EP.786

Does the *MDR1* C34354T polymorphism influence the occurrence of nausea and sexual dysfunction after paroxetine treatment in the Slovak setting?

Vančová, Z.[1], Dragašek, J.[1], Čižmáriková, M.[2]

[1]1st Department of Psychiatry, , Faculty of Medicine, P. J. Safarik University, Louis Pasteur University Hospital, Kosice, Slovak Republic

[2] Department of Pharmacology, Faculty of Medicine, P. J. Safarik University, Kosice, Slovak republic

Correspondence: zuzana.vancova@upjs.sk

Background

Treatment-resistant depression is a common problem in the treatment of depressive disorder (DD), with 60–70% of all patients meeting its criteria. It has been hypothesized that genetic factors contribute to the variability of antidepressant drug efficacy [1]. Additionally, it has been shown that genetic markers involved in the brain bioavailability of antidepressants and/or toxic substances seem to be better predictors of clinical response than those related to antidepressant plasma concentrations [2]. P-glycoprotein (P-gp) is the transmembrane efflux pump coded by the gene of multidrug resistance 1 (MDR1 or ABCB1), which was initially discovered as the precursor to a protein associated with failure of cancer chemotherapy. It has been confirmed that over-expression of MDR1 causes resistance in cultured tumor cells. Generally, P-gp plays an important role in regulating absorption, distribution, and elimination of drugs. It is strategically positioned to “barrier localizations”, including blood-brain barrier and blood-cerebrospinal fluid barrier, and thus modulates the accumulation of different xenobiotics in the brain [3]. Many drugs have been shown to be P-gp substrates, and P-gp activity may influence their pharmacokinetic parameters, interactions, and finally therapeutic efficacy, as well as occurrence of drug side effects [4, 5]. Similarly, many antidepressants interact with P-gp [6]. Some in vitro studies [7] and in vivo studies [8, 9] have also demonstrated the involvement of paroxetine, as a selective serotonin reuptake inhibitor (SSRI), in P-gp inhibitory activity as well as a substrate of P-gp. Currently, more than 300 variants in the MDR1 gene have been reported.

Aim

As the prevalence and severity of side effects follow interindividual variations, it is reasonable to hypothesize a genetic basis for drug tolerability [10]. Several studies have examined the association between the C3435T polymorphism and risk of adverse clinical events in P-gp substrates treated patients, but the results were inconsistent (11-14).

Based on earlier published data, we performed a statistical analysis of the association of this polymorphism with two side effects of paroxetine: nausea and sexual dysfunction (SD) referred to in the summary of product characteristics as very common (≥1/10).

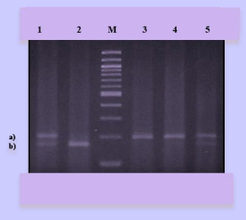
Materials and Methods

Blood samples were collected from 50 patients: 17 males (34%) and 33 females (66%) aged from 20 to 61 years) satisfying ICD-10 criteria for DD (first depressive episodes and recurrent depressive disorder). All cases were of Slovak origin (Caucasians) from different regions of Eastern Slovakia. Research protocol was approved by ethical committee of P. J. Safarik University and written informed consent was obtained from each participant prior to inclusion. Evaluations were made by two independent psychiatrists blind to genetic data Patients were either drug free or after washout phase of an ineffective antidepressants (three weeks for fluoxetine and one week for other antidepressants). Paroxetine was administered in monotherapy at an initial dose of 10–20 mg/day and increased to reach a dose of 40 mg/day from day 12–15 until the end of the trial. Concomitant psychotropic drugs were not allowed, except a low dose of symptomatic benzodiazepine treatment for a minimal duration.

Paroxetine tolerance was assessed through the Utvalg for Kliniske Undersogelser (UKU) rating scale of side effects at baseline and after 6 weeks of treatment, with a focus on the frequency of the side effects of nausea and SD.

DNA was extracted from blood lymphocytes using standard methods and screening for *MDR1* C3435T polymorphism was performed by restriction fragment length polymorphism (Fig.1).

Figure 1: Electrophoretic patterns for *MDR1* (C3435T) polymorphism evaluated by PCR-RFLP based assay:
- ❖ CC genotype (Lane 2), 158 bp (b)
- ❖ CT genotype (Lane 1. 5), 197 and 158 bp (a, b)
- ❖ TT genotype (Lane 3, 4) 197 bp (a)
- ❖ M (Marker, 100 bp ladder)



bp = base pairs

Results

- ❖ We observed a statistically significant association between occurrence of T allele and absence of SD after 6 weeks of the treatment with paroxetine (Table 1).

Table 1: C3435T genotype and allele frequencies: without SD vs with SD, n=50

Genotype/allele	With SD n=15 (%)	Without SD n=35 (%)	P	OR	95% CI
C	13 (43,3%)	21 (30,0%)		1,00	Ref.
T	17 (56,7%)	49 (70,0%)	[a]0,039*	3,47	1,03-11,68
CC	2 (13,3%)	3 (8,6%)		1,00	Ref.
CT	9 (60,0%)	15 (42,9%)	[b]1,000	1,11	0,15-7,98
TT	4 (26,7%)	17 (48,6%)	[b]0,558	2,83	0,35-23,03
CT+TT	13 (86,7%)	32 (91,4%)	[b]0,629	1,64	0,24-11,0
TT	4 (26,7%)	17 (48,6%)		1,00	Ref.
CT	9 (60,0%)	15 (42,9%)	[b]0,205	0,39	0,1-1,54
CC	2 (13,3%)	3 (8,6%)	[b]0,558	0,35	0,04-2,87
CC+CT	11 (73,3%)	18 (51,4%)	[b]0,215	0,39	0,1-1,45

- ❖ After exclusion of 16 patients who reported SD also at the beginning of the treatment (symptom of depression?), we observed the statistically significant association in a residual sample – all patients with at least one C allele reported after 6 weeks of treatment with paroxetine the occurrence of SD (Table 2).

