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Influence of Kidney Function on Serum Risperidone Concentrations in Patients Treated With Risperidone

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ABSTRACT

Objective: Risperidone is one of the most commonly prescribed antipsychotics worldwide. Its main metabolite, 9-hydroxyrisperidone (9-OH-RIS), is excreted renally. The present study examined the relationship of kidney function and serum risperidone concentrations in a large sample of risperidone-treated patients.

Methods: Serum concentrations of risperidone and its active metabolite 9-OH-RIS, as well as creatinine concentrations, from which glomerular filtration rates (GFRs) were estimated, were determined in 175 risperidone-medicated patients (75 female, 100 male). Data were collected between July 2013 and December 2016. Patients were clustered in 4 groups according to their estimated GFR (eGFR) (30–60; > 60–90; > 90–120; and > 120 mL/min/1.73 m^2), and serum concentrations of risperidone and 9-OH-RIS and their sum (active moiety [AM]) were compared groupwise. Additionally, serum concentrations were correlated with kidney function.

Results: Dose-corrected AM and dose-corrected 9-OH-RIS concentrations were significantly higher in patients with an eGFR of 30–60 mL/min/1.73 m^2 than in patients with an eGFR > 90–120 mL/min/1.73 m^2 ($P < .001$ for dose-corrected AM and $P = .001$ for dose-corrected 9-OH-RIS) or > 120 mL/min/1.73 m^2 ($P = .036$ and .021, respectively). Dose-corrected AM levels were more than doubled in the 30–60 mL/min/1.73 m^2 group compared to the > 90–120 mL/min/1.73 m^2 group (mean ± SD = 22.2 ± 14.0 [ng/mL]/[mg/d] vs 10.1 ± 7.7 [ng/mL]/[mg/d]). In the total group, eGFR and dose-corrected 9-OH-RIS and dose-corrected AM were weakly but statistically significantly correlated (Spearman rank correlation coefficient [R_s] = −0.2, $P = .004$, and $R_s = −0.17$, $P = .01$, respectively).

Conclusions: Kidney function is an important determinant of risperidone clearance. These data suggest reducing the risperidone dose by 50% in patients with a GFR below 60 mL/min.

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Risperidone has been one of the most widely prescribed antipsychotics worldwide for over 20 years. It belongs to the group of second-generation antipsychotics (SGAs). According to the Neuroscience-based Nomenclature (NbN), it is a receptor antagonist at D_2 dopamine, 5-HT_2 serotonin, and α_2 norepinephrine receptors.[1] In addition, 5-HT_7, α_1-adrenergic, and, to a lesser extent, H_1 histamine receptors are antagonized. Risperidone has no anticholinergic effects.[2] Its main indications are psychotic disorders and mania, but the compound is also approved for the treatment of psychomotor arousal and aggression.

Risperidone is metabolized by cytochrome P450 2D6 (CYP2D6) to 9-hydroxyrisperidone (9-OH-RIS, known as paliperidone), which, like risperidone itself, is pharmacologically active. In poor metabolizers, risperidone is preferentially metabolized by CYP3A4 to 9-OH-RIS.[3] In extensive metabolizers, to which most patients belong, the elimination half-life of risperidone is about 3 hours, and the half-life of 9-OH-RIS is approximately 20 hours. In poor metabolizers, the elimination half-life of risperidone is about 19 hours, and the half-life of 9-OH-RIS remains the same. However, these data are based on a total of only 12 subjects, and only 2 of them were poor metabolizers.[4] In extensive metabolizers, the metabolite is predominantly present (metabolite-to-parent ratio = 3.6–22.7 after oral administration and 1.2–4.3 in patients treated with long-acting injectable risperidone[5]), which is why it usually plays the more significant role in the action of risperidone.[6] Risperidone is mainly metabolized hepatically to 9-OH-RIS, which is largely excreted renally, approximately half by renal filtration and half by an unknown renal transporter.[7] Accordingly, kidney function is thought to play a central role in the elimination of 9-OH-RIS. However, published data on the influence of renal function on serum or plasma concentrations of risperidone, 9-OH-RIS, and the sum of both (ie, active moiety [AM]) are surprisingly scarce. To date, only 1 scientific publication[8] has described the influence of age and liver and kidney function on the metabolism of risperidone. Even in the latest revision of the US Food and Drug Administration (FDA) manufacturer package label from 2009,[9] there is only a brief reference to reduced risperidone elimination in patients with impaired kidney function. Meanwhile, the FDA requires studies on renal impairment before admission of new drugs; however, risperidone was introduced into the market before the introduction of these requirements.[10]

