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ORIGINAL PAPER

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# Risperidone plasma levels, clinical response and side-effects

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**Abstract** *Introduction* Assessment of the relation between oral risperidone dose, serum drug levels and clinical response may provide important information for rational treatment decisions. Inter-individual differences in the liver cytochrome P450 system, especially in the CYP2D6 subsystem, which account for a significant portion of risperidone metabolism, may also influence plasma drug levels and alter clinical response parameters. We thus prospectively investigated risperidone serum concentrations in relation to clinical efficacy and side-effects and genotyped major CYP2D6 polymorphisms to determine their effect upon these parameters. *Methods* Neuroleptic monotherapy with risperidone was administered to schizophrenia patients in a 6-week open dose clinical trial. Weekly assessments including CGI and PANSS ratings to assess psychopathology; SAS to assess medication side effects; and blood draws to quantify steady state plasma levels of risperidone and 9-OH-risperidone were carried out. In addition, major CYP2D6 polymorphisms including alleles *4, *6 and *14 were genotyped. *Results* Eighty-two patients were recruited. Mean oral dose of risperidone was 4.3 ± 0.9 mg. Mean plasma level of both risperidone and 9-OH-risperidone together ("active moiety") was 41.6 ± 26.6 ng/ml. Significant improvements in PANSS scales and the various subscales ensued. There was a positive linear correlation between active moiety plasma levels and dose ($r = 0.291$, $p = 0.015$) and between risperidone and 9-OH-risperidone levels ($r = 0.262$; $p = 0.016$). Nonresponders to pharmacotherapy (PANSS-Improvement < 30 %) showed significantly higher active moiety plasma levels (49.9 ± 30.7 ng/ml) than responders (38.2 ± 17.0 ng/ml; $p = 0.045$) without significantly higher oral doses ($p = 0.601$). Patients with longer illness duration (≥ 3 years) had significantly higher plasma drug levels than those with a shorter course (< 3 years; $p = 0.039$). Extrapyramidal side effects (EPS) and plasma levels were not correlated ($r = 0.028$; $p = 0.843$), but higher plasma levels at week 2 predicted an incidence for EPS ($p < 0.050$). Accordingly, patients initially receiving higher oral doses of risperidone were significantly more likely to respond with EPS in the trial course. Eight patients (9.8 %) were heterozygous carriers of the CYP2D6 allele *4. CYP2D6 polymorphisms did not predict clinical response, but predicted a tendential increase in the plasma risperidone to 9-OH-risperidone ratio (0.5 ± 0.6 vs. 1.9 ± 1.8; $p = 0.120$). *Discussion* The major finding was that responders to risperidone treatment had significantly lower blood levels of risperidone and 9-OH risperidone than patients who did not respond to the treatment despite administration of similar oral doses. The observed CYP2D6 polymorphisms did not contribute to altered clinical efficacy, but affected risperidone to 9-OH-risperidone ratios. Increased plasma levels of the active moiety in patients with longer illness may represent general aging effects. Conversely, the observed higher plasma levels in nonresponders may derive from unaccounted genetic metabolism abnormalities or Phase II metabolism disturbances. Patients initially receiving higher oral risperidone doses were more likely to respond with extrapyramidal side effects which reaffirms the need for careful titration. The high inter-individual variability in risperidone and 9-OH-risperidone metabolization and the relationship between clinical outcome and plasma levels warrants regular plasma level monitoring of both compounds to assess for the clinically relevant active moiety.

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## Introduction

Schizophrenia treatment was revolutionized in the 1950s with the advent of antipsychotic medications such as chlorpromazine and haloperidol. Their efficacy has been well-established, although they have arguably better efficacy against positive symptoms of schizophrenia than against negative symptoms. However, a significant portion of patients do not sufficiently respond to treatment with these agents, and many developed serious acute side effects, such as akathisia, dystonia and parkinsonism (Nasrallah and Mulvihill 2001). The atypical antipsychotics are presumed to have better efficacy in the treatment of negative symptoms than classical neuroleptics (Möller 1999 and 2003), both due to better tolerability and more complex neurotransmitter action. Furthermore, atypical drugs with favorable side effect profiles represent important key features in schizophrenia care, since long-term treatment is often warranted; significant side effects only contribute to treatment-noncompliance with medication, probably leading to long-term clinical deterioration (Fenton et al. 1997).

