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PHARMACOKINETICS AND DISPOSITION

Pharmacokinetic patterns of risperidone-associated adverse drug reactions

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Abstract
Purpose The aim of the study was to investigate a correlation between plasma concentrations of risperidone (RIS), its active metabolite 9-hydroxyrisperidone (9-OH-RIS) and the active moiety (AM) (RIS + 9-OH-RIS), and adverse drug reactions (ADRs) in a naturalistic sample.
Methods Plasma concentrations of RIS, 9-OH-RIS, and AM in patients out of a therapeutic drug monitoring (TDM) database complaining ADRs were categorized according to the Udvalg for Kliniske Undersogelser side effect rating scales (UKU) (n = 97) and compared to patients without ADRs (n = 398).
Results Patients in the ADR group received a significantly lower daily dosage of risperidone (trimmed mean 3.64 mg/day) than patients without ADRs (4.40 mg/day). No differences were found for active moiety plasma concentrations between the groups (p = 0.454). Differences were detected only in the case of dose-adjusted plasma concentration values (concentration-by-dose, C/D) for 9-OH-RIS, being higher in patients reporting ADRs (4.78 ng/mL/mg) than in patients without ADRs (4.3 ng/mL/mg) (p = 0.037 for Mann-Whitney U test). Note that differences for non-adjusted 9-OH-RIS plasma levels between groups failed to reach significance (p = 0.697).
Conclusions Our findings are consistent with previous data supporting a prominent role of 9-hydroxyrisperidone, but not of risperidone with regard to ADRs. When studying the various subgroups of reported ADRs separately, the size of these subsamples offers some plausible limitations by reducing the power of the analysis.

Keywords Antipsychotics · Drug metabolism · Psychopharmacology · Schizophrenia · Pharmacokinetics

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Introduction

Risperidone (RIS) is a second-generation antipsychotic (SGA) with selective antagonistic properties at serotonin 5-HT_{2A} and dopamine D_2 receptors [1]. RIS has been used effectively in the treatment of schizophrenia and a broad spectrum of other psychiatric disorders [2, 3]. The primary pathway of RIS metabolism is a CYP2D6-catalyzed 9-hydroxylation, and the main active metabolite is 9-hydroxyrisperidone (9-OH-RIS) [4, 5]. Preclinical studies indicated that 9-OH-RIS has approximately 70 % of the pharmacological activity of RIS [6]. Therefore, clinicians consider the combined concentration of RIS plus 9-OH-RIS (active moiety, AM) as the most relevant measure. According to the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) consensus guidelines, a therapeutic reference range

is suggested as 20–60 ng/mL for the active moiety and, in order to ensure personalized psychopharmacotherapy, therapeutic drug monitoring (TDM), i.e., the quantification of serum or plasma concentrations of medications for dose optimization, has proven a valuable tool [7]. TDM studies addressing the relationship between RIS and 9-OH plasma concentrations and various adverse drug reactions (ADRs) yielded hitherto conflicting results. Regarding hyperprolactinemia, a commonly reported risperidone-induced ADRs, consistent data of Japanese researchers have demonstrated no correlation between prolactin levels and active moiety serum concentrations in schizophrenic patients [8, 9]. However, in smaller clinical samples, serum concentrations of 9-OH-RIS, but not of the parent compound (RIS), were associated with increased prolactin levels [10, 11], corroborated by a long-term study [12]. Contrastingly, this finding was not replicated in Chinese female patients [13]. A bigger study of non-medicated Chinese patients of both sexes reported no correlation between increased prolactin serum concentrations and pharmacokinetic parameters after 8 weeks of treatment with risperidone [14]. This large variability may partially be explained by the variance of the demographics of study samples. Note that the prolactin increasing effect of risperidone seems to decelerate over time in patients [12].