Renal function can be very different interindividually; in particular, it decreases physiologically with age. Glomerular filtration rate (GFR), the clinically most valuable index of

Clinical Points

- Risperidone's main metabolite, 9-hydroxyrisperidone, is excreted renally, but data regarding the influence of kidney function on serum concentrations of the drug are lacking.
- In every patient treated with risperidone, glomerular filtration rate and active moiety should be assessed at least once. In patients with impaired kidney function, the dosage should be adjusted accordingly.

renal function, ranges between 90 and 120 mL/min in young healthy individuals. It declines by approximately 0.4 mL/min per year.[11] In industrialized countries, diabetic nephropathy and hypertension are the most common causes of impaired renal function or renal insufficiency.[12] Accordingly, serum concentrations of renally eliminated medications may increase significantly if the dose is not adjusted for renal function.

Therapeutic drug monitoring (TDM) is an established method for guidance of psychotropic drug treatment based on the determination of serum or plasma concentrations of applied drugs.[5,13] Using a TDM database and corresponding laboratory data, we examined the dependence of serum concentrations of risperidone, 9-OH-RIS, and AM on renal function in a large group of patients with schizophrenia or schizoaffective disorder.

METHODS

Patients

The study was conducted at the Department of Psychiatry, Psychotherapy and Psychosomatics of the University Hospital Aachen, Aachen, Germany. The retrospective evaluation of the database was approved by the ethics committee of the Uniklinik RWTH Aachen. A large TDM database of in- and outpatients, which contains data for 274 patients treated with risperidone, was evaluated. Data collection took place between July 1, 2013, and December 31, 2016. The owner of this database is the Uniklinik RWTH Aachen, Department of Psychiatry, Psychotherapy and Psychosomatics, Aachen, Germany. There is no public access to the data, but it can be reviewed on demand. All patients who were treated with risperidone for at least 3 days were included, regardless of their psychiatric diagnosis. All patients for whom GFR was not assessed a maximum of 1 week prior to or after blood sampling were excluded. The GFR was determined in all cases using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.[14] In some patients, risperidone levels were below the limit of quantification (0.5 ng/mL), whereas the 9-OH-RIS levels were evidently higher. In these cases, we decided to calculate the AM as sum of the 9-OH-RIS levels and the limit of quantification (0.5 ng/mL) divided by 2, assuming that this was on average the closest to the true value.[15] The final sample comprised 175 patients (75 female, 100 male). Patient characteristics are shown in Table 1. No patient was treated with a CYP3A4 inducer or inhibitor. Six patients were treated with inhibitors of CYP2D6 (strong inhibitor: paroxetine, 2 patients; moderate inhibitors: duloxetine, 3 patients; bupropion, 1 patient). In none of these patients was GFR below 75 mL/min/1.73 m^2.

Table 1. Patient Demographics in the 4 eGFR Groups

eGFR (mL/min/1.73 m^2)	n	Age, mean (SD), y	Sex, % (n)		Risperidone Dose, mg/d
			Female	Male	
30–60	10	64.1 (9.2)	70 (7)	30 (3)	3.3 (1.4)
>60–90	36	53.6 (15.2)	52.8 (19)	47.2 (17)	3.9 (1.7)
>90–120	89	41.7 (11.6)	38.2 (34)	61.8 (55)	4.5 (1.6)
>120	40	27.1 (6.7)	40.0 (16)	60.0 (24)	3.9 (1.6)

Abbreviation: eGFR = estimated glomerular filtration rate.

Quantification of Risperidone and 9-OH-Risperidone Levels

Blood was taken in the morning before drug administration; steady-state conditions were assumed and considered as trough levels of the drug. At steady-state, drug-intake is equal to drug-elimination, leading to almost constant drug concentrations in serum; steady-state is achieved after constant administration of an oral treatment for 4 to 6 half-lives.[13] We used serum concentrations as the indicator for drug concentrations in blood. A rapid, sensitive, and specific ultraperformance liquid chromatography (UPLC) method (ACQUITY UPLCs BEH Column; Waters Corporation; Milford, Massachusetts) was used for the quantitative determination of risperidone and 9-OH-RIS. The method is linear from the designated limit of quantification of 0.5 ng/mL up to the upper limit of 51.0 ng/mL for risperidone and of 0.8 ng/mL up to 212.0 ng/mL for 9-OH-RIS. For risperidone, intraassay precision is 3.8% at 10.1 ng/mL and 2.0% at 18.7 ng/mL; for 9-OH-RIS, it is 3.6% at 31.8 ng/mL and 1.3% at 73.0 ng/mL. Interassay precision is 6.5% at 8.7 ng/mL and 9.0% at 13.2 ng/mL for risperidone and 5.9% at 8.7 ng/mL and 9.3% at 13.2 ng/mL for 9-OH-RIS.

