Eur Arch Psychiatry Clin Neurosci
DOI 10.1007/s00406-016-0736-z

ORIGINAL PAPER

Clinical response in a risperidone-medicated naturalistic sample: patients' characteristics and dose-dependent pharmacokinetic patterns

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Received: 23 June 2016 / Accepted: 25 September 2016

Abstract The purpose of this study was to disentangle an association between plasma concentrations of risperidone (RIS), its active metabolite 9-hydroxyrisperidone (9-OH-RIS) and the active moiety, AM (RIS + 9-OH-RIS), and clinical response in a naturalistic sample. Plasma concentrations of RIS, 9-OH-RIS and AM in patients out of a therapeutic drug monitoring (TDM) database were compared between responders ($n = 64$) and non-responders ($n = 526$) using the Clinical Global Impressions (CGI) Scale. Daily dosage of risperidone did not differ between responders and non-responders. Differences for active moiety plasma levels between the two groups did not reach statistical significance. However, responders showed lower plasma concentrations of the parent compound RIS as well as lower metabolic ratios RIS/9-OH-RIS than non-responders ($p = 0.017$ and $p = 0.034$). These differences did not remain after controlling for age and baseline symptoms. Furthermore, the cohort was split into two subgroups based on the daily dosage: patients under high (≥6 mg/day) (R_H, $n = 187$) and patients under lower dosages (<6 mg) (R_L, $n = 403$) of risperidone. Differences between responders and non-responders after controlling for demographic and clinical characteristics remained only for plasma concentrations of active moiety in the lower-dose medicated groups; non-responders showed higher active moiety plasma concentrations than responders. Understanding the mechanisms involved and factors associated with the clinical response in patients medicated with antipsychotics is of great interest. Our data imply that clinical response to an antipsychotic treatment cannot be attributed to a single pharmacokinetic pattern. It seems to be rather a complex patchwork of influencing factors such as demographic and clinical characteristics as well as the metabolizer status as surrogate of CYP activity. It seems that the ratio between RIS and 9-OH-RIS may play a crucial role in mediating the clinical effect.

Keywords Risperidone · Therapeutic drug monitoring · Plasma concentration · CGI · Treatment response

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Introduction

Therapeutic drug monitoring (TDM) is a specific method of clinical pharmacology for quantification and interpretation of drug concentrations in blood for dose and hence treatment optimization. It is a valuable tool of precision medicine, since it considers the high interindividual variability of pharmacokinetics for personalized psychopharmacotherapy. Benefits of TDM include the reliable assessment of treatment adherence, dose adjusting in cases of missing response, monitoring of side effects [33, 34] and a

Published online: 01 October 2016

less complicated drug titration in terms of switching from an oral to a long-acting injectable form of medication—and back [5]. Therapeutic drug monitoring databases, i.e., collections of clinical and non-clinical parameters associated with a psychotropic drug treatment, are a valuable source for a better understanding of potential pharmacokinetic interactions, thereby helping to minimize adverse effects [27, 28, 33].

Risperidone (RIS) is a second-generation antipsychotic (SGA) with selective antagonistic properties at serotonin 5-HT_2 and dopamine D_2 receptors that has been used effectively in the treatment of a broad spectrum of psychiatric diseases over the last two decades [12, 46, 47]. The primary pathway of RIS metabolism is a cytochrome CYP2D6-catalyzed 9-hydroxylation, and the main active metabolite is 9-hydroxyrisperidone (9-OH-RIS) which is mainly eliminated by renal excretion. In vitro findings have revealed that CYP3A4 and CYP3A5 might also be involved in the metabolism of risperidone [43]. Preclinical studies indicate that 9-OH-RIS has approximately 70 % of the pharmacological activity of RIS [15]. Therefore, 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 is suggested as 20–60 ng/mL for the active moiety [16].

Although several studies tried to assess pharmacokinetic parameters of risperidone and its metabolite and clinical outcome [23], an irrefutable therapeutic concentration window or reference range based upon TDM data for controlling psychiatric symptoms has not yet been fully established even with regard to different core symptoms of treatment decisions. So it is not surprising that clinical trials attempting to correlate drug concentrations and clinical outcome failed so far, underscoring the difficulties to align drug concentrations and clinical response [29]. However, the only way to better define therapeutic windows or reference ranges is to better explore the correlation between plasma concentrations of both, RIS and 9-OH-RIS, and clinical outcome in patients undergoing a treatment with risperidone.

