ORIGINAL ARTICLE

Relevance of CYP2D6 variability in first-episode schizophrenia patients treated with risperidone

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Submitted: 2011-11-22 Accepted: 2012-02-13 Published online: 2012-04-25

Key words: **Cytochrome P-450; CYP2D6; pharmacogenetics; CYP2D6 analysis; schizophrenia; risperidone**

Neuroendocrinol Lett 2012; **33**(2):236–244 **PMID:** 22592207 NEL330212A16

Abstract

OBJECTIVE: The objective of this prospective, naturalistic study, conducted in first-episode psychosis patients from a Central-European population, was to assess the utility of Cytochrome P-450 2D6 (CYP2D6) genotype testing under normal clinical setting.

METHODS: A total of 35 patients diagnosed for the first time with schizophrenia or acute schizophrenia-like psychotic disorder and treated with risperidone were enrolled in the study. These patients underwent sequentiation of the CYP2D6 gene and evaluations of symptoms and severity of adverse effects using the PANSS and UKU scales, respectively. Doses of antipsychotics and other co-medication were monitored as well. In statistical analysis, Fisher's exact test was used to compare ratios and the Wilcoxon rank-sum test was used in the comparison of continual variables.

RESULTS: PM patients showed a significantly lower reduction in psychotic symptoms and a greater severity of psychotic symptoms following risperidone treatment and higher doses of antipsychotics not metabolized by CYP2D6, which were used as co-medication.

CONCLUSIONS: Based on these results, patients with the PM genotype experiencing first-episode schizophrenia don't appear to be optimal recipients of risperidone treatment. However, as the main limitation of this study was the relatively small sample-size, replication with a larger scale study is needed to confirm these findings.

Abbreviations:

AP	- Antipsychotic
AUC	- Area under the curve
BBB	- blood-brain barrier
CYP	- Cytochrome P-450
CYP2D6	- Isoenzyme 2D6 of the Cytochrome P450
DNA	- Deoxyribonucleic acid
EEG	- Electroencephalography
EM	- Extensive-metabolizer
ICD-10	- International Statistical Classification of Diseases and Related Health Problems, 10th Revision
IM	- Intermediate-metabolizer
IQR	- Inter-quartile range
MRI	- Magnetic resonance imaging
PANSS	- Positive and negative syndrome scale, scale for assessment schizophrenia symptoms
PM	- Poor metabolizer
SD	- Standard deviation
UKU	- Udvalg for Kliniske Undersøgelser, scale for assessment of drug adverse effects
UM	- Ultra-rapid metabolizer

INTRODUCTION

Cytochrome P-450 (CYP), a large family of xenobiotic-metabolizing enzymes, has, in recent years, been hinted as a potential source of inter-individual variability of treatment response (Zhang & Malhotra 2011). One member of this family, CYP2D6, has drawn special attention: it metabolizes approximately 30% of all CYP targets including risperidone, haloperidol, chlorpromazine and aripiprazole (Arranz & de Leon 2007) and shows the greatest variability among all Cytochrome P450 isoenzymes (Zhang & Malhotra 2011). There are 4 basic phenotypical variants of CYP2D6 activity. The ultra-rapid metabolizer (UM) shows a greater than two-fold increase in CYP2D6 function than the most common variant, which is the extensive metabolizer (EM); the intermediate metabolizer's (IM) CYP2D6 activity is impaired, while the poor metabolizer (PM) shows minimal or no CYP2D6 activity at all (Zhang & Malhotra 2011). This variability has a partially genetic basis. In total, more than 100 alleles of CYP2D6 have been described, whose expression can result in molecules with different levels of enzymatic function – fully, partially functioning enzyme, or an enzyme with no function at all. For example, CYP2D6*1 produces a fully functioning enzyme, while the product of alleles CYP2D6*3, *4 and *5 show negligible activity (Fleeman *et al.* 2010). According to de Leon, the UM has three or more copies of the active CYP2D6 gene; EM has one or two functional copies; IM has one non-functional CYP2D6 allele and one low-activity allele; and PM have two non-functional CYP2D6 alleles (de Leon *et al.* 2005). Several other definitions of IMs have been proposed, and in such cases definitions of EMs and PMs differ as well. (Kirchheiner *et al.* 2004)