The analytic methods were as previously described.[16]

Quantification of Glomerular Filtration Rate

The GFR is usually given in mL/min. Due to its complex measurement, an established clinical routine is to calculate it based on blood creatinine levels with several formulas, eg, the CKD-EPI formula.[14] In these cases, it is normalized per body surface, which yields mL/min/1.73 m^2 as the unit of measure. The calculated GFR is referred to as estimated GFR (eGFR).

Statistics

Patients were classified in 4 groups according to their eGFR: 30–60, >60–90, >90–120, and >120 mL/min/1.73 m^2. Means and standard deviations of nonadjusted (Table 2) and dose-adjusted (Table 3) serum concentrations of risperidone, 9-OH-RIS, and AM were calculated for each group. The ratio of 9-OH-RIS to risperidone was determined to assess the patients' CYP2D6 metabolizer status.[17]

Further statistical analyses were conducted with nonparametric tests, because a Shapiro-Wilk test showed

Table 2. Plasma Concentrations of Risperidone, 9-OH-RIS, and AM and Metabolic Ratios of 9-OH-RIS/Risperidone in the 4 eGFR Groups

eGFR (mL/min/1.73 m^2)	Risperidone (ng/mL)	9-OH-RIS (ng/mL)	AM (ng/mL)	9-OH-RIS/ Risperidone Ratio
30–60	32.1 (48.2)	40.2 (20.4)	72.3 (52.6)	6.1 (9.8)
>60–90	10.1 (11.5)	36.2 (23.8)	46.3 (26.4)	24.2 (57.4)
>90–120	12.1 (16.6)	29.8 (18.4)	41.9 (25.4)	16.5 (32.5)
>120	15.6 (24.4)	27.9 (13.3)	43.5 (27.5)	8.8 (11.4)

Abbreviations: AM = active moiety, eGFR = estimated glomerular filtration rate, 9-OH-RIS = 9-hydroxyrisperidone.

Table 3. Dose-Adjusted Serum Concentrations of Risperidone, 9-OH-RIS, and AM in the 4 eGFR Groups

eGFR (mL/min/1.73 m^2)	Risperidone ([ng/mL]/[mg/d])	9-OH-RIS ([ng/mL]/[mg/d])	AM ([ng/mL]/[mg/d])
30–60	10.0 (13.2)	12.3 (4.0)	22.2 (14.0)
>60–90	3.0 (2.7)	10.4 (7.8)	13.3 (8.6)
>90–120	2.8 (3.9)	7.3 (6.6)	10.1 (7.7)
>120	3.9 (5.5)	7.9 (4.5)	11.7 (6.5)

Abbreviations: AM = active moiety, eGFR = estimated glomerular filtration rate, 9-OH-RIS = 9-hydroxyrisperidone.

that the data were not normally distributed. The primary hypothesis that dose-adjusted serum concentrations of risperidone, 9-OH-RIS, and AM negatively correlated with eGFR was tested with a 1-tailed Spearman rank-order correlation. To test for differences in serum concentrations of risperidone, 9-OH-RIS, and AM, respectively, in the 4 different groups, a Kruskal-Wallis test was performed. Post hoc comparisons of the serum concentrations in the 4 groups were performed with Dunn-Bonferroni tests (corrected for multiple comparisons). The significance level was set at .05 for all analyses.

Statistical analyses were conducted with SPSS (version 23.0.0.3; IBM; Armonk, New York).