Studies that had been dedicated to this issue have been hitherto contradictory and do not provide clear evidence of the value of TDM for the assessment of the efficacy in risperidone-treated patients. A small clinical trial failed to detect a linear correlation between any pharmacokinetic parameters and clinical scales using the Positive and Negative Syndrome Scale, PANSS [20], a finding that was later replicated in bigger samples [18, 41]. Interestingly, no pharmacokinetic patterns, e.g., plasma concentrations of RIS and 9-OH-RIS, could be correlated with specific disease stages such as acute versus chronic or in patients with a first episode of schizophrenia as well [40].

Nevertheless, other studies have indicated associations between clinical response and pharmacokinetic parameters. In a group of acutely exacerbated schizophrenic patients under a stable daily dosage of 6 mg risperidone, plasma concentrations of RIS and AM were related to clinical response, assessed by improvement in the Brief Psychiatric Rating Scale (BPRS) [45]. Another study illustrated a curvilinear correlation between plasma levels of the active moiety and therapeutic response [22]. Hints for such a curvilinear correlation were also reported by Odou et al. [25]; however, findings of this study did not reach statistical significance. Another research group used diverse scales to assess therapeutic response; correlations were detected between pharmacokinetic parameters (9-OH-RIS and AM) and the Global Assessment of Functioning Scale (GAF) changes but not in PANSS [1]. A single study reported a negative correlation between clinical response (assessed by PANSS) and plasma levels of AM; researchers attributed this finding to a possible involvement of genetic factors or disturbances in the metabolic pathway of risperidone in non-responders [31]. Similarly, a negative correlation was reported between AM concentrations and cognitive performance [6].

Taken together, a striking discrepancy is observed regarding findings of studies on pharmacokinetic patterns and clinical response in patients under a treatment with risperidone. There is a series of methodological factors that might explain the lack of consensus; the heterogeneity of the clinical response criteria applied in the various studies may substantially account for the conflicting evidence. Moreover, studies over the last decades consistently reported a high inter-patient variation in pharmacokinetic parameters of risperidone, attributed to important factors such as age, genetic variability and drug–drug interactions (DDI) [3, 15, 35]. This variability is barely taken into account in a considerable number of these studies. Furthermore, risperidone dosages are rarely fixed, and therefore, pharmacokinetic parameters can extremely vary between the different trials.

Consequently, the predictive role of TDM still remains insufficiently validated despite being a common clinical practice. Hence, the aim of this study was to identify pharmacokinetic parameters of risperidone closely related to clinical response, taken into account the critical but unmet need for more sensitive prediction of treatment response in the treatment of different psychiatric diseases.

Materials and methods

A large TDM database as part of KONBEST (www.konbest.de), a web-based laboratory information management system for TDM laboratories [14] containing plasma

concentrations of RIS and 9-OH-RIS of 2293 pseudonymous samples from adult in- and outpatients who had been treated with different dosing regimens of risperidone for different reasons of which 1584 patients received risperidone as an oral formulation, was analyzed. Data collection took place between 2006 and 2015 as part of the clinical routine in different institutions as part of the AGATE, 'Arbeitsgemeinschaft Arzneimittelsicherheit bei psychischen Erkrankungen,' a cooperation for drug safety in the treatment of psychiatric diseases (for details, see www.amuep-agate.de). Retrospective analysis of clinical data for this study was in accordance with the local regulatory authority of RWTH Aachen University Hospital.

In this naturalistic database, patients were under medication with risperidone (RIS) for different reasons, and only patients with organic mental disorders were excluded. Patients that received depot formulations and patients that were under concomitant medication with possible CYP2D6 inhibitory or CYP3A4 inhibitory or inducing properties were also excluded from analysis as well as samples with missing data of RIS, its pharmacokinetic parameters or clinical response [16, 39]. Data regarding clinical response assessed with Clinical Global Impressions (CGI) Scale [13] were acquired by treating clinicians with regard to the current medication. The Clinical Global Impressions (CGI) Scale comprises two one-item measures: one for severity, rated from 1 to 7 points (CGI-S), and other for improvement, rated from 1 to 5 points (CGI-I). Patients were classified as responders if they showed a CGI (CGI-I) of one (very much improved) or two (much improved), while patients with a CGI-I higher than two were classified as non-responders. Information of side effects was explicitly available only in some patients, and lacking information on side effects may be interpreted as an absence of side effects. However, as data about side effects were not available for every patient, the information was not included in the analysis as an additional measure of clinical response.