Genetic determinants serve as a basis for CYP2D6 activity, which is then modified by environmental factors. The best-described factors influencing CYP2D6 activity are compounds reducing CYP2D6 function. Many of these inhibitors are drugs that are widely used in many psychiatric disorders: antipsychotics (chlorpromazine, haloperidol, methotrimeprazine), antidepressants (fluoxetine, paroxetine, bupropion, clomipramine, imipramine, citalopram, fluvoxamine). (Ingelman-Sundberg 2005)

In recent years, a relatively large degree of attention has been given to the possible interaction of variability in CYP2D6 and risperidone treatment response. This possibility is justified by several recently described differences between risperidone and 9OH-risperidone, especially the different affinities to several receptors (risperidone has higher activity at 5HT3, alpha1 and alpha2 adrenergic receptors (NIMH Psychoactive Drug Screening Program 2011)) and differences in blood-brain-barrier (BBB) permeation (it appears that risperidone permeates the BBB more easily, possibly because of a lower affinity for p-glycoprotein) (de Leon *et al.* 2010). The fact that variability in CYP2D6 activity has an effect on the 9OH-risperidone/risperidone blood level ratio has been repeatedly proved (Berecz *et al.* 2002; Laika *et al.* 2009; Scordo *et al.* 1999; Olesen *et al.* 1998), but no indisputable, straightforward connection between the variability of CYP2D6 and treatment response has been found. Despite the studies (Bork *et al.* 1999; Laika *et al.* 2009; de Leon *et al.* 2005; Llerena *et al.* 2004; Troost *et al.* 2007) and case reports (Albrecht *et al.* 2004; Koehnke *et al.* 2002) in which there was at least some effect of CYP2D6 variability in the subject's response to risperidone, there are many negative reports (Kakihara *et al.* 2005; Olesen *et al.* 1998; Plesnicar *et al.* 2006; Roh *et al.* 2001; Scordo *et al.* 1999; Jovanovic *et al.* 2010) that fail to show a connection.

OBJECTIVES

The objective of this prospective, naturalistic study conducted in first-episode psychosis patients of Central-European population was to asses the utility of CYP2D6 genotype testing under conditions of normal clinical setting.

METHODS

Patients

All patients enrolled in the study were hospitalized in the Department of Psychiatry, University Hospital, Brno between 2007 and 2010. Inclusion criteria were: diagnosis of schizophrenia (F20) or acute schizophrenia-like psychotic disorder (F23.2), in accordance with ICD-10 diagnostic criteria for research concluded for the first time in patient's life; an age range of 18–65 years; signed informed consent; and no prior history of psychopharmacological treatment and initial treatment

with risperidone. Diagnosis was concluded by a consensus of at least 2 trained psychiatrists after a mental status examination. All patients underwent further examinations (toxicological examination, fundus oculi examination, EEG, MR imaging) to exclude other possible causes of psychotic symptoms. Exclusion criteria included: any other psychiatric disorder diagnosed before or during index hospitalization; hospitalization against a patient's will; deprivation of legal capacity and contraindication for risperidone.

The entire study was approved by the local ethics committee and all patients provided a signed, informed consent for the study.

Time-course

All patients were observed for 1–7 weeks. Observation started with admission of the patient, followed by a diagnosis and the initiation of risperidone treatment. The endpoint of observation was the cessation of risperidone treatment; change of the antipsychotic agent; or the patient's release. Clinical evaluation using specific scales for symptom and adverse effect severity was conducted at the start of observation, at one-week intervals throughout the time-course of the study, and at the endpoint.

The study was performed in a naturalistic setting and did not interfere with normal clinical procedures, therefore, there weren't strict regulations with regard to possible co-medication use. Antiparkinsonics, benzodiazepines, antihistaminics and beta-blockers). Antipsychotics other then risperidone were allowed as long as they were only used a limited number of times and only as a sedative during acute agitation. Doses of co-medication were monitored at one-week intervals.

A CYP2D6 genotype examination was carried out once during hospitalization. Before the genotype examination, patients signed an informed consent for the genetic examination. The results of this exam were not available to the physician or the person rating effects, during hospitalization, and therefore the course of treatment was not influenced by any knowledge of a patient's CYP2D6 activity status.