Risperidone, a benzisoxazole derivative, has high binding affinity for both dopamine D2 and serotonin 5-HT2 receptors (Marder and Meibach 1994) and has proven efficacy in the treatment of schizophrenic positive and negative symptomatology (Carman et al. 1995; Marder and Meibach 1994). Risperidone is readily absorbed orally, and steady-state plasma levels of the active moiety are reached after 24 hours (Heykants et al. 1994). Metabolization is largely effected through hydroxylation and N-dealkylation by the liver cytochrome P450 (CYP450) system, especially CYP2D6 (Scordo et al. 1999; Prior et al. 2003), and to a lesser extent by CYP3A4 (Fang et al. 1999). Risperidone and its main metabolite, 9-OH-risperidone, form the active serum compound (termed "active moiety"). 9-OH-risperidone exhibits a similar CNS receptor occupancy profile as risperidone, and it is presumably equally effective (Van Beijsterveldt et al. 1998). Elimination half-life of risperidone is about 6–7 hours, and of 9-OH-risperidone about 24 hours.

According to the manufacturer's suggestions, risperidone is administered in daily oral doses between 4 and 6 mg for the treatment of schizophrenia. However, studies of pharmacokinetic properties of risperidone have revealed large interindividual variability between oral dose and actual plasma levels (Odou et al. 2000; de Jong 1997). Environmental factors such as age or body weight have been implicated (Balant-Gorgia et al. 1999). Further, genetic influence such as CYP2D6 status may be important (Berecz et al. 2002). CYP2D6 activity is determined by allelic variants of the CYP2D6 gene, and, when compared to the wild type allele, ranges from complete deficiency to ultra-rapid metabolizer status (Sachse et al. 1997). About 7 % of the Caucasian population are poor metabolizers, which is inherited as an autosomal recessive trait (Alvan et al. 1990) and effects relatively higher steady-state plasma drug levels. About 1 % have multiple copies of a functional CYP2D6 allele (Dahl et al. 1995) with a relatively high CYP2D6 activity and comparably low drug plasma levels ("ultra-rapid metabolizers"). The remaining majority of the population is referred to as extensive metabolizers (Broly et al. 1990). Similarly, coadministration of other psychiatric drugs such as SSRI or thiordiazine may also potently inhibit CYP2D6 and increase the plasma concentration of the target drug (Prior and Baker 2003).

Current oral dosage recommendations largely fail to incorporate such aspects present in individual patients. Thus, drug plasma level monitoring may represent a reasonable alternative approach to establish required medication doses and account for these differences. Importantly, risperidone plasma levels have been shown to directly correspond to brain receptor occupancy (Van Beijsterveldt et al. 1994) and may thus serve as better indicators of optimal therapeutic doses than the usual practice of oral dose quantification.

To further establish the relation between CYP2D6 status, plasma drug levels and clinical parameters in a schizophrenia patient population, we prospectively investigated the steady-state risperidone and 9-OH-risperidone plasma levels and assessed both clinical response and extrapyramidal side effects while accounting for important CYP2D6 genotypes.

## Methods

A 6 week open-label trial with risperidone monotherapy in patients carrying a DSM-IV diagnosis of schizophrenia (APA 1994) was conducted. Prior to entering the trial, patients were required to sign informed consent according to procedures approved by the University of Munich Ethics Committee.

Inclusion criteria were age between 18 and 65 years and DSM-IV diagnosis of schizophrenia. Exclusion criteria were serious medical co-morbidities, ECG and/or EEG abnormalities, laboratory studies more than 20 % out of reference range, positive urine drug screen, Hepatitis, HIV, substance dependence, pregnancy.

### Clinical assessments

Initially, every patient received a thorough medical workup including physical examination, measurement of vital signs and body weight, EEG, ECG, and laboratory studies (Bilirubin, ALT, AST, g-GPT, TSH, T3, T4, CBC with differential, cholesterol, triglycerides, LDL, HDL, urine drug screen, urine pregnancy test for females). Similar workups were done at the end of week 3; and upon study completion or at dropout.

