Brief Report CNPT9(2018)3-6

The Japanese Society of Clinical Neuropsychopharmacology
Clinical Neuropsychopharmacology and Therapeutics

Serum creatine kinase elevation by atypical antipsychotics and genetic polymorphisms of the 5-HT2A receptor and the cytochrome P450 2D6: a preliminary finding

Akifumi Nakamura, M.D., Ph.D., Kazuo Mihara, M.D., PhD., Goyo Nagai, M.D., PhD., Noboru Sakumoto, M.D., Ph.D., Tsuyoshi Kondo, M.D., Ph.D.

Department of Neuropsychiatry, Graduate School of Medicine, University of the Ryukyus, Japan

ABSTRACT

Purpose: Marked elevations of serum creatine kinase (CK) activity in schizophrenia treated with atypical antipsychotics is regarded as a sign of neuroleptic malignant syndrome or rhabdomyolysis. It is suggested that atypical antipsychotics antagonize the 5-HT2A receptor in skeletal muscle, leading to changes in the sarcolemma which increases its permeability to CK. The 5-HT2A receptor gene (*HTR2A*) contains the T102C and His452Tyr polymorphisms, both of which affect the 5-HT2A receptor function. Meanwhile, the cytochromeP450 2D6 (CYP2D6), which shows a genetic polymorphism, may be involved in the development of CK elevation, because most antipsychotics are predominantly metabolized by this enzyme. This study aimed to investigate the relationship between the occurrence of CK elevation by atypical antipsychotics and these polymorphisms.

Methods: The subjects were 15 Japanese schizophrenic patients who had developed CK elevation during the administration of atypical antipsychotics. The *HTR2A* T102C and His452Tyr, and *CYP2D6* polymorphisms were determined by the polymerase chain reaction methods.

Results: The allele frequencies of these polymorphisms were as follows: 102T, 40% vs. 102C=60%; His452, 100% vs. 452Tyr=0%; wild type for *CYP2D6*, 77% vs. **10*=13% vs. **5*=10%, respectively. Genotype patterns and allele frequency were nonspecific.

Conclusions: These findings suggest that these genetic polymorphisms are not related to the development of CK elevation by atypical antipsychotics.

Keywords: creatine kinase, atypical antipsychotics, 5-HT2A T102C and His452Try polymorphisms, CYP2D6 polymorphism

Received January 19, 2018 / Accepted February 13, 2018 / Published March 14, 2018.

INTRODUCTION

There have been many case reports which have showed marked elevation of serum creatine kinase (CK) during the treatment with atypical antipsychotics [1]. The CK elevation is regarded as a major sign of rhabdomyolysis due to the damage of the skeletal muscle by atypical antipsychotics or

Corresponding Author: Kazuo Mihara, M.D., Ph.D., Department of Neuropsychiatry, Graduate School of Medicine, University of the Ryukyus, 207 Uehara, Nishihara-cho, Okinawa 903-0215, Japan; Tel.: +81-98-895-1157, Fax: +81-98-895-1419, E-mail: miharak@med.u-ryukyu.ac.jp

neuroleptic malignant syndrome, although the elevation seems to be self-limiting in some cases [1]. Hermesh et al. [2] have suggested that high CK level in schizophrenic patients treated with antipsychotics is a risk factor for the future development of neuroleptic malignant syndrome. In either case, the causative drugs should be rapidly discontinued, and intravenous hydration is sometimes necessary as an early intervention. However, no definite risk factors for CK elevation have ever been found.

Atypical antipsychotics have potent 5-HT2A receptor antagonistic property, and the receptor is widely distributed in skeletal muscles [1]. It has been hypothesized that atypical antipsychotics antagonize the 5-HT2A receptor in skeletal muscle, leading to changes in the sarcolemma which increases its permeability to CK [1]. Meanwhile, among several 5-HT2A receptor gene (*HTR2A*) polymorphisms, the T102C polymorphism is in linkage disequilibrium with the -1438A/G polymorphism in the promoter region which may affect expression of 5-HT2A promoter activity [3]. Another *HTR2A* polymorphism, His452Tyr, which causes an amino acid change, leads to a blunted signal downstream of receptor activation [3]. Therefore, it is possible that these polymorphisms are related to the development of the CK elevation by atypical antipsychotics.