Table 2: C3435T genotype and allele frequencies: without SD vs with SD, n=34

Genotype/allele	With SD n=7 (%)	Without SD n=27 (%)	P	OR	95% CI
C	8 (57,1%)	15 (27,8%)		1,00	Ref.
T	6 (42,9%)	39 (72,2%)	[a]0,057	3,47	1,03-11,68
CC	1 (14,3%)	1 (3,7%)		1,00	Ref.
CT	6 (85,7%)	13 (48,1%)	[b]1,000	2,17	0,11-40,84
TT	0 (0,0%)	13 (48,1%)	[b]0,133	27	0,72-1007
CT+TT	6 (85,7%)	26 (96,3%)	[b]0,374	4,33	0,24-79,64
TT	0 (0,0%)	13 (48,1%)		1,00	Ref.
CT	6 (85,7%)	13 (48,1%)	[b]0,059	0,08	0-1,51
CC	1 (14,3%)	1 (3,7%)	[b]0,133	0,04	0-1,38
CC+CT	7 (100,0%)	14 (51,9%)	[b]0,029*	0,07	0-1,38

*[a] = χ^2-test; [b] = Fisher exact test; * = significant result; Ref. = reference genotype*

Conclusion

- ❖ We observed a statistically significant association between *MDR1* C3435T polymorphism of *MDR1* gene and occurrence of SD
- ❖ In our study, it was present a statistically significant association between occurrence of T allele and absence of SD after 6 weeks of the treatment with paroxetine
- ❖ After exclusion of patients who reported SD also at the beginning of the treatment. we observed the statistically significant association: all patients with at least one C allele reported after 6 weeks of treatment with paroxetine the occurrence of SD
- ❖ The occurrence of nausea in our sample was not statistically significant influenced by aforementioned polymorphism (statistical data not shown)

References

1. Crisafulli C, Fabbri C, Porcelli S et al: Pharmacogenetics of antidepressants. Front Pharmacol, 2011; 2: 6
2. Gassó P, Rodríguez N, Mas S et al: Effect of CYP2D6, CYP2C9 and ABCB1 genotypes on fluoxetine plasma concentrations and clinical improvement in children and adolescent patients. Pharmacogenomics J, 2014; 14(5): 457–62
3. Thuerauf N, Fromm MF. The role of the transporter P-glycoprotein for disposition and effects of centrally acting drugs and for the pathogenesis of CNS diseases. Eur Arch Psychiatry Clin Neurosci, 2006; 256: 281–86
4. Eichelbaum M, Fromm MF, Schwab M: Clinical aspects of the MDR1 (ABCB1) gene polymorphism. Ther Drug Monit, 2004; 26: 180–85
5. Ieiri I, Takane H, Otsubo K: The MDR1 (ABCB2) gene polymorphism and its clinical implications. Clin Pharmacokinet, 2004; 43(9): 553–76
6. Lee G, Bendayan R: Functional expression and localization of P-glycoprotein in the central nervous system: Relevance to the pathogenesis and treatment of neurological disorders. Pharm Res, 2004; 21: 1313–30
7. Feng B, Mills JB, Davidson RE et al: In vitro P-glycoprotein assays to predict the in vivo interactions of P-glycoprotein with drugs in the central nervous system. Drug Metab Dispos, 2008; 36: 268–75
8. Doran A, Obach RS, Smith BJ et al: The impact of P-glycoprotein on the disposition of drugs targeted for indications for the central nervous system: Evaluation using the MDR1A/1B knockout mouse model. Drug Metab Dispos, 2005; 33: 165–74
9. Uhr M, Grauer MT, Holsboer F: Differential enhancement of antidepressant penetration into the brain in mice with ABCB1ab (MDR1ab) P-glycoprotein gene disruption. Biol Psychiatry, 2003; 54: 840–46
10. Murphy GM Jr., Hollander SB, Rodrigues HE et al: Effects of the serotonin transporter gene promoter polymorphism on mirtazapine and paroxetine efficacy and adverse events in geriatric major depression. Arch Gen Psychiatry, 2004; 61(11): 1163–69
11. Luo M, Li J, Xu X et al. ABCB1 C3435T polymorphism and risk of adverse clinical events in clopidogrel treated patients: a meta-analysis. Thromb Res, 2012; 129(6): 754-759
12. Takakuwa O, Oguri T, Uemura T et al. ABCB1 polymorphism as a predictive biomarker for amrubicin-induced neutropenia. Anticancer Res, 2014; 34(7): 3517-3522
13. Suzuki Y, Tsuneyama N, Fukui N et al. Effect of risperidone metabolism and P-glycoprotein gene polymorphism on QT interval in patients with schizophrenia. Pharmacogenomics J, 2014; 14(5), 452-456
14. Ozbey G, Celikel FC, Cumurcu BE et al. Influence of ABCB1 polymorphisms and serum concentrations on venlafaxine response in patients with major depressive disorder. Nord J psychiatry, 2017; 71(3): 230-237

Acknowledgements

This project was supported by the Slovak Grant Agency for Science (VEGA grant No. 1/0302/10).