Clinical evaluation

The following scales were used during patient observation in the study: The Positive and negative syndrome scale (PANSS) (Kay *et al.* 1987) to evaluate the clinical state of patients, and the Udvalg for Kliniske Undersøgelser (UKU) scale (Lingjaerde *et al.* 1987) to evaluate adverse effects severity. Pharmacotherapy – risperidone dosage, adjuvant medication administration and dosage, change in medication – was observed, as well as the frequency and causes of drop-outs (risperidone treatment cessation due to insufficient or adverse effects). The percentage of the PANSS score reduction was computed as a fraction (percentage) of the baseline PANSS score. Symptomatic remission was defined according to the Remission in Schizophrenia Working Group as the reduction to a value less than, or equal to, 3 in P1, P2, P3, N1, N4, N6, G5, G9 PANSS items (Andreasen *et al.* 2005).

In the assessment of adverse effects, the medians of the total UKU score, and all UKU sub-scores using data from all patients, were computed. Percentages of patients in each CYP2D6 activity group having UKU scores higher than the aforementioned medians were then used as a measure of adverse effect severity.

Risperidone doses were described in milligrams. Doses of all utilized antipsychotics were converted into chlorpromazine equivalents.

Genotypization in detail

The genomic DNA used for analyses was extracted from the peripheral blood of patients. To prevent an unspecific amplification of pseudo-genes CYP2D7 and CYP2D8, pre-amplification was performed using specific primers (Sistonen *et al.* 2005). The resulting pre-amplicons were used as a template for continuous PCR. All exons were amplified from these pre-amplicons. The PCR products were visualized on NAT gel and purified. These purified products were used for further sequencing analyses. Bi-directional sequencing was performed with BigDye® Terminator v1.1 Cycle Sequencing Kit (Applied Biosystems) on ABI PRISM 3100 (Applied Biosystems). Any polymorphisms found were described using CYP2D6 allele nomenclature, which also included information about the expected phenotype (Human Cytochrome P450 Allele Nomenclature Committee 2011). To detect entire allele deletion and duplication, long-range PCR was used (Daly 1995). Basically, by using these methods, any known and described CYP2D6 polymorphism could have been observed. Patients were categorized into different CYP2D6 activity groups in accordance to de Leon (de Leon *et al.* 2005) on basis of a configuration of their CYP2D6 alleles as was described in the Introduction.

Statistical evaluation

The main hypothesis was that groups of patients with a different CYP2D6 activity differ in at least some monitored measures. To analyze group differences in remission, drop-out, frequency of adverse effects, and frequency of patients using different co-medication, Fisher's exact test was used. Between-group differences in continual variables were tested by the Wilcoxon rank-sum test. All statistical evaluations were conducted using the R software library (R Development Core Team 2011).

RESULTS

The basic sample characteristic is summarized in Table 1. In total, 35 patients were enrolled in the study. 21 (60%) of these patients were male and 14 (40%) were female. The mean age was 29.2 years (SD = 11.36). The median of the time of observation was 4 weeks for the

entire sample. The minimal time of observation was 1 week, while the maximum was 7 weeks. There were no statistically significant differences in length of observation between the different groups.

Genotype

The most frequent allele in the entire sample was allele 4* coding a non-functional enzyme (allele frequency 22.86%). The second and third most common alleles were those coding the fully functional enzyme – 2* (20%) and 1* (18.57%). The frequency of all observed alleles is summarized in Table 2.

Out of 35 genotyped patients, 1 patient (approx. 2.86%) was UM, 22 patients (62.86%) were EMs, 7 patients (20%) were IMs and 5 patients were (14.29%) PMs. Due to the relatively small sample size, EM and IM group were merged and all analyses were conducted by comparing extreme cases – patients with no functional allele (PM) against patients with at least one partially functional allele (EM and IM, further designated as EM + IM). The other extreme case – a patient with multiplication of a functional allele (UM) – was removed from all subsequent analyses.

Tab. 1. Basic sample characteristics.

Gender	Males		Females	
Percentage	60%		40%	
Diagnosis	F20		F23.2	
Percentage	74.3%		25.7%	
Age	mean		SD	
	29.2		11.35	
Genotype	UM	EM	IM	PM
Percentage	2.63%	57.89%	18.42%	13.56%

Sample size = 35

Tab. 2. Alleles observed in the sample, corresponding predicted activity of CYP2D6, allele frequency and comparison with a frequency in the European population according to Sistonen (Sistonen *et al.* 2007).