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). Risperidone and 9-OH-risperidone concentrations were determined by high-performance liquid chromatography (HPLC) with ultraviolet detection (HPLC/UV) [2]. The method was validated according to DIN 32645 (Deutsche Industrie Norm 32645, described in guidelines of GTFCh (Society of Toxicology and Forensic Chemistry) in consideration of ISO 5725 (International Organization for Standardization) [26], FDA (US Food and Drug Administration) guidances [38] and ICH (International Conference on Harmonization) requirements [17]. The laboratory regularly runs internal quality controls and participates in external quality assessment schemes by INSTAND (Düsseldorf, Germany, www.instandev.de). The limit of detection (LOD), defined as signal-to-noise ratio of 3:1, was 5 ng/ml for both risperidone and 9-OH-risperidone. The inter-day precision, determined as duplicates on three different days at 5 ng/ml, was 5.56 % of mean and 5.21 % of mean, respectively. Usually twice the limit of detection is accepted as limit of quantification (LOQ). However, the analytical process using HPLC with ultraviolet detection (HPLC/UV) also detects both risperidone and 9-OH-risperidone values below the LOQ, and we decided to include these defined values into our analysis as they were true values above 0.

Statistical analysis

The analysis included a main group receiving RIS without cytochrome enzyme influencing co-medication [39]. We sought for associations between the plasma concentration of active moiety (RIS + 9-OH-RIS) and the clinical response assessed with Clinical Global Impressions improvement (CGI-I) scores [13, 39]. For this purpose, we transformed CGI-I to a dichotomous variable with '0' for non-response and '1' for response. In the current analysis, a responder was defined as someone demonstrating a CGI-I value of one (very much improved) or two (much improved). Patients with CGI-I of more than two were classified as non-responders. Secondary outcomes included the plasma concentrations of RIS and 9-OH-RIS plasma concentrations as well as plasma concentrations corrected by the daily dose, the so-called concentration-by-dose (C/D). These were computed in accordance with the AGNP consensus guidelines [16]. Finally, we included the ratios of RIS/9-OH-RIS, which is considered as a reliable measure of CYP2D6 activity [8, 21]. As the data were not normally distributed, a nonparametric Mann–Whitney U (M-W-U) test with a significance level of 0.05 was conducted for group differences. To control for the effect of covariates, we used a robust bootstrapping analysis of covariate (ANCOVA) with the same significance level. Statistical analysis was carried out using IBM SPSS Statistics version 18.0 (IBM GmbH, Ehningen, Germany).

Results

After the exclusion of patients due to potentially confounding co-medications (for a detailed list, see [39]), 590 out of 1584 patients met the inclusion criteria. The demographic and clinical data of responders and non-responders are summarized in Table 1.

Table 1 Patients' demographic and clinical characteristics

Group	Number	Age (years)	BMI (kg/m^2) median (range)	Gender (% females)	CGI-S median (range)	DD RIS (mg/day) median (range)
Responders	64	46.1 (18–82)	28.0 (16–49)	56.3	5 (2–6)	4.0 (1.00–10.0)
Non-responders	526	40.9 (18–87)	27.0 (16–58)	43.9	5 (2–7)	4.0 (1.00–10.0)

Table 2 Median plasma concentrations (range) and metabolic ratios in the study groups

Group	RIS	9-OH-RIS	RIS + 9-OH-RIS	RIS/9-OH-RIS
Responders	2.8 (0.2–52.0) ↓*	15.0 (1.4–101.0)	19.7 (2.0–107.0)	0.15 (0.1–3.5) ↓*
Non-responders	4.3 (0.2–224.0)	17.0 (0.3–196.5)	24.3 (1.8–264.0)	0.25 (0.01–23.68)

* Plasma concentration values and metabolic ratios for RIS in responders were significantly lower than in non-responders ($p = 0.017$ and $p = 0.034$ for Mann–Whitney U test)

Table 3 Median dose-adjusted plasma concentrations (C/D) of risperidone in the different groups

Group	C/D RIS	C/D 9-OH-RIS	C/D RIS + 9-OH-RIS
Responders	0.67 (0.04–13.00)	4.58 (0.35–16.83)	5.81 (0.5–21.00)
Non-responders	1.1 (0.05–74.67)	4.4 (0.08–42.00)	6.05 (0.5–88.00)

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

Table 3 shows the dose-adjusted plasma concentrations, C/D, in [ng/mL/mg], for RIS, 9-OH-RIS and RIS + 9-OH-RIS for each of the two groups.