A medication washout period lasting 2 to 7 days was followed by a week-long titration phase of risperidone to clinical response. Thereafter, once weekly risperidone dose adjustments were permitted. During the entire trial, maximum daily doses of up to 4 mg Lorazepam to counteract agitation, 15 mg Zolpidem for sleeplessness, and 6 mg Biperiden against extrapyramidal symptoms, but no other comedication were allowed. Weekly assessments of psychopathology and side effects were carried out and incorporated PANSS ratings (Kay et al. 1987), Simpson–Angus Scale (SAS; Simpson and Angus 1970), Barnes Akathisia Scale (BAS; Barnes 1989), and Clinical Global Impression

Scale (CGI, Guy et al. 1976). All assessments were done by MD level staff. Further, weekly blood draws were carried out; blood was drawn on the scheduled morning before breakfast and risperidone morning dose administration, centrifuged within 3 hours and stored frozen at –80 °C until further examination. Pending dose adjustments were done after blood draws to ensure stable plasma levels. Blood levels of risperidone and 9-OH-risperidone were measured after the end of the study and were thus not reported to the investigators.

### Determination of drug plasma levels

**Sample extraction.** Prior to HPLC determination, 1 ml of fluid/fluid extracted serum were enriched with 100 µl internal standard and 1 ml of 2 µM $NaHCO_3$ (pH 10.5), mixed with 6 ml of hexane containing 1 % isoamyl alcohol, fluffed for 15 minutes, and centrifuged at 3600 rpm for 15 minutes. Then, 5 ml of the supernatant (hexane phase) were pipetted into 100 µl 0.1 M $H_3PO_4$, again fluffed for 15 minutes and subsequently centrifuged for 30 minutes at 3600 rpm. The supernatant (hexane phase) was discarded and 100 µl of the aqueous phase were transferred to autosampler vials.

**HPLC method.** The HPLC system consisted of a Waters 2690 Separations Module (WATERS, Milford, MA). The operational isocratic chromatographic conditions for this HPLC system were set as follows: column temperature 40 °C; injection volume: 75 µl; flow-rate: 0.8 ml/min. The mobile phase consisted of 50 mM $NaH_2PO_4$, 12.5 mM octanesulfonic (pH 2.2, adjusted with $H_3PO_4$), 27 % $CH_3CN$, 3 % MeOH. This solution was filtered through an 0.47 µm membrane filter and degassed before use. A Waters 2487 Dual λ Absorbance Detector was used for detection (channel 1 λ = 210 nm; channel 2 λ = 280 nm). The analytical column was a 250 mm x 4 mm Supersphere 60 RP-select B, packed with C8 (MERCK LiChroCART 250–4, Darmstadt, Germany). Approximate run time after injection until detection of the compounds was about 16.2 min for 9-OH-risperidone and 24.2 min for risperidone.

In order to control the extraction process, 100 µl of internal standard was added to every probe as well as to every calibration standard. The substance Ly1701 222 ([750 ng/ml] in 0.1 M $H_3PO_4$), graciously provided by E. Lilly and Co., was used. The calibration standards were extracted from healthy blood donors, to which the native substances were added in defined quantities. Controls were obtained via the same procedure, and used prior and after every analysis course. The 5 point standard curves ranged from 10 to 200 ng/ml. The entity concentrations were established through comparison of peak heights of the single substances with the peak heights of the internal standard. Assessment software was Millenium 3.05/EMPOWER (Waters).

The accuracy of the method was calculated with control serum through 20 repeat measures of the medication and its metabolite over a median concentration area. The average mean deviation was between 3.7 and 4.8 %. Mean intraassay variance was calculated during eleven 15 h runs, established initially and post-run, and was between 1.76 and 3.15 %. The control samples used contained a concentration of 80 ng/ml risperidone and 80 ng/ml 9-OH-risperidone. The detection limit for risperidone and 9-OH-risperidone was between 0.63 ng/ml and 1.25 ng/ml, respectively. Recovery of the extraction method was 86 % for risperidone and 69 % for 9-OH-risperidone.

### Genotyping

Fifty-nine of the 82 patients agreed to participate in the genotyping. Genotyping was performed using the pyrosequencing method using a PSQ 96MA system (Pyrosequencing, Uppsala, Sweden) described by Zackrisson and Lindblom (2003). Primers for the initial amplification were designed using conventional standard criteria regarding the specific amplification of the CYP2D6 gene. In a second PCR the sequence containing the CYP2D6 alleles *4, *6 and *14 was amplified. In the pyrosequencing assay, three sequencing primers were used simultaneously, annealing in the region of the SNP. The resulting pyrograms were analyzed by the PSQ 96MA software and verified manually.

