Risperidone-induced extrapyramidal side effects: is the need for anticholinergics the consequence of high plasma concentrations?

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Antipsychotic drugs can induce various undesirable adverse motor reactions, such as extrapyramidal side effects (EPS). A widely accepted pharmacodynamic mechanism underlying EPS includes an increase in striatal D_2-receptor occupancy. However, less is known about the pharmacokinetic background of EPS. The aim of this study was to analyze in-vivo possible pharmacokinetic patterns underlying biperiden-treated EPS in risperidone (RIS)-medicated patients. A large therapeutic drug monitoring database containing plasma concentrations of RIS and its metabolite 9-hydroxyrisperidone (9-OH-RIS) of 2293 adult inpatients and outpatients was analyzed. Two groups were compared: a group receiving RIS ($n = 772$) and a group comedicated with biperiden ($n = 68$). Plasma concentrations, dose-adjusted plasma concentrations (C/D) of RIS, 9-OH-RIS, and active moiety (AM) (RIS + 9-OH-RIS) as well as ratios of concentrations for metabolite to parent drug (9-OH-RIS/RIS) were computed. We compared the plasma concentrations of the different compounds between the two groups considering the prescription of biperiden as an indirect report of EPS. The daily dosage of RIS did not differ between groups. No differences were detected in case of plasma concentrations and C/D of RIS and active metabolite between the groups. However, plasma concentrations of the AM were significantly higher in the comedicated group ($P = 0.032$) and showed a trend in terms of the active metabolite 9-OH-RIS ($P = 0.053$). Data indicate enhanced AM plasma concentrations of RIS in patients comedicated with biperiden as an EPS treatment. This might underscore an association between higher plasma concentrations of the AM and treatment-requiring EPS. *Int Clin Psychopharmacol* **00:000–000**

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Introduction

Treatment with first-generation antipsychotics is consistently associated with a variety of undesirable adverse motor reactions, widely known as extrapyramidal side effects (EPS). These symptoms include acute dystonia, akathisia, and parkinsonism (Simpson *et al.*, 1981; Tarsy, 1983; Haddad and Dursun, 2008) or tardive dyskinesia (TD) after a prolonged antipsychotic treatment (Casey, 2004).

The development of atypical (or second-generation) antipsychotics (SGA) led to high expectations in terms of the improvement of the safety profile (Glazer, 2000; Caroff *et al.*, 2002; Gebhardt *et al.*, 2006). Accordingly, the original concept of atypical antipsychotics included the lack of EPS, but this concept has been considerably broadened to include aspects such as efficacy against negative and cognitive symptoms, lack of prolactin elevation, and efficacy in treatment-resistant patients (Gründer *et al.*, 2009). Unfortunately, EPS remains the most serious problem in patients with schizophrenia, even in the era of SGA. EPS can exert deleterious effects on the clinical outcome, compliance, and quality of life (Hammer and Haddad, 2007).

The pharmacological mechanism of EPS seems to be a relative dopamine deficiency on the basis of a striatal dopamine D_2-receptor occupancy and a relative acetylcholine excess (Ginovart and Kapur, 2012). Apart from the EPS-inducing effect, the D_2 antagonistic affinity has been considered to be the main antipsychotic property of first-generation antipsychotics. An increase in a hypothetical threshold of striatal D_2-receptor occupancy of about 80% is associated with EPS (Farde *et al.*, 1992).

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Gründer *et al.* (2009) proposed that the low incidence of EPS, which characterizes atypical antipsychotics, can be ascribed to the fact that the drugs leave dopaminergic neurotransmission in extrapyramidal motor systems intact.

Anticholinergic drugs including biperiden play a widespread and established role in therapeutic strategies for the acute management or the prevention of EPS (McEvoy, 1983). In case of parkinsonism, dose adjustment and anticholinergic drugs might be essential; in constrast, in the management of TDs, anticholinergics are not recommended. Tapering of prescribed anticholinergics and switch to SGAs may result in better efficacy (Soares and Mcgrath, 2000).

