006). Amlodipine seems to have an enhanced safety profile in patients with concomitant diabetes (Fukao et al., 2011) and there is some evidence supporting cardioprotective effects (Kjeldsen et al., 2014; Lee et al., 2014). To date, there is no clear evidence for CYP inhibiting or inducing properties of amlodipine resulting in increased or decreased drug concentrations of concomitantly applied CYP-metabolized drugs except some data about inhibitory effects on CYP3A4 mediated metabolism of the lipid-altering 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA) reductase inhibitor simvastatin (Son et al., 2014; US Food and Drug Administration, 2014).

Metoprolol is a cardioselective beta-1-adrenoreceptor blocker without intrinsic sympathomimetic activity. Approximately 70–80% of oral metoprolol is metabolized by CYP2D6 in the liver (Li and Wang, 2006). A very recent study by Hefner et al. investigated a potential inhibitory effect of metoprolol on the CYP-mediated metabolism of venlafaxine (VEN) but found no effect on CYP2D6-catalysed formation of O-desmethylvenlafaxine (ODV). The lack of differences in plasma concentrations of VEN and ODV between the metoprolol group and the control group makes it unlikely that metoprolol could have a pharmacokinetic interaction potential via other CYP isoenzymes that are involved in VEN metabolism such as CYP3A4 or CYP 2C19, (Hefner et al., 2015).

As data on the inhibitory effects of amlodipine on CYP2D6 and/or CYP3A4/5 with regard to psychotropic drugs are missing and data about the effects of metoprolol remain inconsistent, we analysed data from a TDM survey obtained from patients whose antipsychotic treatment with RIS was individually optimized using TDM to further investigate potential effects of amlodipine and metoprolol on CYP2D6 mediated hydroxylation of RIS.

Materials and methods

The study was conducted as 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. A large TDM database containing plasma concentrations of RIS and 9-OH-RIS of 1584 patients with a broad spectrum of psychiatric diseases (exception: organic mental disorders) was analysed. Data collection took place between 2006–2015 as part of the clinical routine in different institutions as part of the Arbeitsgemeinschaft Arzneimittelsicherheit bei psychischen Erkrankungen (AGATE), a cooperation for drug safety in the treatment of psychiatric diseases (for details see www.amuep-agate.de). The database consists of 1584 samples from in- and outpatients who had been treated with RIS. Retrospective analysis of clinical data for this study was in accordance with the local regulatory authority.

We considered three groups in this naturalistic database; a group of adult patients that received RIS as an oral formulation without a potentially CYP influencing co-medication (control group, R_0) (Hiemke et al., 2011; US Food and Drug Administration, 2014), a group that was co-medicated with amlodipine (R_A) and a third group that was co-medicated with

Table 1. Patients' demographic characteristics.

Group	Number	Age (years)	Gender		DD RIS (mg/day)
			% Females	% Males	Median (range)
Amlodipine (R_A)	27	61.0 (27-80)[a]	74.1[b]	25.9	4.0 (1.00–8.0)
Metoprolol (R_M)	41	49.8 (21–87)[a]	36.6[b]	63.4	4.0 (1.00–8.0)
Control (R_0)	852	41.25 (18–87)[a]	44.2[b]	55.8	4.0 (1.00–10.0)

DD: daily dosage; RIS: risperidone.
[a]Age values in the R_A group were significantly higher than in the R_M and the control group ($p<0.001$ for Kruskal-Wallis test).
[b]Gender distributions differed between groups, with female patients being more in the R_A group than in the control group and R_M ($p=0.005$ for Kruskal-Wallis test).

Table 2. Median plasma concentrations (range) and metabolic ratios of risperidone (RIS) in the study groups.

Group	RIS	9-OH-RIS	RIS+9-OH-RIS	9-OH-RIS/RIS
Amlodipine (R_A)	5.6 (0.3–67.0)	19.00 (4.5–49.0)	30.50 (6.7–112.0)	2.00 (0.23–56.67)
Metoprolol (R_M)	6.7 (0.5–54.0)	17.00 (2.0–48.0)	26.00 (2.8–82.0)	2.90 (0.04–31.0)
Control (R_0)	4.4 (0.1–224.0)	17.00 (0.3–196.5)	24.0 (1.8–264.0)	3.8 (0.04–290.0)

9-OH-RIS: 9-hydroxyrisperidone.

metoprolol (R_M). No matching processes for age, diagnoses, severity of illness, length or onset of illness were undertaken, and information on trough value or steady-state conditions were lacking and could therefore not be considered in the study. Moreover, patients under concomitant medication with possible CYP2D6 inhibitory or CYP3A4 inhibitory or inducing properties were also excluded. Samples with missing data of RIS or its metabolite were also not included in the analysis.