### Statistical analysis

The analysis encompassed all patients randomized with baseline data and at least one post-baseline measure (i. e. intent-to-treat subjects). LOCF (last observation carried forward) was used to substitute for missing values. Main outcome variables were changes in PANSS scores. Descriptive analysis was also carried out; and t-tests were employed to compare means of two variables where appropriate. Primary time-point for efficacy and safety analysis was end of week 6. Risperidone and 9-OH-risperidone levels were quantified separately and analyzed cumulatively as the "active moiety", since both metabolites equally contribute to drug efficacy. Steady-state drug plasma concentrations corresponding to oral doses were calculated at week 5, thereby eliminating potential titration-phase influences. Clinical response was defined as PANSS Total Score improvement of > 30 % from baseline. For calculation of response to treatment, LOCF was used only for patients who participated at least 3 weeks in the study. To further elucidate the relation of illness duration and drug plasma levels, a random cut-off of 3 years of illness duration was chosen to define longer vs. shorter illness duration and resulting plasma levels were compared. Similarly, to quantify possible contributions of drug plasma concentrations to extrapyramidal side effects, the SAS mean was calculated; this mean value was subsequently used as cut-off between two groups of more and less pronounced side effects. According to the genotype, metabolizers were classified as either extensive metabolizers, carrying the wildtype or poor metabolizers, carrying allele *4 (Zackrisson and Lindblom, 2003).

## Results

Eighty-two patients (43 males and 39 females) were included. Mean age was 36.2 ± 12.9 years. Mean age of onset was 31.7 ± 16.5 years, mean illness duration was 6.7 ± 8.7 years. Fifty-three patients carried a diagnosis of paranoid schizophrenia (DSM-IV 295.3), 12 were classified as disorganized (295.1), 10 as schizoaffective (295.7), 4 as undifferentiated (295.9) and 3 had schizophreniform disorder (295.4).

### Oral dose, plasma levels, and genotypes

Mean oral dose of risperidone was 4.3 ± 0.9 mg. Mean plasma level of the active compound was 45.8 ± 27.4 ng/ml (Table 1). There was a linear correlation of oral risperidone dose and plasma level of the active compound ($r = 0.291$, $p = 0.015$; Fig. 1) and between risperidone and 9-OH-risperidone plasma levels ($r = 0.262$, $p = 0.016$).

Fifty-one probands participating in the genotyping (86.4 %) carried the wildtype of CYP2D6 and eight (13.6 %) were heterozygous carriers of the CYP2D6 allele *4. Plasma levels of the active compound were not significantly different between extensive metabolizers (42.1 ± 27.3 ng/ml) and poor metabolizers (41.4 ± 24.2 ng/ml; $p = 0.944$). Similarly, no significant differences were observed between risperidone plasma levels with extensive (11.8 ± 16.6 ng/ml) and poor metabolizers (21.9 ± 23.1 ng/ml; $p = 0.271$). Between 9-OH-risperidone plasma levels with extensive (35.0 ± 18.0 ng/ml) and poor metabolizers (22.9 ± 17.2 ng/ml; $p = 0.097$), only a tendentially significant difference was seen. Correspondingly, CYP2D6 genotypes predicted a

**Table 1** Baseline and endpoint clinical characteristics

| Medication (mg) | Baseline | Endpoint | Mean ± SD | |
|---|---|---|---|---|
| Risperidone | 2.0±0.4 | 5.1±1.4 | 4.3±0.9 | |
| Lorazepam | 0.6±1.1 | 0.4±0.8 | 0.5±0.8 | |
| Biperiden | 0.3±1.0 | 1.3±2.2 | 0.9±1.4 | |
| **PANSS** | **Baseline** | **Endpoint** | | **p** |
| Positive | 20.5±6.3 | 13.2±4.9 | | < 0.05 |
| Negative | 22.6±7.0 | 18.0±7.1 | | < 0.05 |
| Global | 42.3±11.0 | 31.9±11.2 | | < 0.05 |
| Total | 85.4±19.4 | 63.0±21.3 | | < 0.05 |
| **Plasma levels (ng/ml)** | **Visit 1** | **Endpoint** | **Mean ± SD** | |
| Risperidone | 5.8±8.6 | 22.9±28.7 | 13.1±18.6 | |
| 9-OH-risperidone | 18.7±23.9 | 42.0±25.2 | 32.8±7.6 | |
| Active moiety | 24.5±26.1 | 65.6±38.4 | 45.8±27.4 | |