Biperiden is a weak anticholinergic agent and the mechanism of action is considered to be related to competitive antagonism of acetylcholine at cholinergic receptors in the corpus striatum, which then restores the balance in acute episodes of extrapyramidal disturbances sometimes encountered during treatment with antipsychotic agents. Despite its wide usage, the metabolic pathway of biperiden remains unclear; evidence implies an extensive hepatic extraction with the possible involvement of CYP2D6 (Grimaldi *et al.*, 1986). In terms of pharmacokinetic interactions, studies have reported a low pharmacokinetic interaction potential (Yisak *et al.*, 1993, Isawa *et al.*, 1999), whereas one study suggests biperiden as a competitive inhibitor of CYP2D6 (Ieiri *et al.*, 2003).

Risperidone (RIS) is a SGA with selective antagonistic properties at serotonin 5-HT_2-receptors and dopamine D_2-receptors (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 satisfactory safety profile (Leucht *et al.*, 1999). Nevertheless, a series of case reports have congruently shown the EPS-inducing and particularly TD-inducing effects of RIS, especially in therapeutic regimens with multiple psychotropic drugs (Saran, 1998; Hong *et al.*, 1999). Other researchers have reported a linear relationship between RIS dosage and the occurrence of EPS (Umbricht and Kane, 1996). The primary pathway of RIS metabolism is a CYP2D6-catalyzed 9-hydroxylation and the main active metabolite is 9-hydroxyrisperidone (9-OH-RIS). In-vitro findings have shown that CYP3A4 and CYP3A5 might also be involved in the metabolism of RIS (Fang *et al.*, 1999; Yasui-Furukori *et al.*, 2001; Xiang *et al.*, 2010). Preclinical studies indicated that 9-OH-RIS has ~70% of the pharmacological activity of RIS (Heykants *et al.*, 1994). Therefore, clinicians consider the combined concentration of RIS and 9-OH-RIS [active moiety (AM)] as the most relevant measure (Regenthal *et al.*, 2005). According to the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) consensus guideline, a so-called therapeutic reference range is suggested to be 20–60 ng/ml for the AM (Hiemke *et al.*, 2011).

Therapeutic drug monitoring (TDM) databases are a valuable source for a better understanding of potential pharmacokinetic interactions helping to minimize adverse effects (Spina *et al.*, 2001; Spina *et al.*, 2016) by revealing problematic drug combinations showing up in elevated or decreased drug concentrations.

Here, we analyzed data from a TDM survey conducted in patients whose antipsychotic treatment with RIS was optimized individually using TDM. Considering the individual prescription of biperiden as an indirect report of existing EPS, we investigated differences between patients under a combined treatment with RIS and biperiden and patients without anticholinergics to further investigate potential pharmacokinetic interactions as enhanced active metabolite (9-OH-RIS) concentrations in RIS-treated patients under concomitant medication with biperiden have already been reported (Balant-Gorgia *et al.*, 1999). Furthermore, we aimed to elucidate whether biperiden-medicated patients were characterized by higher plasma concentrations of RIS, 9-OH-RIS, and AM reflecting a potentially higher dopamine D_2-receptor occupancy leading to a higher incidence of EPS. We addressed the hypothesis that patients who were medicated with biperiden had higher plasma concentrations exceeding the hypothetical threshold for EPS of striatal D_2-receptor occupancy of about 80% at a higher percentage than patients without anticholinergics.

Materials and methods

The study was carried out as a collaboration 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 as part of KONBEST, a web-based laboratory information management system for TDM laboratories (Haen, 2011) containing plasma concentrations of RIS and 9-OH-RIS of 2293 patients, was analyzed. Data collection was performed between 2006 and 2015 as part of the clinical routine in different institutions of the AGATE, 'Arbeitsgemeinschaft Arzneimittelsicherheit bei psychischen Erkrankungen', a cooperation for drug safety in the treatment of psychiatric diseases, (for details, see *http://www.amuep-agate.de*). The database consists of 2293 samples from adult inpatients and outpatients who had been treated with RIS for different reasons. Retrospective analysis of clinical data for this study was carried out in accordance with the local regulatory authority.