The M-W-U test detected no differences between responders and non-responders regarding gender and body mass index of the groups ($p = 0.061$ and $p = 0.069$). However, responders were older than non-responders ($p = 0.011$). Similarly, the median daily dosage of RIS did not differ significantly between the two groups ($p = 0.08$) (mean daily dose 3.86 mg/day, SD = 2.00 for responders and 4.35 mg/day, SD = 1.99 for non-responders). Furthermore, non-responders showed higher baseline CGI scores than responders ($p = 0.001$). Differences regarding the plasma levels of active moiety between the groups did not reach statistical significance ($p = 0.109$). The comparison of the distribution of the other plasma concentrations between the two groups yielded significant differences only for RIS, with responders showing lower plasma concentrations of the parent compound ($p = 0.017$), but not for 9-OH-RIS ($p = 0.510$, see Fig. 1; Table 2). No significant differences were detected for dose-adjusted plasma concentrations between the two groups ($p = 0.94$ for C/D AM, $p = 0.131$ for C/D RIS and $p = 0.314$). However, metabolic ratios were significantly lower in responders ($p = 0.034$, see Fig. 2).

To control for the effect of age and the initial CGI scores (CGI-S) on plasma concentrations of RIS and metabolic ratios, we used a bootstrapping ANCOVA. Hereafter, differences did not remain significant, neither for RIS nor for metabolic ratios ($p = 0.16$ and $p = 0.389$).

Taken the huge interindividual variability in daily dosages into account, we then split the sample on the basis of the daily risperidone dosage into two distinct dosage groups: patients who received high dosages (≥6 mg/day) (R_H, $n = 187$) and those who received lower dosages (<6 mg) (R_L, $n = 403$) of risperidone. We repeated the comparisons between responders and non-responders using the Mann–Whitney U test (M-W-U) in both subsamples. In the high-dosage group (R_H, $n = 187$), no significant differences regarding pharmacokinetic parameters other than plasma concentrations of the active metabolite ($p = 0.046$) were detected between responders ($n = 16$) and non-responders ($n = 171$). The percentage of responders in the high-dosage group was 8.55 % ($n = 16$). The median daily dosage of risperidone did not differ between these two groups ($p = 0.945$). However, the two groups differed in terms of gender and age ($p = 0.005$ and $p = 0.044$). Plasma concentrations and C/D values of RIS did not differ between the groups ($p = 0.948$ and $p = 0.975$). Similarly, no differences were detected in case of the active moiety ($p = 0.160$ for AM and $p = 0.214$ for C/D AM) and metabolic ratios ($p = 0.322$). There was a trend considering differences for C/D of 9-OH-RIS values between the groups, which did not reach statistical significance ($p = 0.06$). Due to age and gender distribution differences, we conducted a bootstrapping ANCOVA with age and gender as covariates to detect possible effects on 9-OH-RIS differences between