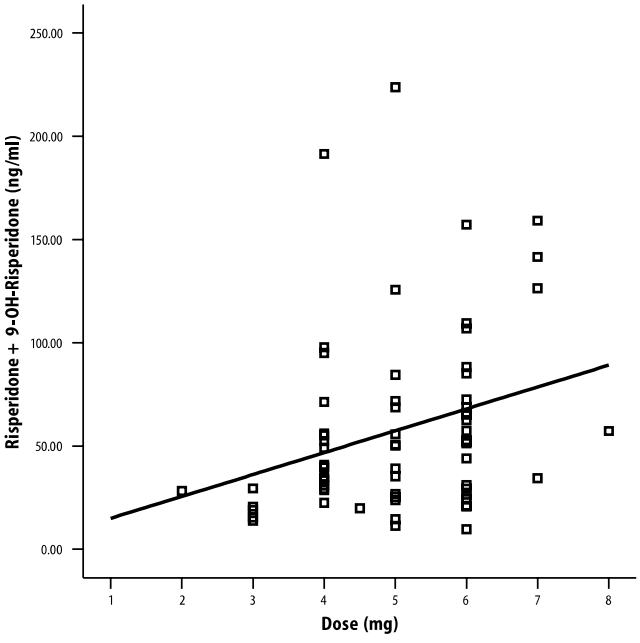


**Fig. 1** Positive correlation between oral dose and plasma levels of the active moiety (r = 0.291; p = 0.015)

tendential increase in the risperidone to 9-OH-risperidone ratio (0.5 ± 0.6 vs. 1.9 ± 1.8; p = 0.120). The spread of poor and extensive metabolizers is depicted in Fig. 2. Additional comparisons of dose-corrected plasma level ratios between the two genotypes did not adduce any significant differences to these findings.

## Clinical parameters

Table 1 also contains baseline and endpoint clinical characteristics. PANSS Total scores and subscores improved significantly throughout the study sample.

Nonresponders to pharmacotherapy (PANSS Total

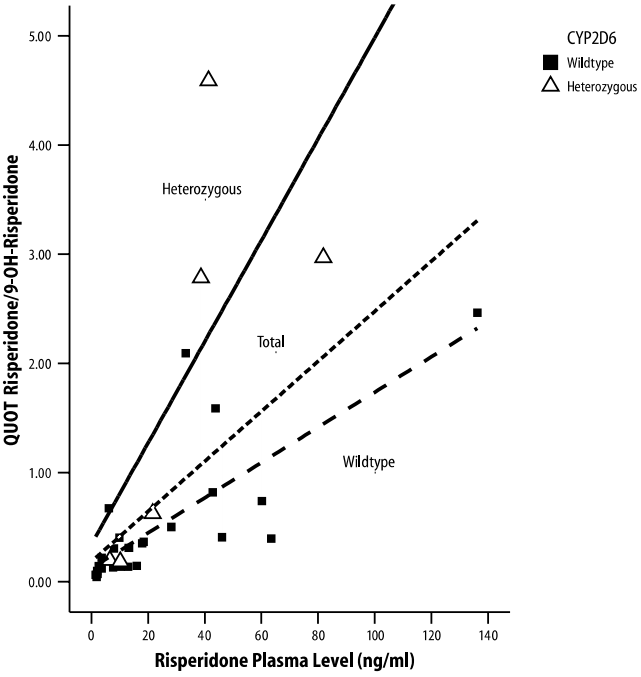


**Fig. 2** Relation between poor and extensive metabolizers. Tendential increase in the risperidone/9-OH-risperidone ratio between the CYP2D6 genotype groups (0.5 ± 0.6 vs. 1.9 ± 1.8; p = 0.120). The correlation curves are given for patients carrying the wildtype (dashed line), carriers of allele *4 (continuous line), and all patients (dotted line)

Score improvement < 30 %) showed significantly higher plasma drug concentrations (49.9 ± 30.7 ng/ml) than responders (38.2 ± 17.0 ng/ml; p = 0.045) without significantly higher oral doses (p = 0.601; Fig. 3). This finding is not accounted for by environmental factors such as age (p = 0.885) or weight (p = 0.257), since no statistically significant differences were observed for these factors. Moreover, responders and nonresponders did not differ regarding PANSS total score at baseline (p = 0.275). Characteristics of responders and non-responders are depicted in Table 2. CYP2D6 genotypes did not predict clinical response (assessed by improvement in PANSS Total Scores over six weeks; p = 0.947).