In this naturalistic database, patients were under medication with RIS. Patients under concomitant medication with possible CYP2D6 inhibitory or CYP3A4 inhibitory or inducing properties were excluded (Hiemke *et al.*,

2011; US Food and Drug Administration, 2014). Samples with missing data of RIS, its pharmacokinetic parameters, or clinical response were also not included in the analysis. In a minimal number of cases, missing BMI data were detected and were consequently substituted by the median values.

Quantification of risperidone and 9-OH-risperidone

Blood was asked to be drawn just before drug administration (trough concentration) at steady state (>5 elimination half-lives under the same drug dose). RIS and 9-OH-RIS concentrations were determined by high performance liquid chromatography with ultraviolet detection (Bader *et al.*, 2005). The method was validated according to Deutsche Industrie Norm 32645 described in the guidelines of GTFCh (Society of Toxicology and Forensic Chemistry) in consideration of International Organization for Standardization 5725 (Paul *et al.*, 2009), FDA (US FDA) guidances (US Food and Drug Administration, 2001), and International Conference on Harmonization requirements (ICH expert working group, 1996). The laboratory regularly runs internal quality controls and participates in external quality assessment schemes by INSTAND (Düsseldorf, Germany; *http://www.instandev.de*).

Statistical analysis

The analysis included mainly the comparison of two study groups: a group receiving RIS without cytochrome enzyme influencing comedication (control group, R_0) and a group receiving RIS plus the anticholinergic agent biperiden (R_B). 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-by-dose', (C/D), and the ratios of 9-OH-RIS/RIS for identification of the CYP2D6 metabolizer status. Both were calculated in accordance with the AGNP consensus guidelines (Hiemke *et al.*, 2011). Histograms yielded evidence of non-normally distributed data so that a nonparametrical Mann–Whitney *U*-test and a median test with a significance level of 0.05 was performed. In a minimal number of cases, missing BMI data were detected and were consequently substituted by the median values. Statistical analysis was carried out using IBM SPSS statistics, version 18.0 (IBM GmbH, Ehningen, Germany).

Results

After exclusion of potentially confounding comedications, 840 out of 2293 patients fulfilled the inclusion criteria. Data of these patients were included in the analysis and were assigned to two groups: R_B and R_0. The demographic data of these patients are summarized in Table 1. The biperiden group included 68 patients, whereas the control group included 772 patients.

Table 1 Patients' demographic characteristics

Group	Number	Age (years)	BMI (kg/m^2)	Sex (%)		DD RIS [median (range)] (mg/day)
				Females	Males	
R_B	68	40.32 (18–74)	26.25	52.9	47.1	4.5 (1.00–10.00)
R_0	772	41.25 (18–87)	27.04	43.1	56.9	4.0 (1.00–10.00)

DD, daily dose; RIS, risperidone.

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 shown in Table 2.

Table 3 shows the dose-adjusted plasma concentrations, C/D (ng/ml/mg), for RIS, 9-OH-RIS, and RIS + 9-OH-RIS for each of the two groups.

Because of the skewness of the distribution, we performed comparisons on the basis of the Mann–Whitney *U*-test. The median daily dosage of RIS (Table 1) did not differ between the two groups ($P = 0.095$). Groups did not differ in demographic characteristics ($P = 0.667$ for age, $P = 0.118$ for sex, and $P = 0.144$ for BMI). The comparison of the distribution of the plasma concentrations of RIS, 9-OH-RIS, and the AM (RIS + 9-OH-RIS) between the two groups did not yield significant differences in the case of RIS ($P = 0.108$) and in the case of 9-OH-RIS ($P = 0.053$). However, in the case of the AM, patients under concomitant anticholinergic medication showed significantly higher values than the control group ($P = 0.032$) (Fig. 1). This difference was not reflected in the findings of the comparison of C/D values of AM ($P = 0.421$). Differences in the C/D values in all other cases and the ratios of concentrations 9-OH-RIS/RIS did not reach statistical significance ($P = 0.369$ for C/D RIS, $P = 0.42$ for 9-OH-RIS, and $P = 0.706$ for 9-OH-RIS/RIS, respectively).