Statistical analysis

The analysis included mainly the comparison of three study groups; a group receiving RIS without CYP enzyme influencing co-medication (control group, R_0), a group receiving RIS + metoprolol (R_M) and a group receiving RIS + amlodipine (R_A). We compared the medians and the distributions of the plasma concentration of RIS, 9-OH-RIS and the AM (RIS+9-OH-RIS) between the groups. Further comparisons included the plasma concentration corrected by the daily dose, the so called 'concentration-to-dose ratio', (C/D), and the ratios of 9-OH-RIS/RIS for identification of the metabolizer status. Both were calculated in accordance with the AGNP consensus guidelines (Hiemke et al., 2011). Kolmogorov-Smirnov and the Shapiro-Wilk tests of normality indicated that the data were not normally distributed. Therefore, the non-parametrical Kruskal-Wallis test (K-W) with a significance level of 0.05 was conducted. For each comparison of the two different groups (R_M, R_A) with the control group (R_0) we used the Mann Whitney U test with the same significance level. Finally, the Jonckheere-Terpstra test (J-T) was used to further assess the different patterns of distribution of the adjusted C/D. Statistical analysis was carried out using IBM SPSS Statistics version 18.0 (IBM GmbH, Ehningen, Germany).

Results

After exclusion of potentially confounding co-medications, 920 out of 1584 patients met the inclusion criteria. Data from these patients were included in the analysis and were assigned to the three groups, R_A, R_M, and R_0. The demographic data of these patients are summarized in Table 1. The amlodipine group consists of 27 patients, the metoprolol group of 41 patients, while the control group consists of 852 patients.

We conducted comparisons based upon the K-W with a nominal significance $p<0.05$. The K-W detected no differences regarding the median daily dosage of RIS (Table 1) between the three groups ($p=0.708$); the mean daily doses for RIS were 4.34 mg/d, standard deviation (SD)=2.03 in the R_0-group, 4.13 mg/d, SD=2.39 for R_M and 3.9 mg/d, SD=2.07 for R_A. Age and gender distributions showed significant differences between groups ($p<0.001$ and $p=0.005$); patients under co-medication with amlodipine were older than patients under co-medication with metoprolol and control group patients. Furthermore, there were more women in the R_A-group than in the R_0 and the R_M (see Table 1). The comparison of the distribution (subscript indices 'D') and the medians (subscript indices 'M') of the plasma concentrations of RIS, 9-OH-RIS, and the AM (RIS+9-OH-RIS) between the three groups did not yield any significant differences (RIS_D, $p=0.062$, 9-0H-RIS_D, $p=0.698$ and RIS+9-OH-RIS_D, $p=0.369$); RIS_M ($p=0.191$; 9-0H-RIS_M, $p=0.898$ and RIS+9-OH-RIS_M, $p=0.266$).

The median plasma concentrations (ng/mL) of RIS, 9-OH-RIS, the AM (RIS+9-OH-RIS), as well as the metabolic ratios (9-OH-RIS/RIS) are displayed in Table 2.

The metabolic ratio (9-OH-RIS/RIS) and the adjusted C/D for the active metabolite 9-OH-RIS did not differ between the groups (9-OH-RIS/RIS_D, $p=0.059$, 9-OH-RIS/RIS_M, $p=0.124$; C/D 9-OH-RIS_D, $p=0.125$, C/D 9-OH-RIS_M, $p=0.208$).

Table 3 shows the C/Ds (ng/mL/mg), for RIS, 9-OH-RIS and RIS+9-OH-RIS for each of the three groups.

The distribution of C/Ds for RIS and for the AM (RIS+9-OH-RIS) showed significant differences between the three study groups ($p=0.006$ and $p=0.005$ respectively) as well as the medians of C/D for RIS and RIS+9-OH-RIS ($p=0.040$ and $p=0.041$) (Figure 1).

Using the J-T to detect the different patterns of distribution of the latter parameters (C/D (RIS) and C/D (RIS+9-OH-RIS)), we

Table 3. Median concentration-to-dose ratios (C/Ds) of risperidone (RIS) in the different groups.