Patients with an illness duration of ≥ 3 years had significantly higher plasma drug concentrations (48.3 ± 33.1 ng/ml) than those with a duration of < 3 years (35.5 ± 17.8 ng/ml; p = 0.039) without significantly higher dosages (p = 0.316). This subgroup was also significantly older (40.1 ± 12.2 years vs. 31.9 ± 12.3 years; p = 0.004).

## Side-effect assessment

No correlation between plasma levels of the active moiety and extrapyramidal side effects as measured by the SAS (r = –0.040; p = 0.722) was found. Comparison of patients with more pronounced and less EPS yielded significant results in terms of patients with initially higher drug plasma levels being more likely to develop

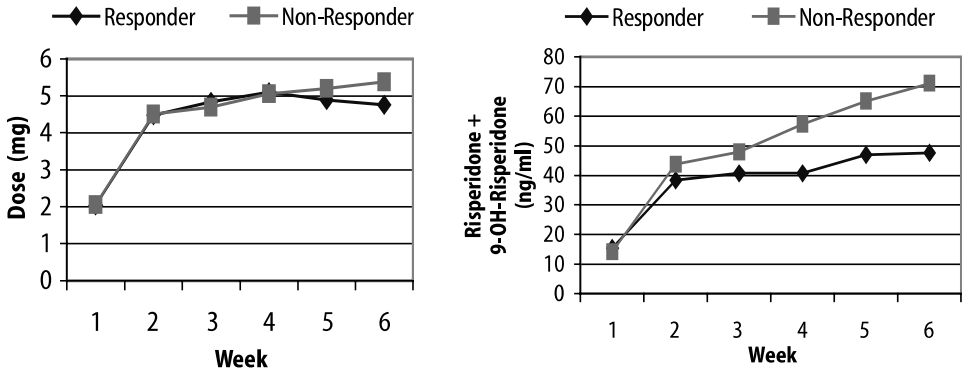


**Fig. 3** Response to treatment, oral dose, and plasma levels. Nonresponders to pharmacotherapy (PANSS-Improvement < 30 %) showed significantly higher active moiety plasma levels than responders (right figure) without significantly higher oral doses (left figure)

| Mean ± SD (week 1–6) | N | Responder | Non-Responder | *p* |
|---|---|---|---|---|
| Dose (mg) | 31/42 | 4.3±0.8 | 4.4±0.8 | 0.601 |
| Plasma Level (ng/ml) | 31/41 | 38.2±17.0 | 49.9±30.7 | 0.045 |

**Table 2** Characteristics of responders and non-responders as defined by a difference in PANSS total scores between baseline and last observation of at least or less than 30 %, respectively

| Mean ± SD | N | Responder | Non-Responder | p |
|---|---|---|---|---|
| Sex (male/female) | 38/35 | 18/13 | 20/22 | |
| Age (years) | 31/42 | 35.9±12.3 | 36.3±13.4 | 0.885 |
| Age of onset | 25/39 | 34.3±18.3 | 31.1±16.8 | 0.475 |
| Illness duration | 30/41 | 56.0±78.5 | 94.9±108.6 | 0.084 |
| Weight (kg) | 24/39 | 72.6±13.4 | 76.9±16.1 | 0.257 |
| Diagnosis | | | | |
| Paranoid | 48 | 25 | 24 | |
| Disorganized | 10 | 2 | 8 | |
| Schizoaffective | 7 | 2 | 5 | |
| Undifferentiated | 4 | 0 | 4 | |
| Schizophreniform | 2 | 2 | 0 | |
| Medication | | | | |
| Risperidone | 31/42 | 4.3±0.8 | 4.4±0.8 | 0.601 |
| Lorazepam | 25/37 | 0.5±0.6 | 0.6±0.9 | 0.346 |
| Biperiden | 25/37 | 0.8±1.3 | 1.1±1.6 | 0.447 |
| PANSS | | | | |
| Total (baseline) | 31/42 | 88.8±20.0 | 83.6±19.2 | 0.275 |
| Genotype | | | | |
| Wildtype | 45 | 19 | 26 | |
| Heterozygous | 6 | 2 | 4 | |

EPS (Fig. 4). Interestingly, high plasma levels during treatment did not correspond to elevated risk for EPS, when initial plasma levels were comparably low.