Another widely studied ADR includes extrapyramidal motor symptoms (EPS). The underlying pharmacological mechanism of EPS seems to be a relative dopamine deficiency based upon a high striatal dopamine D_2 receptor blockade and a relative acetylcholinergic excess [15]. A number of studies showed no correlation between pharmacokinetic parameters of risperidone and extrapyramidal side effects in samples of schizophrenic patients [16–19]. Nevertheless, some studies addressing ADRs based upon the Simpson-Angus Scale (SAS), a rating scale for drug-induced parkinsonism, found higher scores in patients with higher active moiety plasma concentrations [20, 21]. Albeit, using SAS for the assessment of EPS, other researchers reported no correlation between EPS and risperidone plasma concentrations [22]; however, the overrepresentation of females in the latter sample may limit the comparability of these results. A positive correlation between ADRs and serum concentrations of the active moiety was replicated in small samples [23, 24].

Another comprehensive ADR rating scales with well-defined and operationalized items to assess the ADRs of psychopharmacological medications is the Udvalg for Kliniske Undersogelser side effect rating scales (UKU) [25]. Olesen and colleagues did not report any relationship between serum concentrations of the active moiety of risperidone and ADRs evaluated by the UKU [26]. The small number of reported ADRs did not enable further analyses of single items or subgroups of items of the UKU. Contrastingly, in patients under a stable daily dosage of 6 mg of risperidone, serum concentrations of RIS and AM were positively correlated with ADRs assessed by the UKU. Considering the subscales of the UKU separately, authors reported a relationship between psychic (mental) ADRs and enhanced active moiety serum concentrations [27].

The aim of the study was to identify pharmacokinetic parameters such as the distribution of the plasma concentration of the unmetabolized RIS and the active metabolite 9-OH-RIS as well as the plasma concentration of the AM (RIS + 9-OH-RIS) and their relation to documented ADRs under an ongoing treatment with risperidone.

Materials and methods

The study was conducted as the 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. KONBEST, a large TDM database [28, 29] containing thousands of plasma concentrations of RIS and 9-OH-RIS, was the source of our data. In the case of multiple available plasma concentrations for one single patient, only the most recent value was included in the analysis. After adjusting the database for multiple values and after excluding patients with depot formulations, RIS and 9-OH-RIS plasma concentrations were available for 1584 adult inpatients and outpatients who had been treated with risperidone for different reasons. Data collection took place between 2006 and 2015 as part of the clinical routine in different institutions as part of the AGATE ("Arbeitsgemeinschaft Arzneimitteltherapie bei psychischen Erkrankungen"), a cooperation for drug safety in the treatment of psychiatric diseases (for details, visit www.amuep-agate.de). A retrospective analysis of clinical data for this study was in accordance with the local regulatory authority of RWTH Aachen University Hospital. For this type of study, formal consent is not required. Patients under concomitant medication with possible CYP2D6 inhibitory or CYP3A4 inhibitory or inducing properties were excluded [30]. Samples with missing data of RIS, 9-OH-RIS, and AM or missing reports of clinical state (present ADRs or no ADRs) were also not included in the analysis. In a minimal number of cases, missing body mass index data was detected and was consequently substituted by the median values. ADRs were assessed by clinicians, who provided brief written reports. Consequently, reports were classified to four major groups, psychic, neurological, autonomic, and other following the categories of the UKU.

Statistical analysis

The analysis included a main group receiving RIS without cytochrome enzyme influencing co-medication. We sought for associations between the plasma concentrations of the active moiety (RIS + 9-OH-RIS) and reported ADRs [7]. In the current analysis, we used a dummy variable encoding the presence, encoded as "1", or the absence of ADRs encoded as "0" respectively. Secondary outcomes included the plasma concentrations of RIS and 9-OH-RIS as well plasma concentrations 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 metabolizer status. Both were calculated in accordance with the AGNP consensus guidelines [7]. As the data were not normally distributed, a non-parametrical Mann-Whitney (M-W) *U* test and a median test with a significance level of 0.05 were conducted for group differences. Statistical analysis was carried out using IBM SPSS Statistics version 18.0 (IBM GmbH, Ehningen, Germany).