RESULTS

One hundred seventy-five patients met the inclusion criteria. Dose-corrected serum concentrations of risperidone, 9-OH-RIS, and AM of the 4 eGFR groups are presented in Table 3. Both dose-corrected AM and dose-corrected 9-OH-RIS concentrations were significantly different between groups (dose-corrected AM: $\chi^2_3 = 23.0$, $P < .001$; dose-corrected 9-OH-RIS: $\chi^2_3 = 21.0$, $P < .001$). Post hoc comparisons revealed a significantly higher dose-corrected AM concentration in patients with an eGFR of 30–60 mL/min/1.73 m^2 than in the groups with an eGFR of >90–120 mL/min/1.73 m^2 ($P < .001$) and >120 mL/min/1.73 m^2 ($P = .036$). In addition, the dose-corrected AM concentration was significantly higher in the group with an eGFR of >60–90 mL/min/1.73 m^2 than in the group with an eGFR of >90–120 mL/min/1.73 m^2 ($P = .011$). Similar results were obtained by the analysis of the dose-corrected 9-OH-RIS concentrations. The values of dose-corrected 9-OH-RIS were significantly higher in patients with an eGFR of 30–60 mL/min/1.73 m^2 than in patients with an eGFR of >90–120 mL/min/1.73 m^2 ($P = .001$) or >120 mL/min/1.73 m^2 ($P = .021$). Here, too, the serum levels were higher in the group with an eGFR of 60–90 mL/min/1.73 m^2 than in the group with an eGFR of 90–120 mL/min/1.73 m^2 ($P = .009$). The comparison of the dose-corrected risperidone concentrations yielded no significant difference between the groups, illustrating that renal clearance is of minor importance for the elimination of risperidone because it is relatively rapidly transformed hepatically to 9-OH-RIS.

Table 4. Plasma AM Concentration and Dose of Risperidone in the 4 eGFR Groups

eGFR (mL/min/1.73 m^2)	AM (ng/mL)	Risperidone Dose (mg)
30–60	72.3 (52.6)	3.3 (1.4)
>60–90	46.3 (26.4)	3.9 (1.7)
>90–120	41.9 (25.4)	4.5 (1.6)
>120	43.5 (27.5)	3.9 (1.6)

Abbreviations: AM = active moiety, eGFR = estimated glomerular filtration rate.

The dose-corrected serum AM concentration was more than twice as high in the group with an eGFR of 30–60 mL/min/1.73 m^2 as in the group with an eGFR of >90–120 mL/min/1.73 m^2 (30–60 mL/min/1.73 m^2: mean ± SD = 22.2 ± 14.0 [ng/mL]/[mg/d]; >90–120 mL/min/1.73 m^2: 10.1 ± 7.7 [ng/mL]/[mg/d]). Further, Table 4 shows that patients with an eGFR below 60 mL/min/1.73 m^2 had a mean serum AM concentration of 72.3 ng/mL, which is above the therapeutic reference range of 20–60 ng/mL.[5] Mean AM values in patients with an eGFR >60 mL/min/1.73 m^2 were all in this range.

When dose-corrected risperidone, 9-OH-RIS, and AM concentrations of all 175 patients were correlated with eGFR values, a relatively weak, but statistically significant negative relation between eGFR and the dose-corrected 9-OH-RIS (Spearman R [R_s] = −0.2, $P = .004$) and AM ($R_s = -0.17$, $P = .01$) concentrations was detected. By contrast, the correlation between eGFR and dose-corrected risperidone concentration was not significant ($R_s = -0.08$, $P = .14$). Thus, the drug concentrations increased significantly with decreasing eGFR.

DISCUSSION

Risperidone is one of the most widely prescribed antipsychotics in the treatment of schizophrenia and bipolar mania. While the drug is also approved for the treatment of severe aggression in children over the age of 5 years, it is often used for other indications for which it is not FDA-approved. The age range in which it is used is therefore extremely wide. Since its active metabolite 9-OH-RIS is mainly excreted renally, the elimination rate is directly dependent on renal function. If kidney function decreases, the serum concentration of the active metabolite 9-OH-RIS increases if the dosage is not adjusted accordingly. Renal function, in addition to being highly interindividually variable, decreases with age, so that serum risperidone (ie, AM) concentrations may vary with GFR.

These considerations are supported by our study: there was a statistically significant negative correlation between eGFR and dose-corrected AM ($R_s = -0.17$, $P = .01$). Furthermore, patients with an eGFR of 30–60 mL/min/1.73 m^2 showed dose-corrected AM values that were on average more than twice as high as in patients with an eGFR of >90–120 mL/min/1.73 m^2 (30–60 mL/min/1.73 m^2: mean ± SD = 22.2 ± 14.0 [ng/mL]/[mg/d]; >90–120 mL/min/1.73 m^2: 10.1 ± 7.7 [ng/mL]/[mg/d]). The recommended therapeutic reference range for AM concentrations of risperidone is 20–60 ng/mL.[5] While the patient groups with an eGFR >60 mL/min/1.73 m^2 were within this therapeutic reference range, patients with an eGFR of <60 mL/min showed a mean AM concentration of 72.3 ng/mL, which exposes those patients to unjustifiably high drug concentrations. Thus, in patients with an eGFR below 60 mL/min/1.73 m^2, the therapeutic reference range is already reached at risperidone doses of 1–2 mg/d, and patients at 3 mg daily exceed the upper threshold. These results emphasize the relevance of our study, especially considering that more detailed investigations into that issue were conducted neither before nor after approval of risperidone. However, it should be mentioned that the dose-corrected AM values determined in our present study are somewhat higher than in a larger sample we previously reported (with a median dose-corrected AM value of 6.3 [ng/mL]/[mg/d]).[18]