Allele	**CYP2D6 activity**	**Frequency**	**Allele frequency in European population**
1*	normal	17.10526	34.4
1*xn	increased (multiplication)	1.31579	0.6
2*	normal	18.42106	28.7
4*	none	21.05264	17.2
5*	none (deletion)	2.63158	3.2
6A*	none	1.31579	0.6
9*	decreased	3.94737	2.5
10A*	decreased	7.89474	2.5
27*	normal	1.31579	unknown
33*	normal	1.31579	unknown
41*	decreased	6.57895	7

Symptoms

The total baseline and endpoint PANSS scores, as well as the scores of all the PANSS sub-scales, are summarized in Table 3 and Figure 1.

No statistically significant differences in baseline symptom severity were found. However, PM showed a statistically significantly higher score in endpoint negative (Wilcoxon rank-sum test, p=0.04569) and general PANSS sub-scale (p=0.01053) as well as a higher endpoint total PANSS score (p=0.0171). Patients with PM genotype showed a trend toward having a higher score in the endpoint positive PANSS sub-scale, as well (p=0.05811).

Lower symptom reduction, measured as a percentage of PANSS score reduction, was found in the PM genotype group (see Table 3). This result was statistically significant (Wilcoxon rank-sum test, p=0.01715).

Adverse effects

The PM genotype group generally showed higher rates of patients with severe adverse effects. However, only the difference in the "autonomic" UKU sub-scale (accommodation disturbances, increased or reduced salivation, nausea and vomiting, diarrhea, constipation, polyuria and polydipsia, orthostatic dizziness, palpitations and tachycardia, increased tendency to sweat) showed a trend to be statistically significant (Fisher's exact test, p=0.06291).

Treatment outcome

For rates of patients achieving remission, and rates of drop-outs due to different causes, see Table 3. There were no statistically significant results in any of these parameters.

Medication

The doses of all antipsychotics are summarized in Table 3. The PM genotype group generally used higher doses of all antipsychotics (p=0.05746), especially higher doses of antipsychotics not metabolized by CYP2D6 (p=0.01465). With regard to risperidone doses and doses of antipsychotics metabolized by CYP2D6, no significant result was found.

Observed co-medication and its possible effect on CYP2D6 activity is summarized in Table 4. When comparing co-medication use between different genotype groups, a higher usage of antiparkinsonics and benzodiazepines by the PM group was found. However, this result did not reach statistical significance.