## Discussion

Monitoring of drug plasma levels to assess clinical response variability became a focus of interest some time ago (Ereshevsky 1995). Close clinical observation together with frequent drug plasma level monitoring can improve precision in optimizing individual dosage strategies (Darby et al. 1997). For example, haloperidol levels have been established in order to maximize efficacy while keeping side effects to a minimum (Balant-Gorgia and Balant 1995). Routine monitoring of clozapine levels improves treatment outcome and safety and may also provide important treatment guidelines in treatment-resistant patients (Spina et al. 2000; Perry et al. 1991; Kronig et al. 1995). On the contrary, Olanzapine monitoring has yielded mixed results in the prediction of clinical responses (Callaghan et al. 1999; Perry et al. 1997).

Our study results suggest that the active moiety blood plasma levels consisting of both risperidone and 9-OH-risperidone are correlated with clinical response, albeit their ratios show considerable inter-individual variation (Heykants et al. 1994). While risperidone plasma levels alone were correlated to oral risperidone intake, 9-OH-risperidone levels were not and were likely determined by CYP2D6 polymorphisms. For example, some alleles of the CYP2D6-isoenzyme such as the allele 4 found in several of our subjects are highly correlated with a poor metabolizer status with respect to the hydroxylation of risperidone to 9-OH-risperidone. Heterozygote carriers of such a mutant allele 4 show a tendential increase in the risperidone to 9-OH-risperidone ratio without an additional change in active moiety (Yasui-Furukori et al. 2003). Consequently, the clinical response is not altered. Yet, for the same reasons, it seems important to measure both compounds and calculate the active moiety to effectively relate plasma levels to clinical response.

Animal models have shown a correlation between dopamine D2 receptor occupancy in the CNS and the serum level of the active moiety of risperidone (Sumiyoshi et al. 1994). Undoubtedly, antipsychotic effects of neuroleptics are mainly due to dopamine D2 occupancy; the observed differences between oral doses and plasma levels in our study predict a large variety of clinical responses within a given 24 hour time frame, provided similar oral doses are administered. 9-OH-

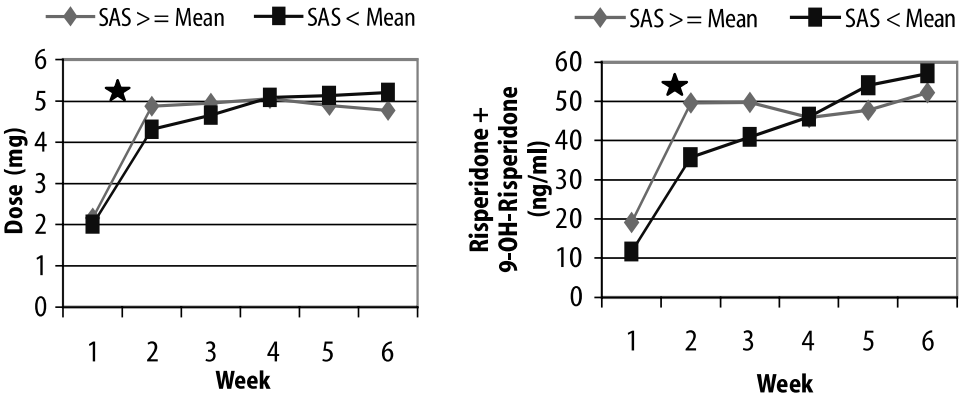


**Fig. 4** Comparison between oral dose and active moiety plasma levels in patients with more vs. less pronounced EPMS (Simpson-Angus Scale, mean = 0.9 ± 2.0). Plasma levels at week 2 predicted an incidence for EPS (right figure). Accordingly, patients initially receiving higher oral doses of risperidone were significantly more likely to respond with EPS in the trial course (left figure).* $p < 0.05$

risperidone levels were generally higher than risperidone levels, which is concordant with previous studies (Aravagiri et al. 2003). Aravagiri and Marder (2002) found pharmacokinetic differences between risperidone and 9-OH-risperidone in rat brain tissue concentration after oral administration, but the difference did not significantly influence overall exposure to the active compound. In this respect, risperidone seems rather unusual in terms of a significant contribution of its metabolite 9-OH-risperidone to clinical efficacy, especially as the plasma concentrations of the metabolite are consistently higher than concentration of the "parent" compound risperidone itself. The contribution of antipsychotic metabolites to the clinical efficacy of other antipsychotic drugs such as clozapine, fluphenazine or other classical antipsychotics is thought to be only minor, if at all present (Baldessarini et al. 1993).