Although physicians—intuitively or based on TDM—seem to adjust risperidone doses (Table 4), these dose adaptations are not sufficient in patients with reduced kidney function. Our data suggest that the dose of risperidone should be reduced by 50% to achieve a serum AM concentration within the therapeutic reference range if the GFR is below 60 mL/min.

On the basis of our data, it is recommended that the GFR be determined at least once in every patient treated with risperidone. Doing so is particularly important in patients with potentially compromised kidney function, such as elderly or obese patients or those with diabetes. In addition, the TDM consensus guidelines published by the AGNP (Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie)[5] suggest to routinely monitor serum or plasma risperidone concentrations (recommendation level 2: "recommended"). Routine monitoring of serum or plasma risperidone concentrations provides further information on potentially relevant pharmacokinetic influences of variables beyond kidney function such as CYP genotype or coadministration of CYP2D6 inhibitors.[19–21]

Limitations of our study are its retrospective nature and the relatively low number of patients with an eGFR below 60 mL/min/1.73 m^2. In addition, although TDM represents an ideal instrument for controlling medication adherence, that the patients in our study were partly incompliant cannot be excluded. Furthermore, we used only data from the latest measurement of drug levels with their respective GFR; therefore, the results are not validated longitudinally. Also, we included all patients who had taken risperidone for at least 3 days. While this is usually too short to reach steady-state serum concentrations, the number of patients who had been administered risperidone for such a short time was very low. We did not increase the threshold of the duration of risperidone treatment to 5 days, because in clinical practice risperidone levels are sometimes determined before steady-state is reached, and we wanted to depict a naturalistic clinical setting. On the other hand, our sample is by far the largest in the literature that compares kidney function with serum drug concentrations, and the results are highly plausible and clinically relevant.

To keep our study as naturalistic as possible, we did not exclude from the analysis the small number of patients (n = 6) who were taking CYP2D6 inhibitors. To minimize any factors that influence drug pharmacokinetics would have meant to also exclude poor and ultrarapid metabolizers (which was impossible, because genotyping was not performed). The significance of our results despite the presence of some confounds indicates the clinical relevance of our study in naturalistic settings.

Finally, in patients who took risperidone in a single, undivided dose at night, the measured serum concentrations might not represent trough levels. In these cases, it can be assumed that the true trough levels were somewhat lower. On the other hand, for compounds with a long elimination half-life that are in steady-state (such as 9-OH-RIS), the timing of blood sampling is of minor importance, because fluctuations between peak and trough are small.[22] Serum concentrations of risperidone, due to its much shorter elimination half-life, are more susceptible to the timing of the blood sampling. These considerations, however, do not change the evidence of our findings.

In conclusion, our study demonstrates that kidney function is an important determinant of risperidone elimination. Reducing the daily risperidone dose by 50% in patients with a GFR below 60 mL/min is strongly recommended.

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Potential conflicts of interest: **Dr Paulzen** is co-founder of InMediCon GmbH (Pentling, Germany), and has received a speaker's fee from Neuraxpharm. **Dr G. Gründer** has served as a consultant for Allergan, Boehringer Ingelheim, Eli Lilly, Janssen-Cilag, Lundbeck, Otsuka, Recordati, Servier, and Takeda; has served on the speakers' bureau of Eli Lilly, Janssen-Cilag, Neuraxpharm, Lundbeck, Otsuka, Recordati, Roche, Servier, and Trommsdorf; has received grant support from Boehringer Ingelheim, Lundbeck, and Saladax; and is co-founder of Mind and Brain Institute GmbH (Zornheim, Germany), Brainfoods GmbH (Zornheim, Germany) and InMediCon GmbH (Pentling, Germany). **Drs Augustin** and **P. Gründer** report no conflicts of interest.

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