Group	C/D RIS	C/D 9-OH-RIS	C/D RIS+9-OH-RIS
Amlodipine (R_A)	2.27 ↑[a] (0.15–16.75)	5.16 ↑[a] (1.2–12.25)	9.12 ↑[a] (2.0–28.0)
Metoprolol (R_M)	1.93 ↑[b] (0.12–27.0)	4.35 (0.58–16.0)	7.25 (0.7–28.0)
Control (R_0)	1.16 (0.02–74.67)	4.33 (0.08–42.0)	6.29 (0.5–88.0)

9-OH-RIS: 9-hydroxyrisperidone.
[a]C/D values for RIS, 9-OH-RIS and RIS+9-OH-RIS in the R_A group were significantly higher than in the control group (p=0.025, p=0.048 and p=0.005 for Mann-Whitney *U* Test).
[b]C/D values for RIS in the RM group were significantly higher than in the control group (p=0.017 for Mann-Whitney *U* Test).

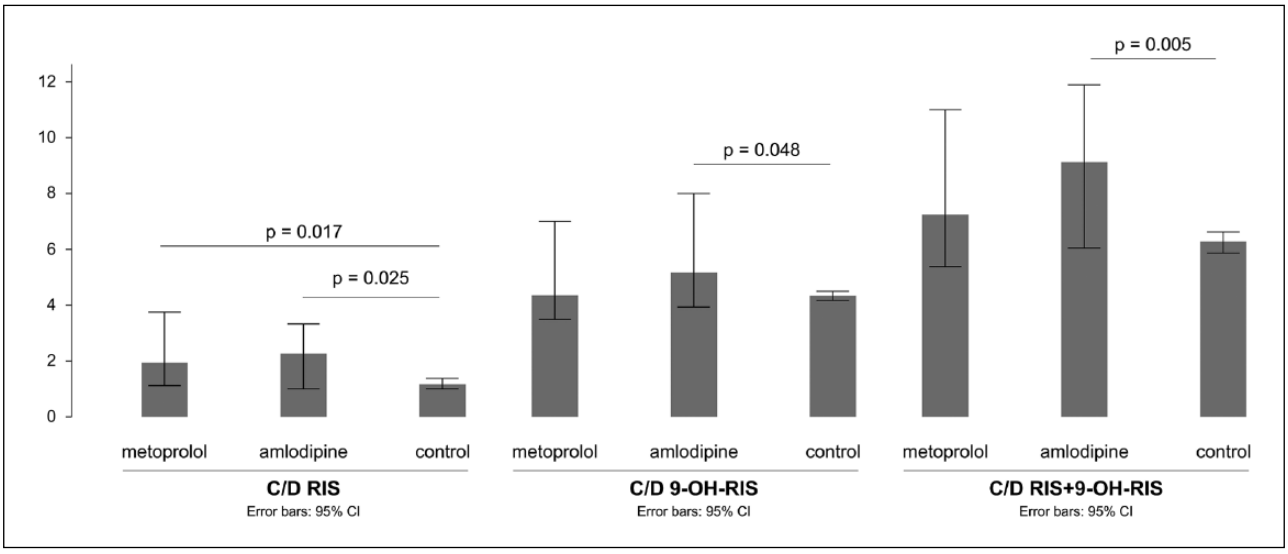

Figure 1. Median concentration-to-dose ratios (C/D) of risperidone (RIS), 9-hydroxyrisperidone (9-OH-RIS) and active moiety in the different groups. CI: confidence interval.

Table 4. Distribution of frequencies of concentration-to-dose ratios (C/Ds) of risperidone (RIS) and active moiety in the different study groups.

		Control	Metoprolol	Amlodipine
C/D RIS	>Median	416	26	18
	⩽Median	436	15	9
C/D RIS +9-OH-RIS	>Median	413	24	19
	⩽Median	439	17	8

9-OH-RIS: 9-hydroxyrisperidone.

found an ascending trend for the medians of C/D (RIS) and C/D (RIS+9-OH-RIS) between R_0, R_M and R_A (standard (std) J-T value=3.22, p=0.001 and 3.086, p=0.002), with R_0 showing the lowest and R_A showing the highest values.

A Mann-Whitney U test was used to control for significant distribution differences between pairs of groups (R_0 vs R_A and R_0 vs R_M). R_0 vs R_A revealed significant distribution differences for C/D RIS (p=0.025), C/D 9-OH-RIS (p=0.048) and C/D AM (p=0.005), with the amlodipine group showing higher values in all cases. The metabolic ratios did not differ between R_0 and R_A (p=0.182).

Comparing R_0 vs R_M yielded no differences regarding the distribution of C/D for 9-OH-RIS and C/D for AM (p=0.57 and p=0.087) while the distribution of C/D RIS significantly differed between the two groups (p=0.017), with higher values in the metoprolol group. The distribution of the metabolic ratios showed a slightly significant difference (p=0.044), with the metoprolol group demonstrating significantly lower values.