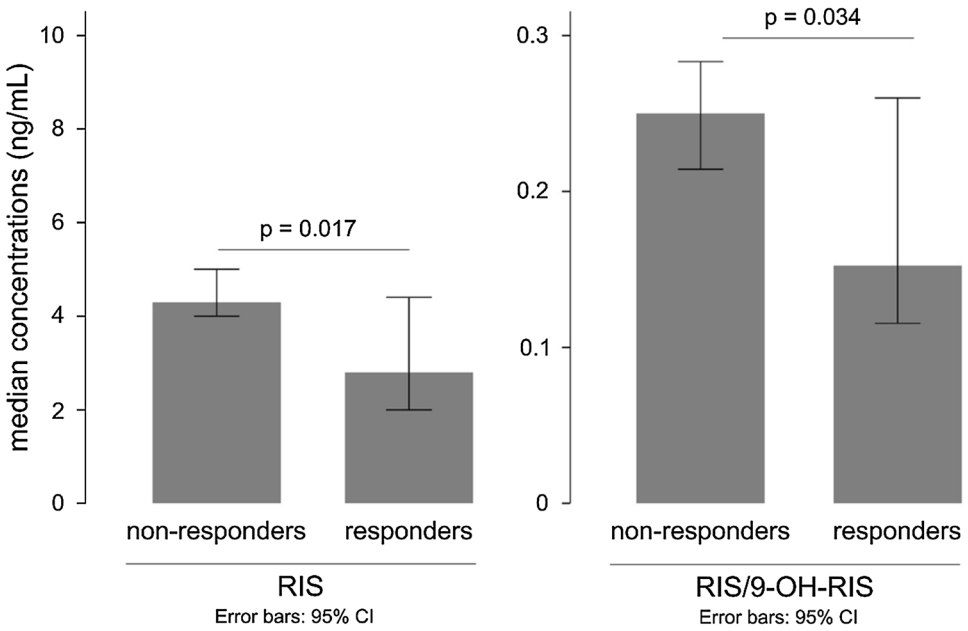

Fig. 1 Plasma concentrations of RIS were significantly higher in the non-responder group ($p = 0.017$), and responders showed a significantly lower metabolic ratio (RIS/9-OH-RIS), $p = 0.034$

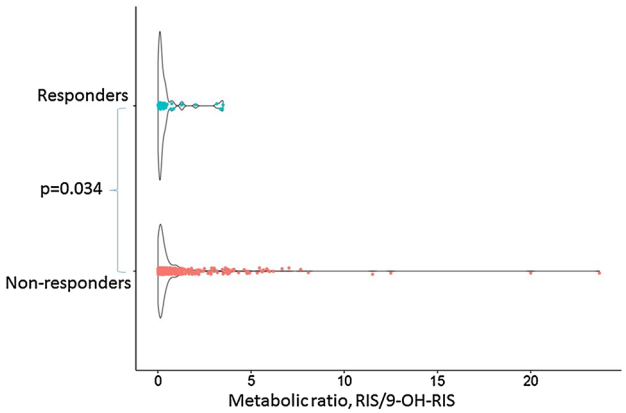

Fig. 2 Responders showed a significantly lower metabolic ratio (RIS/9-OH-RIS), $p = 0.034$

the groups. The differences for 9-OH-RIS values between responders and non-responders did not remain significant after controlling for age and gender ($p = 0.146$).

Consequently, we conducted the M-W-U test in the subgroup of patients under low daily dosages of risperidone (R_L, $n = 403$). The percentage of responders in the low-dosage group was 11.91 % ($n = 48$). Median daily dosage of RIS did not differ between responders and non-responders ($p = 0.662$). Plasma concentrations but not C/D values of RIS were higher in non-responders than in responders ($p = 0.009$ and $p = 0.072$). Similarly, plasma concentrations but not C/D values of AM were higher in non-responders ($p = 0.044$ and $p = 0.481$). Plasma concentrations and C/D levels of 9-OH-RIS did not differ between the groups ($p = 0.388$ and $p = 0.908$). Differences regarding metabolic ratios did not reach statistical significance ($p = 0.055$). Regarding demographic characteristics, the two groups had similar age and gender distribution ($p = 0.079$ and $p = 0.661$), but differed regarding BMI ($p = 0.04$); responders had higher BMI values than non-responders. Moreover, the two groups differed regarding baseline CGI scores ($p = 0.001$), with non-responders showing higher CGI-S scores than responders. To control for the effect of BMI and CGI-S scores on plasma concentrations of RIS and AM, we used a robust bootstrapping ANCOVA, after which differences between groups remained significant only for AM ($p = 0.021$), but not for RIS plasma concentrations ($p = 0.385$).