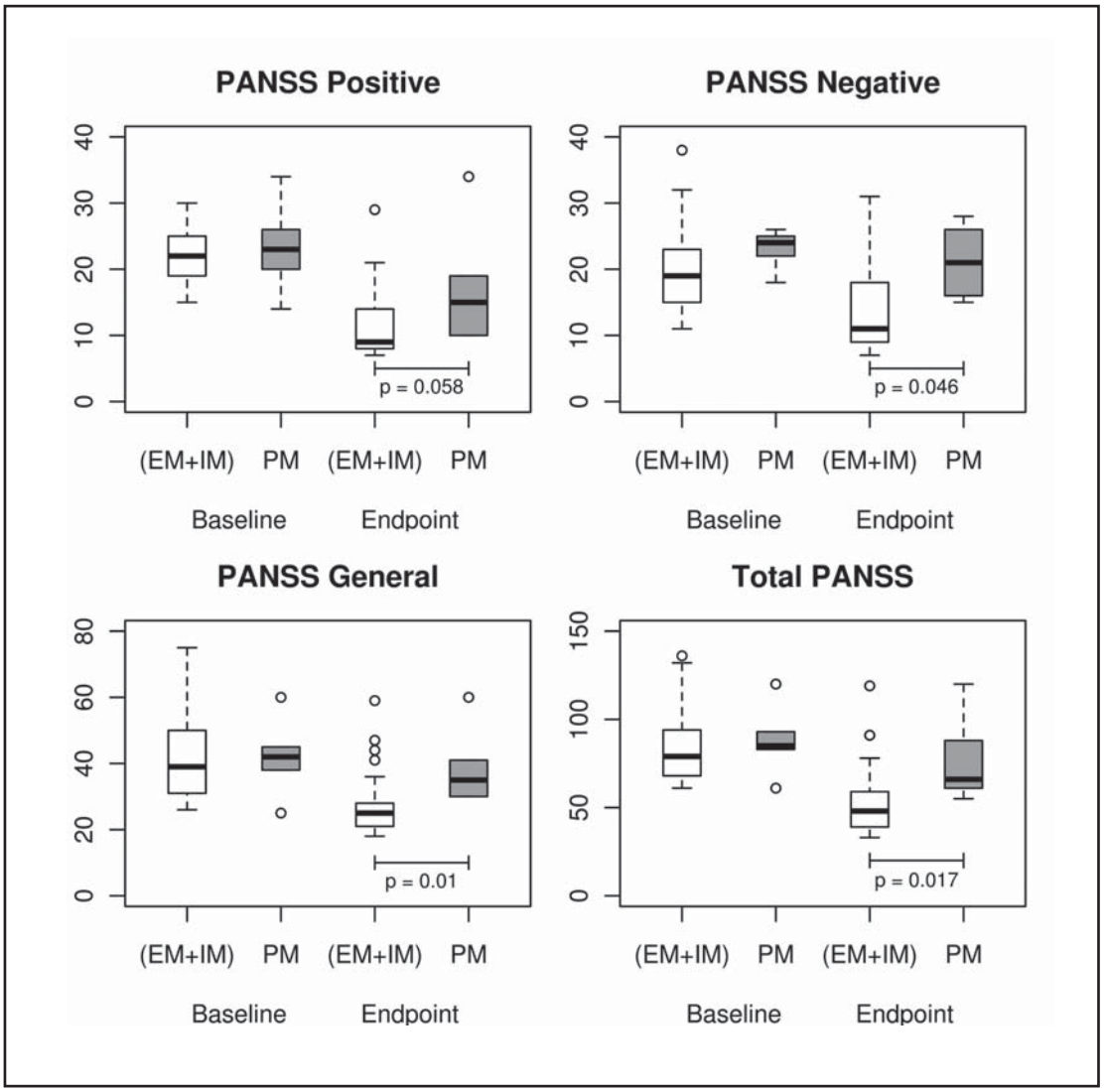

Fig. 1. Baseline and endpoint PANSS values in patients with different CYP2D6 genotypes. Selected *p*-value (Wilcoxon rank-sum test) are highlighted.

DISCUSSION

We have conducted 1–7 week long prospective observation of first-episode psychosis patients in a naturalistic study to assess the effect of CYP2D6 activity on risperidone efficacy and safety.

Efficacy

In our sample, the PM genotype group showed statistically significant lower symptom reduction than the group comprised of EM and IM genotypes. With no statistically significant difference in the baseline symptom profile measured by sub-scales of PANSS, it is not surprising that PM group showed a higher endpoint PANSS score, with a significantly higher value in total PANSS, negative and general symptom sub-scales.

Theoretically, one would assume that in patients with a deficit in CYP2D6 metabolism, a higher risperidone/9-OH-risperidone ratio would result in greater treatment effects, because risperidone has a lower affinity for p-glycoprotein and permeates the blood-brain barrier more easily (de Leon *et al.* 2010). In our sample, this was not the case and it was similar to the findings of Laika *et al.* who reported a positive correlation of treatment response and a number of fully functional CYP2D6 alleles in patients obtaining higher-than-median doses of CYP2D6 substrates (Laika *et al.* 2009). One possible explanation lies in the presence of 9-OH-risperidone during risperidone treatment. Both of these substances have their own antipsychotic action. 9-OH-risperidone has a longer biological half-life (de Leon *et al.* 2010) and its blood levels during risperidone treatment are generally higher than those of risperidone (Aravagiri *et al.* 2003; Riedel *et al.* 2005). Considering this important role of 9-OH-risperidone in risperidone treatment, and the fact that in PM the risperidone/9-OH-risperidone

ratio is shifted in favor of risperidone, it is possible that low levels of 9-OH-risperidone could have caused the lower treatment response observed in our sample. We hypothesize that this effect was not reversed by greater availability of risperidone moiety behind the BBB.