The distribution differences of C/D RIS and C/D AM between the study groups are quintessentially captured in Table 4. In the amlodipine group, the number of patients with a 'higher than the median' C/D, for the AM, RIS+9-OH-RIS, n=19, was more than twice as much as the number of patients having a lower than the median C/D (n=8). The median C/D for the AM was significantly higher in the amlodipine group (p=0.041). The C/D levels for RIS showed a similar pattern in the amlodipine group, so that patients with a 'higher than the median' C/D (RIS) were twice (n=18) as many as the ones with 'lower than the median' C/D

levels (n=9). It should be noted that the C/D (RIS) was significantly higher in the amlodipine group (p=0.04).

Discussion

Cardiovascular diseases including arterial hypertension are highly prevalent in patients with severe mental disorders such as schizophrenia and the pharmacological treatment may be essential in eliminating the excess mortality rate and improving life expectancy (Crump et al., 2013; Ringen et al., 2014). By adding antihypertensive and/or cardioprotective drugs to an ongoing antipsychotic treatment, the risk of pharmacokinetic DDIs is increasing. To predict potential DDIs, knowledge about potential CYP450 mediated interactions as one source of an increased risk is essential to enhance safety and tolerability in the treatment of the psychiatric disease as well as in the treatment of the somatic disease. Knowledge about metabolic pathways of concomitantly applied drugs and the potential of any particular drug to induce or inhibit CYP isoenzymes is of high clinical importance to prevent the patient from unwanted side effects or to prevent the patient from loss of treatment efficacy. Data from TDM surveys provide an essential source to better understand the effects of polypharmacy in clinical settings (Schoretsanitis et al., 2016). The primary aim of this study was to compare the potential of two co-medications, amlodipine and metoprolol, to inhibit CYP2D6 and/or CYP3A4/5 and thereby influence the metabolism of an antipsychotic treatment with RIS which is mainly but not exclusively metabolized via CYP2D6.

To our knowledge, information about potential pharmacokinetic DDIs between amlodipine and RIS as well as between metoprolol and RIS is lacking thus far and our findings support the notion that the selection of the optimal antihypertensive drugs should not only take psychiatric comorbidities into account but also concomitant psychotropic medication.

In our naturalistic sample, patients on a stable dose of RIS in the control group and patients who were co-medicated with amlodipine or metoprolol demonstrated considerably different patterns of plasma concentrations of RIS, 9-OH-RIS and AM as well as different patterns of C/Ds. While the daily dosage of RIS did not differ significantly between the study groups, patients that were co-medicated with amlodipine showed significantly higher median values for the C/Ds of the parent compound, C/D RIS, the active metabolite, C/D 9-OH-RIS and the AM, C/D (RIS+9-OH-RIS), than patients in the control group. Patients that were co-medicated with metoprolol showed significantly higher median values for C/D RIS while C/D 9-OH-RIS and C/D for the AM did not differ from the control group. Furthermore, the distribution of the concentration-to-dose ratios showed an interesting pattern in the sense that patients in the amlodipine group were twice as likely to show C/D levels for RIS and the AM above the median as controls. Although pharmacokinetic parameters showed a high inter-individual variability, which has been detected in other studies as well (Balant-Gorgia et al., 1999; Cabaleiro et al., 2015; Feng et al., 2008), it should be noted that we observed no additional distribution differences regarding plasma concentrations and metabolic ratios of RIS as well as the C/Ds of the active metabolite of RIS (9-OH-RIS) between the groups. To our understanding, the findings presented herein imply a potential inhibiting effect of amlodipine most likely on the CYP3A4/5 mediated metabolism of RIS, leading to significantly higher median values of the concentration-to-dose ratios of RIS, 9-OH-RIS and the AM. This hypothesis might be supported by the fact that amlodipine is metabolized via CYP3A4 on the one hand and is known to have inhibitory effects on CYP3A4 as well. The latter properties have been shown to have clinical relevance for plasma concentrations of the HMG-CoA reductase inhibitor simvastatin which is used to provide cholesterol-lowering effects (Nishio et al., 2005; Son et al., 2014). Consequentially, we suggest a moderate inhibiting effect of amlodipine on CYP3A4 leading to significantly different concentration-to-dose ratios but without significant effects on the plasma concentration of RIS and its active metabolite or the AM. This effect can have potential clinical implications with regard to clinical response and adverse effects (De Leon et al., 2005; Riedel et al., 2005), particularly since antipsychotic polypharmacy is prevalent (Gallego et al., 2012; Spina and de Leon, 2007) and in case of RIS, since 9-OH-RIS is eliminated more slowly which can be seen in a longer half-life time and a lower plasma protein binding than RIS.