Discussion

In our naturalistic sample of RIS-medicated patients, we considered the prescription of an anticholinergic treatment with biperiden as an indication of treatment because of EPS. We therefore sought pharmacokinetic differences not just in terms of RIS metabolism reflecting differences in the plasma concentrations of RIS, 9-OH-

Table 2 Median plasma concentrations (range) for risperidone and 9-hydroxyrisperidone in the study groups without (R_0) and with concomitant biperiden medication (R_B)

Group	RIS	9-OH-RIS	RIS + 9-OH-RIS
R_B	5.65 (0.4–143.0)	18.3 (1.4–106.0)↑[a]	27.0 (5.3–249.0)↑[a]
R_0	4.25 (0.1–224.0)	17.0 (0.3–196.5)	23.9 (1.8–264.0)

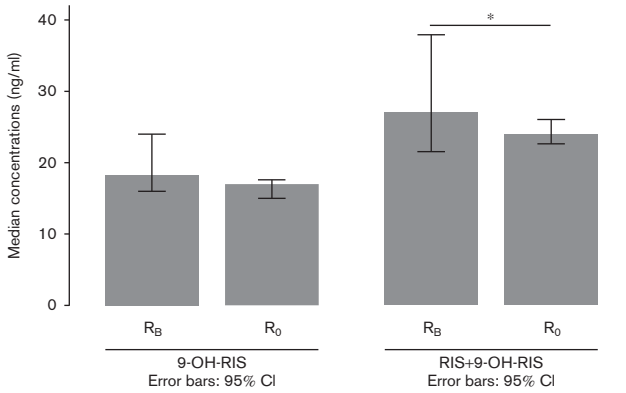
RIS, risperidone; 9-OH-RIS, 9-hydroxyrisperidone.
[a]Plasma concentration values for active moiety in patients under concomitant anticholinergic medication with biperiden were significantly higher than those in the control group ($P = 0.032$ for the Mann–Whitney *U*-test), whereas a trend was detected in the case of 9-OH-RIS ($P = 0.053$).

Table 3 Median dose-adjusted plasma concentrations of risperidone and 9-hydroxyrisperidone in the study groups without (R_0) and with concomitant biperiden medication (R_B)

Group	C/D RIS	C/D 9-OH-RIS	C/D RIS + 9-OH-RIS
R_B	1.31 (0.11–19.33)	4.69 (0.46–42.00)	6.48 (1.18–44.67)
R_0	1.12 (0.02–74.67)	4.33 (0.08–39.30)	6.16 (0.5–88.00)

C/D, dose-adjusted plasma concentrations; RIS, risperidone; 9-OH-RIS, 9-hydroxyrisperidone.

Fig. 1



Comparison of the median plasma concentrations of 9-OH-RIS and active moiety in the control group (R_0, $n = 772$) and the biperiden group (R_B, $n = 68$).*Note the significantly higher plasma concentrations for the active moiety in the biperiden group ($P = 0.032$). CI, confidence interval; 9-OH-RIS, 9-hydroxyrisperidone.

RIS, and AM between the patients receiving biperiden and patients without a concomitant anticholinergic medication. Differences reached statistical significance in case of plasma concentrations of the AM, whereas a trend was detected for plasma concentrations of 9-OH-RIS; patients with treatment requiring EPS showed higher values in both cases. These findings validate results from an older TDM study with significantly higher plasma concentrations of 9-OH-RIS in biperiden-medicated patients (Balant-Gorgia *et al.*, 1999) as well as findings from a study by Aichhorn *et al.* (2005) who found significantly higher concentrations of total plasma concentrations (AM) in biperiden comedicated patients, although the latter study additionally found significantly higher concentrations of the parent compound in the biperiden group.