Results

After exclusion for potentially confounding co-medications, 495 patients met the inclusion criteria. Patients were split up into two groups: one reporting ADRs (R_{ADR}) and one without (R_0). The demographic data of both groups are summarized in Table 1. Regarding the daily dosage of risperidone, we chose to use the 5 % trimmed mean as an indicative value, taking into account the skewness of the daily dosage distributions and the daily dosage distribution differences between the two groups reported by the M-W *U* test ($p < 0.001$). We did not consider using the medians for the daily dosage since they were identical between groups.

The median plasma concentrations (ng/mL) of RIS, 9-OH-RIS, and the active moiety (RIS + 9-OH-RIS); dose-adjusted plasma concentrations [C/D, (ng/mL)/(mg/day)] for RIS, 9-OH-RIS, and RIS + 9-OH-RIS; as well as the metabolic ratios (9-OH-RIS/RIS) are displayed in Table 2.

The M-W *U* test detected no differences regarding age, gender, and the body mass index of the groups between patients with and without ADRs ($p = 0.117$, $p = 0.637$, and $p = 0.458$). However, the daily dosage values of RIS were higher in patients without ADRs ($p < 0.001$ for M-W *U* test) (mean 3.73 mg/day, SD = 1.58 for R_{ADR}, and 4.51 mg/day, SD = 2.04 for R_0). No group differences were detected in the comparison of the distribution of the plasma concentrations of the active moiety ($p = 0.454$). Further, differences failed to reach statistical significance in the case of the distribution of plasma levels of RIS and 9-OH-RIS ($p = 0.442$ for RIS and $p = 0.697$ for 9-OH-RIS). Differences in dose-adjusted plasma concentrations reached statistical significance only in the case of 9-OH-RIS ($p = 0.037$), with patients without ADRs showing lower values; no differences were detected in dose-adjusted plasma concentrations for RIS and AM ($p = 0.527$ for C/D RIS and $p = 0.129$ for C/D AM). Metabolic ratios did not differ between groups ($p = 0.681$).

Table 3 shows the most frequently reported ADRs according to the UKU. In three cases, information about the type of ADRs was not acquired and was therefore not included in the analysis.

Comparing the UKU subgroups of reported ADRs (psychic, neurologic, autonomic, and other) with the control group, R_0 yielded the following results: the group with reported psychic (mental) ADRs ($n = 16$) such as increased fatigability, concentration difficulties, and sedation received higher doses of risperidone than patients without ADRs ($p = 0.032$). No differences were found regarding the drug concentrations and dose-adjusted plasma concentrations (RIS: $p = 0.74$ and $p = 0.324$ for C/D; 9-OH-RIS: $p = 0.182$ and $p = 0.58$ for C/D; AM: $p = 0.197$ and $p = 0.651$ for C/D AM; and $p = 0.469$ for metabolic ratios).

The group reporting neurologic ADRs such as rigidity, tremor, EPS, and akathisia did not differ from the control group regarding the medians of the daily dosage ($p = 0.141$). None of the drug concentrations and the dose-adjusted plasma concentrations (C/D) in the group with neurologic ADRs differed significantly from the control group ($p = 0.55$ for RIS, $p = 0.667$ for 9-OH-RIS, and $p = 0.953$ for AM; $p = 0.976$ for C/D RIS, $p = 0.109$ for C/D 9-OH-RIS, and $p = 0.337$ for C/D AM; $p = 0.65$ for metabolic ratios).

The comparison between the group of patients reporting autonomic ADRs such as constipation, accommodation disturbances, increased salivation, and tachycardia and the control group yielded no significant

Table 1 Patients' demographic characteristics (R_{ADR} = patients reporting ADRs and R_0 = patients without ADRs)

	Number		*p* values
	97	398	
Age (years)	38.61 (18–82)	41.12 (18–85)	0.117
Body mass index (kg/m^2)	26.42	27.15	0.458
Gender (females, %)	45.4	42.7	0.637
Daily dosage of RIS (mg/day), 5 % trimmed mean (range)	3.64 (1.00–9.00)	4.40 (1.00–10.0)	<0.001