Discussion

The detection of pharmacokinetic patterns underlying clinical response to psychotropic agents not only represents a clinical relevant issue, but is indeed a complex scientific challenge [29]. Our study addressed the relation between clinical response and the plasma concentrations of risperidone, its active metabolite and the active moiety in a big naturalistic sample of patients. Additionally, emphasis was put on the effect the dose-adjusted plasma concentrations and the metabolic ratios for each compound, RIS, 9-OH-RIS and AM. The comparison of patients classified as responders versus non-responders revealed differences in case of the plasma concentrations of RIS and metabolic ratios. Our primary outcome was that the active moiety plasma concentration did not correlate with the clinical response. Nevertheless, responders demonstrated lower

plasma concentrations of RIS as well as lower metabolic ratios implying a relationship between the metabolic phenotype and clinical response. In other words, in our sample, patients with a relatively higher proportion of the active metabolite 9-OH-RIS, i.e., a lower metabolic ratio (RIS/9-OH-RIS), were more likely to respond to a treatment with risperidone. This finding is thus one further addition to the findings of a previous study by de Leon, indicating that a CYP2D6 poor metabolizer status might be associated with a higher rate of adverse drug reactions and a higher frequency of drug discontinuation [9]. Differences in 5-HT_{2A}/D_2 binding ratios and the presence of a hydroxyl group in the 9-OH-RIS molecule increasing hydrophilicity might explain slightly differential pharmacological effects between 9-OH-RIS and the parent compound [7], thereby leading to distinct clinical effects. However, in our sample no genetic data were available, so that a comparison of findings faces some obvious obstacles. Moreover, if we consider that a metabolic ratio above one implies a reduced or even lack of CYP2D6 activity, we cannot attribute a CYP2D6 phenotype of poor metabolizer to any of the study groups in our sample.

As baseline clinical parameters (assessed with CGI-S) and age seemed to account essentially for this relationship, we controlled for age and baseline CGI scores (CGI-S) between the groups and found no differences in pharmacokinetic parameters. Apparently, clinical and demographic characteristics might essentially account for the prediction of treatment response.

Another essential factor for clinical response was the daily dosage of risperidone, when examining for differences after splitting patients into a group of patients with relatively high daily dosages of ≥6 mg/day and a group with lower daily dosages of <6 mg/day. In patients with high daily dosages, differences were found in 9-OH-RIS plasma concentrations between responders and non-responders. However, this difference did not remain significant after controlling for age and gender.

Given lower response rates in patients under daily dosages above 6 mg/day, we hypothesize that in clinical practice, dose escalation might be undertaken in case of lacking clinical response omitting the fact that in the absence of any response to a drug, dose escalation often does not lead to benefits in clinical response. In these cases, the lack of clinical response is not due to low plasma concentrations but due to a fundamentally missing response to a drug itself. Dose escalation apparently leads to enhanced plasma concentrations hampering the detection of specific pharmacokinetic patterns associated with clinical response. On the other hand, in patients under a daily dosage of less than 6 mg, non-responders showed higher plasma concentration of RIS and AM ($p = 0.009$ and $p = 0.045$). Responders and non-responders with daily dosages below 6 mg differed regarding the BMI and CGI-S scores. After controlling for the effect of these factors, a significant difference between responders and non-responders only remained regarding AM. This finding aligns with the negative correlation between plasma concentrations of the AM and the clinical response reported by Riedel et al. [31] who interpreted the evidence considering an interference of additional factors such as a high genetic variability. Alternatively, alterations in phase-II drug metabolism in non-responders were assumed. Another research group detected a negative relationship between cognitive performance and AM plasma concentrations [6]. This finding was considered in the light of an inverse U-shaped relation between clinical response and AM plasma concentrations [22], albeit the comparability of these findings might present some limitations due to the dosage variability in patients.

Taken together, our data imply that clinical response to an antipsychotic treatment cannot be attributed to a single pharmacokinetic pattern. It seems to be rather a complex patchwork of influencing factors such as demographic and clinical characteristics as well as the metabolizer status as surrogate of CYP activity. It seems that the ratio between RIS and 9-OH-RIS may play a crucial role in mediating the clinical effect. The therapeutic reference range for risperidone is widely accepted [16] but has not yet been clinically established even with regard to different core symptoms of distinct psychiatric diseases. Based on our data and from a pharmacokinetic point of view, more elaborated models are demanded in order to fully understand the pharmacokinetics of clinical response to a risperidone treatment. Demographic and clinical factors seem to have an immense impact on the pharmacokinetic patterns and should be taken into account when considering optimal therapeutic ranges of pharmacokinetic parameters. Moreover, pharmacokinetics of risperidone and clinical response to it may present dose-dependent features. The detection of clear pharmacokinetic patterns underlying response was further perplexed by the large interindividual variation of risperidone plasma levels in patients. Another missing piece of the puzzle of clinical response may represent pharmacogenomic mechanisms. Increasing data support the possible involvement of genetic polymorphisms without accompanying altered pharmacokinetic patterns in antipsychotic therapeutic efficacy [19, 24, 30, 36, 42, 44]. Therefore, further investigations incorporating multiple aspects, overcoming the limitations of this retrospective study, are demanded to disentangle the relationship between clinical response and drug concentrations, thereby facilitating the establishment of a decision-making algorithm toward a precision medicine based on findings of therapeutic drug monitoring.