As different CYP isoenzymes are involved in the metabolism of RIS to its renally excreted active metabolite 9-OH-RIS, the pharmacokinetic interaction potential of concomitantly applied drugs not only concerning their ability to influence the main metabolic pathway via CYP2D6 have to be considered. Hence, amlodipine with its impact on downstream metabolic pathways of RIS via CYP3A4 is an important example for potential pharmacokinetic interactions offside the main metabolic pathway.

The co-medication with metoprolol slightly altered the concentration of C/D RIS compared with the control group. Patients under metoprolol had higher C/D RIS values than the control group. However, this increase was not reflected in the C/D for the AM, showing no significant difference between the two groups. This illustrates a rather slight inhibitory effect of metoprolol on RIS metabolism, which was further implied by the lower metabolic ratio in the metoprolol group (p=0.044). This finding should be considered in the light of the common metabolic pathway of RIS and metoprolol, since they're both metabolized by CYP2D6. To our knowledge, no data have been reported suggesting an auto-inhibiting effect of metoprolol. Consequently, one might assume a weak effect of metoprolol on secondary metabolic pathways of RIS like CYP3A4, which can lead to a slight increase of C/D of parent compound and/or a competitive effect as both drugs are metabolized via the same pathway.

Based upon this data and from a pharmacokinetic point of view, it should be taken into account when prescribing amlodipine to an ongoing treatment with RIS that the addition leads to changes in C/Ds. This insight might reveal a comparative disadvantage when amlodipine is used as a co-medication. Calcium-channel blockers are widely assumed to be a safe and very well tolerable option for initial antihypertensive therapy (James et al., 2014); however, potential interactions, presumably mediated by the CYP450 pathway of drug metabolism, have to be considered in order to minimize adverse and/or unwanted effects. Theoretically, beta-blockers could be a more favourable choice for treating arterial hypertension in patients with schizophrenia, taking into account a possible underlying adrenergic hyperactivity (Scigliano and Ronchetti, 2013). Even though we examined only one agent of this pharmacological class, the focus should be placed on the rather disadvantageous metabolic profile of other compounds such as metoprolol which, compared to other beta-blockers, has been shown to decrease insulin sensitivity (Ayers et al., 2012; Bakris et al., 2004; Phillips et al., 2008). Taking into account the well-known risk

factors of patients with severe mental illnesses, this could be a less favourable option for the optimal antihypertensive therapy regimen.

Limitations

Our sample comprised a large population of naturalistic nature and relies on retrospective data. A significant amount of clinical parameters (onset and duration of illness, adverse effects, comorbidities, duration of drug exposure) were not available. Furthermore, there is a large individual variation in sampling time as a result of the clinical setting, which may have partially accounted for the pronounced inter-individual variation in plasma concentrations and metabolic ratios. Besides this large inter-individual variability in RIS and 9-OH RIS concentrations has been already reported in the literature during routine TDM (Balant-Gorgia et al., 1999). In the case of multiple plasma concentration determinations we minimized the patient bias by including only one analysis per patient. Regarding analyses of the data, differences in sample characteristics and sample size in the three patient groups occurred; thus the comparability of the study groups with the control group might be restricted. However, in some cases, e.g. regarding the mean age of the different study groups, it appeared plausible that patients under antihypertensive therapy would be older. Consequently, we avoided stratifying for age despite the well-known effect of age on RIS metabolism (Feng et al., 2008). Although the size of the control group is remarkably bigger, we chose not to reduce our control group taking into account the extent of the skewness of the sample distribution.

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Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article:

Ekkehard Haen received speaker or consultancy fees from the following pharmaceutical companies: Servier, Novartis and Janssen-Cilag. He is managing director of AGATE, a non-profit working group to improve drug safety and efficacy in the treatment of psychiatric diseases. He reports no conflict of interest with this publication.

Gerhard Gründer has served as a consultant for Boehringer Ingelheim (Ingelheim, Germany), Cheplapharm (Greifswald, Germany), Eli Lilly (Indianapolis, Indiana, USA), Lundbeck (Copenhagen, Denmark), Ono Pharmaceuticals (Osaka, Japan), Roche (Basel, Switzerland), Servier (Paris, France) and Takeda (Osaka, Japan). He has served on the speakers' bureau of Eli Lilly, Gedeon Richter (Budapest, Ungarn), Janssen Cilag (Neuss, Germany), Lundbeck, Roche, Servier and Trommsdorf (Aachen, Germany). He has received grant support from Boehringer Ingelheim and Roche. He is co-founder of Pharma Image GmbH (Düsseldorf, Germany) and Brainfoods UG (Selfkant, Germany). He reports no conflict of interest with this publication.

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