Moreover, both compounds show antagonism toward several receptor systems with different affinities to different receptors (5HT2, alpha 1, alpha 2 adrenergic, H1 histaminergic and, to a lesser extent, 5HT1C, 5HT1D, 5HT1A, D1) (NIMH Psychoactive Drug Screening Program 2011). While D2 receptor antagonism is indeed important for antipsychotic action, it is not the only one. This is, for example, reported in clozapine, where lower D2 receptor occupancy does not prevent a powerful antipsychotic action (Kapur *et al.* 1999; Nord & Farde 2011). Other receptor systems,

Tab. 3. Summary of observed variables - the baseline and endpoint score of PANSS sub-scales, total PANSS score and percentage PANSS decline, adverse effects incidence, outcome of the treatment, daily doses of risperidone (in mg per day) and other antipsychotics (AP, in chlorpromazine equivalents) and co-medication usage. *p*-values are highlighted: (Wilcoxon rank-sum test): * – p=0.058, $_{\dagger}$ – p=0.046, $_{\ddagger}$ – p=0.01, $_{\S}$ – p=0.017, $_{\|}$ – p=0.017, $_{\P}$ – p=0.058, ** – p=0.014, (Fisher's exact test): $_{\dagger\dagger}$ – p=0.063.

			Genotype			
			EM + IM		PM	
			Median	**IQR**	**Median**	**IQR**
PANSS	Baseline	Positive	22	10	23	12
		Negative	19	12	24	7
		General	39	24	42	20
		Total	79	33	85	32
	Endpoint	Positive	9*	7*	15*	9*
		Negative	$11_{\dagger}$	$11_{\dagger}$	$21_{\dagger}$	$11_{\dagger}$
		General	$25_{\ddagger}$	$10_{\ddagger}$	$35_{\ddagger}$	$11_{\ddagger}$
		Total	$48_{\S}$	$26_{\S}$	$66_{\S}$	$33_{\S}$
	Percentage reduction		$39.76_{\|}$	$50_{\|}$	$9.84_{\|}$	$20.5_{\|}$
Adverse Effects			**Percentage**		**Percentage**	
	Psychic		65.52%		80%	
	Neurological		41.38%		60%	
	Autonomous		51.72% $_{\dagger\dagger}$		100% $_{\dagger\dagger}$	
	Other		41.38%		60%	
	All adverse effects		58.62%		100%	
Outcome	Remission		68.97%		40%	
	Drop-out	All	55.17%		80%	
		Due to insufficient treatment effect	37.93%		60%	
		Due to adverse effects	24.14%		0%	
Dosages			**Median**	**IQR**	**Median**	**IQR**
	Risperidone		21.33	21	20.75	7.25
	All AP		$2567_{\P}$	$2133_{\P}$	$4130.9_{\P}$	$2200_{\P}$
	CYP2D6 dependent AP		2250	2150	2075	725
	non-CYP2D6 dependent AP		60 **	1201**	1917**	2100**
Co-medication			**Percentage**		**Percentage**	
	Antiparkinsonics		34.48%		80%	
	Benzodiazepines		82.76%		100%	
	Beta-blockers		6.9%		0%	

including serotoninergic and adrenergic, were suggested to modify antipsychotic action and the severity of adverse effect (Svensson 2003; Travis *et al.* 1998). In fact, risperidone and 9-OH-risperidone show slight differences in affinities to receptors in these exact systems (NIMH Psychoactive Drug Screening Program 2011). The cause of the differences observed between CYP2D6 genotype group might be the interactions of different ratios of risperidone and 9-OH-risperidone on several receptor systems.

It may also be that the course of the psychosis itself is modified by different CYP2D6 activity. CYP2D6 is present in the brain and affects the metabolism of not only antipsychotics, but of endogenous amines, too (Dutheil *et al.* 2008). For example, some effect on the course of schizophrenia was reported in a Slovenian study where the PM phenotype was associated with more persistent, negative symptomatology (Plesnicar *et al.* 2006). In our study, a similar finding is apparent – PM group showed a higher negative symptomatology after risperidone treatment.

Safety

Even though in our sample the PM group showed trend toward a higher frequency of autonomic adverse effects, no statistically significant difference between the PM group and other genotypes was observed.

Such findings contradict the results of several studies (Bork *et al.* 1999; de Leon *et al.* 2005; Laika *et al.* 2009) and the hypothesis that defective CYP2D6 metabolism leads to higher levels of risperidone which permeates the blood-brain barrier more easily than 9-OH-risperidone, and which leads to more adverse effects.