Limitations

The findings of our retrospective analysis of a large population of naturalistic nature should be considered in the light of some limitations. Patient information could be considered less reliable than in case of a prospective study. A significant amount of clinical parameters including onset and duration of illness and/or episode, duration of treatment and adverse effects, diagnoses and comorbidities was not available limiting further analyses. Furthermore, although drawing of blood was asked at trough-level times, there may be 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. Detached from consequences of clinical routine, a large inter-individual variability in RIS and 9-OH-RIS concentrations has been already reported in the literature [3]. In the case of multiple plasma concentration determinations, we minimized the patient bias by including only one analysis per patient (the most recent one). The remarkably bigger size of the non-responder group was rather expected, since the response rates in patients with severe mental illnesses are heterogeneous [10, 11, 32, 37]. Evaluation of clinical state and therapeutic response was based upon the CGI Scale, which is not a diagnose-specific instrument. Furthermore, its structural properties may present some considerable restrictions to the consistency of the clinical assessment [4]. Another essential limitation must be seen in the temporal dimension. Information of the time point of the clinical global impression (CGI)-improvement assessment was not available, and therefore, we were not able to estimate the overall duration of the risperidone treatment for each individual. Moreover, it was unclear whether the baseline CGI preceded the initiation of risperidone therapy. It is also important to note that in a crucial number of patients, information about side effects was lacking. Lacking information about side effects reduces the power of our findings. Despite the multiple comparisons, we chose not to conduct corrections since all these comparisons address the same basic question in a different way, with variables being hardly independent from each other. However, a considerable risk for type I errors has to be taken into account. Additionally, alternative measures such as dose per bodyweight and concentration per dose and bodyweight could have provided a valuable insight when interpreting our findings; we chose not to include them since they are less frequently embraced in the adult psychiatry. Finally, in order to eliminate confounding factors of pharmacokinetic nature on plasma concentration we excluded patients under concomitant potent modulators of CYP activity from the analysis.

Acknowledgments The authors wish to express their gratitude to the number of people who contributed with excellent professional technical as well as pharmacological competence to build up the KONBEST database with 50.049 clinical pharmacological comments as of February 2, 2016 (ranked among the professional groups in historical order):

A. Köstlbacher created the KONBEST software in his Ph.D. thesis based on an idea of E. Haen, C. Greiner and D. Melchner along the workflow in the clinical pharmacological laboratory at the Department of Psychiatry and Psychotherapy of the University of Regensburg. He maintains together with his colleague A. Haas the KONBEST software and its data mining platform (Haas & Köstlbacher GbR, Regensburg/Germany).

The lab technicians performed the quantitative analysis: D. Melchner, T. Jahner, S. Beck, A. Dörfelt, U. Holzinger and F. Pfaff-Haimerl.

The clinical pharmacological comments to drug concentrations were composed by licensed pharmacists and medical doctors: Licensed pharmacists: C. Greiner, W. Bader, R. Köber, A. Hader, R. Brandl, M. Onuoha, N. Ben Omar, K. Schmid, A. Köppl, M. Silva, B. Fay, S. Unholzer, C. Rothammer, S. Böhr, F. Ridders, D. Braun, M. Schwarz; M. Dobmeier, M. Wittmann, M. Vogel, M. Böhme, K. Wenzel-Seifert, B. Plattner, P. Holter, R. Böhm, R. Knorr.

Furthermore, the authors thank Dr. S. Lammertz and Mr. Nikos Perpinias for their expertise in translating numbers into intriguing figures.

Authors' contributions GS, MP, GG, CH, EH, BS and SU participated in research design; GS and MP performed data analysis. GS, MP, GG, CH, EH, BS and SU wrote or contributed to the writing of the manuscript.

Compliance with ethical standards

Conflict 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 nonprofit 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, Hungary), 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 no conflicts of interest as well. The research study did not receive funds or support from any source.

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