There have been a series of studies assessing correlations between pharmacokinetic parameters and EPS on the basis of various scales. Because of the heterogeneity of study samples and methods, evidence has been conflicting so far. In a group of chronic schizophrenic patients, no correlation was reported between pharmacokinetic parameters of RIS and drug-induced adverse reactions including extrapyramidal and anticholinergic side effects (Mauri *et al.*, 2001). This finding was replicated by Riedel *et al.* (2005), who found no correlation between EPS and plasma concentrations, although they detected a significant role of higher RIS plasma concentrations after 2 weeks in predicting the incidence of EPS. Similarly, in a small group of Chinese patients, scores of the Simpson Angus Scale, a rating scale for drug-induced parkinsonism, did not correlate with pharmacokinetic parameters (Chen *et al.*, 2004). Similarly, in a White sample, no correlation was detected between EPS and RIS plasma concentrations (Jovanovic *et al.*, 2010); the over-representation of women in this sample may, however, limit the validity of the findings; sex and ancestry have been shown to have a critical influence on the pharmacokinetics of RIS (Feng *et al.*, 2008).

In contrast, another research group using the Simpson Angus Scale found consistently higher scores in patients with higher AM plasma concentrations (Yoshimura *et al.*, 2001; Kakihara *et al.*, 2005). A positive correlation between parkinsonian symptoms and plasma concentrations of the AM and the active metabolite was also detected in a small clinical sample (Spina *et al.*, 2001).

Nevertheless, early findings of the relationship between exceeding a threshold of dopamine D_2-receptor blockade by antipsychotic treatment and the occurrence of EPS (Yamada *et al.*, 2002) and the current presented findings of increased AM concentrations as well as the trend of higher plasma concentrations of the active metabolite, 9-OH-RIS, in the biperiden group require further clarification. Comparable receptor-binding affinities for D_2-receptors shown by RIS and 9-OH-RIS and higher concentrations of 9-OH-RIS and AM in the biperiden group might explain the occurrence of EPS and the clinical need for a treatment with the anticholinergic drug because of clinically apparent side effects. Some pharmacodynamic differences between RIS and 9-OH-RIS may offer a plausible explanation; the active metabolite has a longer half-life time and shows a lower plasma protein binding than the mother compound (Huang *et al.*, 1993; Zhou *et al.*, 2006). Furthermore, the formulation of the two enantiomers (+)-9-hydroxyRIS and (−)-9-hydroxyRIS by CYP2D6 and CYP3A4 with different dopamine D_2-receptor blocking properties may contribute toward the interpretation of these data (Yasui-Furukori *et al.*, 2001).

In sum, our data confirm the essential role of pharmacokinetics underlying undesireable clinical side effects, but still a multidimentional model mediating the susceptibility to EPS in schizophrenic patients appears to be more favorable. The data support the recommendation to measure plasma concentrations in case of side effects before starting comedication with biperiden (Hiemke *et al.*, 2011). Using TDM, it can be determined whether the dose can be reduced without the risk of loss of therapeutic efficacy.

Limitations

Our retrospective study of a large group of RIS-treated patients of naturalistic nature might present some limitations. Therefore, patient information could be considered less reliable than in the case of a prospective study. A significant number of clinical parameters including onset and duration of illness, response scales, comorbidities, adverse drug-induced reactions, and duration of previous RIS and biperiden exposure were not available, and therefore, further analyses could not be carried out. Furthermore, there might be a large individual variation in the sampling time as a result of the clinical setting, which may have partially accounted for the pronounced interindividual variation in plasma concentrations and metabolic ratios. Detached from consequences of clinical routine, a large interindividual variability in RIS and 9-OH-RIS concentrations has already been reported in the literature (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 (the most recent one). To eliminate confounding factors of the pharmacokinetic nature of plasma concentration, we excluded patients under concomitant potent modulators of CYP activity from the analysis.

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Conflicts of interest

Ekkehard Haen received speaker's 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. Christoph Hiemke has received speaker's or consultancy fees from the following pharmaceutical companies: Astra Zeneca, Janssen-Cilag, Pfizer, Lilly and Servier. He is managing director of the psiac GmbH which provides an internet based drug–drug interaction program for psychopharmacotherapy. 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, Ind, 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. Georgios Schoretsanitis received grant from the bequest 'in memory of Maria Zaoussi', State Scholarships Foundation, Greece for clinical research in Psychiatry for the academic year 2015–2016. All other authors declare there are no conflicts of interest as well. The research study did not receive funds or support from any source.

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