Table 2 Median plasma and dose-adjusted (C/D) plasma concentrations (range) and metabolic ratios of risperidone in the study groups (R_{ADR} = patients reporting ADRs and R_0 = patients without ADRs)

	Group		*p* values
	R_{ADR}	R_0	
RIS (ng/mL)	4.0 (0.4–46.0)	4.0 (0.2–115.0)	0.442
9-OH-RIS (ng/mL)	17.0 (0.4–87.0)	18.0 (0.3–101.0)	0.697
RIS + 9-OH-RIS (ng/mL)	23.0 (1.8–96.0)	24.0 (2.0–139.0)	0.454
9-OH-RIS/RIS	4.66 (0.14–32.5)	3.84 (0.04–125.0)	0.681
C/D RIS [(ng/mL)/(mg/day)]	1.05 (0.1–28.5)	1.0 (0.05–19.33)	0.527
C/D 9-OH-RIS [(ng/mL)/(mg/day)]	4.78 (0.20–29.00)	4.3 (0.08–42.00)	0.037
C/D RIS + 9-OH-RIS [(ng/mL)/(mg/day)]	6.73 (0.9–33.00)	5.76 (0.5–44.67)	0.129

RIS, plasma concentration of risperidone; 9-OH-RIS, plasma concentration of 9-OH-risperidone; RIS + 9-OH-RIS, plasma concentration of active moiety, 9-OH-RIS/RIS, metabolic ratio, C/D RIS, and C/D 9-OH-RIS; and C/D RIS + 9-OH-RIS, dose-adjusted plasma concentration of the aforementioned parameters

differences concerning drug concentrations and dose-adjusted plasma concentrations of RIS, 9-OH-RIS, and AM (p = 0.783 for RIS, p = 0.864 for 9-OH-RIS, and p = 0.962 for AM; p = 0.773 for C/D RIS, p = 0.172 for C/D 9-OH-RIS, and p = 0.289 for C/D AM; p = 0.568 for metabolic ratios). No differences could be observed for median drug dosage between the groups (p = 0.139 for risperidone dosage).

Finally, the group in the residual category of "other" reported ADRs such as weight gain, galactorrhea, and sexual dysfunction showed also no differences regarding the concentration and dose-adjusted concentration of RIS, 9-OH-RIS, and AM (p = 0.794 for RIS, p = 0.604 for 9-OH-RIS, and p = 0.732 for AM; p = 0.887 for C/D RIS, p = 0.301 for C/D 9-OH-RIS, and p = 0.571 for C/D AM; p = 0.384 for metabolic ratios). Median daily dosages did not differ between the groups (p = 0.715). Females tended to report more often other ADRs including weight gain, galactorrhea, and sexual dysfunctions (p = 0.018).

Discussion

In our naturalistic sample, we sought possible relationships between the distribution of drug concentrations of the active moiety of risperidone and reported ADRs. Additional analyses included risperidone and its active metabolite 9-OH-RIS plasma concentration as well as the plasma concentration adjusted by daily dosage values. Our primary objective was to determine the active moiety concentration which did not correlate with the presence of ADRs. Nevertheless, in the group of patients that reported ADRs, dose-adjusted plasma concentrations (C/D) for the active metabolite, 9-OH-RIS, were significantly higher than those in the control group that reported no ADRs. Interestingly, the patients in the ADR group received a significantly lower daily dosage of risperidone. Our findings are consistent with previous data supporting a prominent role of 9-hydroxyrisperidone, but not of risperidone with regard to ADRs such as increased prolactin, although data from other studies point to a critical effect of gender and inter-ethnic variability and both features had been shown to be of high impact on the pharmacokinetics of risperidone [31]. The mechanism underlying a possible association between an increased rate of ADRs and higher concentrations of the active metabolite 9-OH-RIS remains obscure. Some pharmacokinetic 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 [13]. Furthermore, the formulation of the two enantiomers (+)- and (−)-9-hydroxyrisperidone via CYP2D6 and CYP3A4 with different dopamine D_2 receptor-blocking properties may contribute to the interpretation of this data [32]. Note that pharmacogenetic variability at the receptor level may be an essential factor as well.