On the other hand, most atypical antipsychotics are predominantly metabolized by the cytochromeP450 2D6 (CYP2D6) which shows a genetic polymorphism [4]. The several mutated alleles of the *CYP 2D* locus that inhibit enzyme activity, i.e., *CYP2D6 *5* (*5*) or decrease enzyme activity, i.e., *CYP2D6 *10* (*10*) have been reported [4]. Also, it is possible that lower CYP2D6 activity causes higher drug concentrations, leading to an increased risk for skeletal muscle damages even when giving usual dose of atypical antipsychotics.

Therefore, this study is aimed at investigating the relationship between the CK elevation and these genetic polymorphisms.

SUBJECTS AND METHODS

The subjects were 15 Japanese schizophrenic patients according to DSM-IV. Nine were males, and 6 were females. The mean ± SD of age was 50.1 ± 13.8. They had developed the elevation of CK during the administration of atypical antipsychotics. The causative drugs were risperidone 2-8 mg/day for 11 cases, quetiapine 150 and 400 mg/day for 2 cases, olanzapine 15 mg/day for 1 case, and zotepine 75 mg/day for 1 case.

There was no evidence of intramuscular injection, severe agitation, myotoxic drugs including statins in all the patients. The physical diagnosis including myocardial infarction, polymyositis, myopathy, substance abuse and thyroid disease were ruled out. This study was approved by the Ethics Committee of University of the Ryukyus, and written informed consent was obtained from the patients and their families.

10 ml of blood was drawn from each subject, and DNA was isolated from peripheral leukocytes by the guanidinium isothiocyanate method. These polymorphisms mentioned above were determined by the PCR [3, 4].

RESULTS

Table 1 shows the genotype profiles and the clinical characteristics in 15 patients. The following genotypes were determined: 2 homozyogtes of the 102T allele, 8 heterozygotes of the 102T and 102C alleles, and 5 of homozygotes of the 102C allele for the T102C polymorphism; 15 homozygotes of the 452His allele for the His452Tyr polymorphism; 9 homozygotes of the wild-type (*wt*) allele, 3 of heterozygotes of the **10* and *wt* alleles, and 2 of heterozygotes of the **5* and *wt* alleles, and 1 heterozygotes of the **5* and **10* alleles for the *CYP2 D6* polymorphism. The allele frequencies (Table 2) of these polymorphisms were as follows: 102T, 40% vs. 102C=60%; 452His, 100% vs. 452Tyr= 0%; *wt*, 77% vs. **10*=13% vs. **5*=10%, respectively. Genotype patterns and allele frequency were nonspecific, compared to these values in other studies [5, 6] (Table 2).

DISCUSSION

Although small number of patients did not allow us to compare with the comparative patients without the CK increase, no deviations in genotypes or alleles were observed when comparing previously reported data in Japanese patients with schizophrenia. This study suggests that these polymorphisms are not related to the development of CK increase induced by atypical antipsychotics. This may indicate that genotyping of these polymorphisms does not have predictive values of the CK increase. However

Table 1. Genotype profiles of T102C, His452Try and CYP2D6 polymorphisms and the clinical characteristics of 15 Japanese schizophrenic patients with high CK

Case	Sex	102T/C	His452Try	CYP 2D6	Age at onset of high CK	Causative drugs		Peak serum CK (IU/L)[1]	Time to normalize	Fever (ºC)	Muscular rigidity	Autonomic symptoms[2]
						Daily dose	Duration of treatment					
1	M	102T/T	His452His	w/*10	62	RIS 2 mg	12 days	2237	6 days	37.2	-	-
2	F	102T/T	His452His	wt/wt	37	RIS 3 mg	2 months	882	14 days	38.2	+	+
3	M	102T/C	His452His	*5/*10	23	RIS 2 mg	18 days	4050	10 days	37.0	-	-
4	M	102T/C	His452His	wt/*10	32	RIS 8 mg	14 days	4388	23 days	38.4	++	++
5	M	102T/C	His452His	wt/*10	62	RIS 4 mg	21 days	7120	14 days	37.4	-	-
6	M	102T/C	His452His	wt/wt	50	RIS 6 mg	4 days	1259	17 days	37.8	-	++
7	M	102T/C	His452His	wt/wt	56	RIS 3 mg	1 month	5276	3 months	-	-	-
8	F	102T/C	His452His	wt/wt	66	QTP 150 mg	26 days	958	13 days	39.2	+	++
9	M	102T/C	His452His	wt/wt	58	QTP 400 mg	25 days	4450	1 month	-	+	-
10	M	102T/C	His452His	wt/wt	67	RIS 5 mg	8 days	7120	7 days	38.5	-	++
11	F	102C/C	His452His	wt/*5	48	RIS 6 mg	56 days	877	1 month	39.5	+	-
12	F	102C/C	His452His	wt/*5	39	RIS 6 mg	14 days	774	7 days	39.3	-	-
13	F	102C/C	His452His	wt/wt	54	RIS 8 mg	15 days	2800	9 days	39.0	-	-
14	M	102C/C	His452His	wt/wt	32	OLZ 15 mg	8 days	3033	11 days	37.0	++	-
15	F	102C/C	His452His	wt/wt	48	ZTP 75 mg	9 days	1980	5 days	-	-	-