Risperidone significantly improved psychopathology in the vast majority of study participants over the 6 week treatment period. We found increased active moiety plasma levels in patients with a longer duration of illness, without receiving significantly higher oral doses. This confirms previous observations (Olesen et al. 1998) and may represent a general aging effect rather than genetic or direct cumulative pharmacotherapeutic effects (Zubenko and Sunderland 2000). Surprisingly, nonresponders to pharmacotherapy had higher drug plasma levels than responders despite administration of similar oral doses. This finding is not accounted for by environmental factors such as age or weight, since no statistically significant differences were observed for these factors. Similarly, our trial results do not indicate disturbed CYP450 drug metabolism, as the active moiety plasma concentrations were similar in poor and extensive metabolizers. Absorption differences do not seem to be responsible either; in such an instance, lower plasma levels in nonresponders are to be expected. Thus, hypothetically a genetic component such as differences in P-glycoprotein affinity for risperidone may be involved (Boulton et al. 2002). Alternatively, disturbed Phase II drug metabolism may be responsible for the observed higher plasma drug levels of nonresponders.

Aside from this, both the findings of increased plasma drug concentrations in nonresponders and more chronic patients raise the question which pharmacotherapeutic approach constitutes the most appropriate approach in such cases. Considering current dose suggestions for the treatment of chronic schizophrenia, most clinicians agree that dose escalation is not the number one choice, but rather a longer term trial with low to moderate doses of antipsychotics is warranted (Meltzer 1992; Kane and Marder 1993; Carpenter et al. 1995). This is even more important, as long term observations of risperidone plasma levels have shown a propensity for the active compound to accumulate before leveling out at a higher than baseline level (Darby et al. 1997). Yet, today's managed care environment might pressure clinicians into "action" and lead them to premature dose escalations. Given our trial results, we found that such an approach is rather counterproductive in the long term, especially when considering the disparity between a probable minor additional response and increased likelihood for developing EPS. Medication switch or augmentation treatment should probably be pursued instead (Stahl 1999a, b). At times, even a reduction in oral dose may be adequate.

Extrapyramidal side effects (EPS) were generally mild. Interestingly, accelerated dose escalation of risperidone depicted by both higher oral dose and active moiety plasma levels was associated with a higher likelihood to developing EPS in the initial course of treatment. Looking at the main analysis point at week 5, no significant differences in either oral dose or plasma concentrations were seen between the groups with more vs. less pronounced EPS. These findings replicate results from previous studies (Olesen et al. 1998), but do not confirm results by others (He and Richardson 1995; Yoshimura et al. 2001). Most likely, however, individual susceptibility to neuroleptic-induced extrapyramidal syndromes may be implicated (Keepers and Casey 1991) when accounting for the development of EPS after neuroleptic medication. Our findings are consistent with this notion. Aside from this, careful medication titration in the initial few weeks upon treatment initiation may be warranted to avoid peak active moiety plasma concentrations and thus unnecessary EPS responses.

The usefulness of plasma concentration monitoring to predict clinical response has been disputed (Spina

et al. 2001). Yet, plasma level monitoring is certainly useful in clinical practice, especially in patients not properly responding to pharmacological interventions. In such a population, further dose escalation may not always be the treatment of choice, as drug plasma concentrations may already be high. Rather, sometimes modification of pharmacotherapeutic measures may yield results, and sometimes even simple patience. Furthermore, the influence of the genetically determined CYP metabolizer status has not been paid adequate attention. Although at this point, metabolizer status may be of limited value in a treatment approach with risperidone (Scordo et al. 1999; Roh et al. 2001), future prospects seem quite promising. Customized pharmacotherapy, according to the patient's genetic capability to metabolize a certain drug, with concomitant measurement of drug plasma levels may yield the most effective and at the same time, the most time saving approach to rational pharmacological treatment. Certainly, optimal plasma drug levels need to be established; our study is but one step in this direction.

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