Our sample might have been too small to capture a statistically significant difference in adverse effect severity. This is probable, because the PM genotype group indeed showed higher frequency of patients with more severe adverse effects, albeit insignificantly. However, there is another hypothesis to consider: Some adverse effects might have been wrongly attributed as symptoms of the psychotic disorder measured by the scale of psychotic symptoms. Indeed, comparing the scales used (PANSS and UKU) might lead to discoveries of several similar symptoms. This is especially the case not only for several items in "psychic" and "autonomic" sub-scales of the UKU, but also the "neurological", as well as some items of the "negative" and "general" sub-scales of the PANSS (UKU – PANSS scales compared: 1.1 "concentration difficulties" – G11 "poor attention", 1.5 "depression" – G6 "depression" and G3 "feelings of guilt", 1.6 "tension, inner unrest" – G2 "anxiety" and G4 "tension", 1.10 "emotional indifference" – N2 "emotional withdrawal", most of the "autonomous" items can lead to symptom G1 "somatic concern", 1.2 "asthenia, increased fatigability" and 1.3 "sleepiness, sedation" can lead to G7 "motor retardation"). The PM group, in fact, showed higher rates of adverse effects in several UKU sub-scales.

Tab. 4. Medication used during the observation with the notion about possibility of influence on CYP2D6 activity according to Ingelman-Sundberg (Ingelman-Sundberg 2005).

Compound	CYP2D6 status
amantadine	none
biperiden	none
clonazepam	none
diazepam	none
haloperidol	substrate/medium inhibitor
chlorprothixene	none
levocetirizine	none
metoprolol	substrate
metotrimeprazine	substrate/medium inhibitor
olanzapine	none
oxazepam	none
paliperidone	none
promethazine	substrate
ramipril	none
risperidone	substrate
zolpidem	none
zuclopenthixol	substrate

Doses of antipsychotics and co-medication use

The PMs received significantly higher doses of antipsychotics not metabolized by CYP2D6 than the EMs. This finding appears to support the observation of a lower response to risperidone in the PM group. One should keep in mind that in the present study, the usage of other antipsychotics was limited to antipsychotics in the management of acute agitation. The insufficient treatment response in PMs might have lead to a decision to use more sedative medication, sedative antipsychotics being among them.

Limitations of the study

The most obvious limitation of this study was the small sample size. Diagnostic bias might have been present as well. In the observed sample, there were a significant number of patients with acute schizophrenia-like disorder, and it should be kept in mind that in these patients, all diagnostic criteria of schizophrenia were met with the exception of the duration of symptoms. Another limitation is lack of data with regard to patients with the UM genotype. Had it been possible to gather more patients of this rare genotype, the sample size would have been extended significantly. During the current study, no measurements of risperidone and 9-OH-risperidone blood levels were conducted. In this type of pharmacokinetic study, that might be considered a serious drawback; however, as stated before, the effect

of different CYP2D6 activity on the 9-OH-risperidone/risperidone ratio had already been repeatedly demonstrated (Berecz *et al.* 2002; Laika *et al.* 2009; Scordo *et al.* 1999; Olesen *et al.* 1998). This was a naturalistic study and control of different factors – especially co-medication and other antipsychotic use – were limited. This could have lead to unspecific interactions and modifications of risperidone effects. Differences in risperidone and co-medication dosage made any subsequent analysis more difficult to be conducted and generalized. Patients were only observed for a limited time period. These results, therefore, do not relate to long-term schizophrenia treatment.

CONCLUSIONS

In this study, CYP2D6 poor metabolizers treated with risperidone showed a significantly lower reduction in psychotic symptoms, a higher severity of psychotic symptoms after risperidone treatment, especially in negative and general symptoms, and a higher dose of antipsychotics not metabolized by CYP2D6.

Based on these results, patients with the PM genotype, with first-episode schizophrenia, don't appear to be optimal recipients of risperidone treatment. It may be that in PM patients, treatment with antipsychotics not metabolized by CYP2D6 could yield a more favorable outcome.

All the above-mentioned findings and recommendations should be taken with caution. Replication on a larger scale and under more controlled conditions is needed.

ACKNOWLEDGEMENTS

This work was supported by the project "CEITEC – Central European Institute of Technology" (CZ.1.05/1.1.00/02.0068) from the European Regional Development Fund and by research grant NS9676-4/2008 from the Ministry of Health of the Czech Republic, which provided financial support for genotype analysis and covered material expenses of the study.

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