Abbreviations: RIS: risperidone; QTP: quetiapine; OLZ: olanzapine; ZTP: zotepine

[1]CK level, normal values, 34-190 IU/L for male and 29-135 IU/L for female

[2]Hypertension, tachycardia, profuse diaphoresis, and dysuria

Table 2. Allele frequencies in this and other studies

	102T	102C	His452	Tyr452	*Wt*	**10*	**5*
This study	40	60	100	0	77	13	10
Other studies*	49	51[a]	99	1[b]	65	31	4[c]

*Previously reported data in Japanese schizophrenic patients. Values are %.

[a]Ohara et al[5]: *n*=119; [b]Kawanishi et al[6]: *n*=94; [c]Suzuki et al[7]: *n*=89.

there are some possible explanations for these negative results.

First, the severity and course of CK elevation in the patients was not evaluated. Because of ethical reasons, atypical antipsychotics were discontinued immediately when increased CK level was found in all cases. Therefore, it was unclear whether the CK increase was self-limiting or not. The possibility that these polymorphisms affect the degree and prognosis of CK elevation cannot be entirely ruled out. Second, the polymorphisms were not studied in relation to the causal drugs due to the small number of patients. Some polymorphisms could be vulnerable to certain drugs thus affecting the development of the CK elevation. Third, as mentioned above, the comparative patients was not included in the present study. Thus, well-controlled comparison in larger-scaled studies should be warranted.

CONFLICTS OF INTEREST

Dr. Mihara has received research grants from Mitsubishi Pharma Research Foundation, Japan. The other authors declare no competing interests to report.

ACKNOWLEDGEMENT

This study was supported by a grant from the Japanese Ministry of Education, Culture, Sports, Science and Technology (#16790696, #19591366, #25461736, and 17K10311). We thank Mr. David Webb, Dr Yuzuru Nakamoto and Dr Shumpei Takahara for thier helpful advice.

REFERENCES

[1] Laoutidis ZG, Kioulos KT. Antipsychotic-

induced elevation of creatine kinase: a systematic review of the literature and recommendations for the clinical practice. Psychopharmacology 2014; 231:4255-4270.

[2] Hermesh H, Manor I, Shiloh R, Aizenberg D, Benjamini Y, Munitz H, Weizmen A. High serum creatinine kinase level: possible risk factor for neuroleptic malignant syndrome. J Clin Psychopharmacol 2002; 22: 252-256.

[3] Serretti A, Drago A, De Ronchi D. HTR2A gene variations and psychiatric disorders: a review of current literature and selection of SNPs for future studies. Curr Med Chem 2007; 14: 2053-2069.

[4] Teh LK, Bertilsson L. Pharmacogenetics of *CYP2D6*: molecular genetics, interethnic differences and clinical importance. Drug Metab Pharmacokinet 2012; 27: 55-67.

[5] Ohara K, Nagai M, Tani K, Tsukamoto T, Ohara K. Schizophrenia and the serotonin-2A receptor promoter polymorphism. Psychiat Res 1999; 85: 221-224.

[6] Kawanishi C, Hanihara T, Shimoda Y, Suzuki K, Sugiyama N, Onishi H, Miyakawa T, Yamada Y, Kosaka K. Lack of association between neuroleptic malignant syndrome and polymorphisms in the 5-HT_{1A} and 5-HT_{2A} receptor genes. Am J Psychiatry 1998; 155: 1275-1277.

[7] Suzuki T, Mihara K, Nakamura A, Kagawa S, Nagai G, Nemoto K, Kondo T. Effects of genetic polymorphisms of CYP2D6, CYP3A5, and ABCB1 on the steady-state plasma concentrations of aripiprazole and its active metabolite, dehydroaripiprazole, in Japanese patients with schizophrenia. Ther Drug Monit 2014; 36: 651-655.