By exploring different types of ADRs according to the UKU separately, two main findings are noteworthy.

First, there was a positive correlation between a higher daily dosage of risperidone and reported psychic (mental) ADRs such as increased fatigability, concentration difficulties, and sedation. While researchers had demonstrated a

Table 3 ADRs classified into four major categories (psychic, neurologic, autonomic, and other) (n = 94)

Categories (UKU)	ADRs (%)
Psychic	16 (16.5)
Neurologic	38 (39.2)
Autonomic	18 (18.6)
Other	22 (22.7)

In three cases, data regarding the type of ADRs was not provided and was therefore not included

linear relationship between risperidone dosage and the occurrence of EPS [33], data suggesting a dose-dependent induction of psychic ADRs were missing so far. A negative association between a higher dosage of (first-generation) antipsychotic drugs and neuropsychological functioning has been frequently reported [34–36]; however, the impact of second-generation antipsychotic drugs such as risperidone on cognition has not been shown in a comparable manner or even less impairing than first-generation antipsychotics [37–39]. However, some preliminary studies reported that risperidone dose reduction led to improved cognitive function [40], while daily dosages above 5 mg were associated with poor cognitive outcomes [41]. Other studies detected no association between drug dosage and cognitive performance [42, 43]. The heterogeneity of data and the assessing methods underpinning this conflicting evidence does not allow drawing simple conclusions with regard to a dose-dependent effect of risperidone on cognition.

Secondly, female patients reported more frequently other ADRs such as weight gain, galactorrhea, and sexual dysfunctions; according to literature reviews, an increased susceptibility of females for neuroleptic-induced weight gain and its secondary effects as well as hyperprolactinemia are consistently reported [44–46]. Differing hormonal homeostasis and different tissue distributions between sexes seem to comprise the mechanism underpinning these findings [45]. By putting the pieces of the puzzle of pharmacokinetic factors leading to ADRs together, it becomes obvious that there is not an easy explanation for a relationship between pharmacokinetics and susceptibility to ADRs. A missing piece of this puzzle may incorporate individual factors such pharmacogenetics with or without the mediation of altered pharmacokinetic patterns [47–49], or other idiosyncratic factors enhanced the sensitivity for ADRs.

Limitations

Our retrospective study of a large population 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 amount of clinical parameters including onset and duration of illness, response scales, comorbidities, and duration of prior risperidone exposure was not available, and therefore, further analyses could not be undertaken. Regarding ADRs, data concerning their severity was not acquired and, therefore, could not be included in the current analysis. Furthermore, there might be an 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. Detached from consequences of clinical routine, a large inter-individual variability in RIS and 9-OH-RIS concentrations has already been reported in the literature [50]. The aforementioned factors admittedly arise considerable limitations regarding the generalizability of our evidence to certain patient populations. Another shortcoming is introduced when considering the quantification of RIS and 9-OH-RIS plasma concentrations. Notably, the analytical process also detected both risperidone and 9-OH-risperidone values below the limit of quantification. Our decision was to include these defined values into our analysis; their exclusion would, to our opinion, have led to an incomplete analysis of the plasma concentrations. Nevertheless, this methodological option may arise concerns of bias. In the case of multiple plasma concentration determinations, we minimized the patient bias by including only one analysis per patient (the most recent one). Nevertheless, this might exert a crucial influence on results if we make several assumptions, e.g., that clinicians had had time to reduce daily dosage in patients reporting ADRs based upon previous enhanced concentrations. Therefore, the results of the present study do not exclude that a concentration-ADR relationship (instead of a dose-adjusted concentration-ADR relationship) could have been revealed if the first sampling from each patient had been considered. In order to eliminate confounding factors of pharmacokinetic nature on plasma concentration, we excluded patients under concomitant potent CYP activity modulators of various pharmacological classes [51, 52]. When studying the various subgroups of reported ADRs separately, the size of these subsamples offers some plausible limitations by reducing the power of the analysis. Finally, it has to be noted that reports of ADRs were short and therefore focused on the major ADRs.

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