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

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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 His452Tyr polymorphisms, CYP2D6 polymorphism

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...
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 homozygotes 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 CYP2D6 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
tics of 15 Japanese schizophrenic patients should be warranted. Above, the comparative patients was not included in the study. Further, the polymorphisms were not studied in all cases. Therefore, it was unclear whether the CK elevation immediately when increased CK level was found in all cases. Thus, well-controlled comparison in larger-scaled studies should be warranted.

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 | CYP2D6 | Age at onset of high CK | Causative drugs | Duration of treatment | Peak serum CK (IU/L) | Time to normalize | Fever (°C) | Muscular rigidity | Autonomic symptoms |
|------|-----|--------|-----------|--------|-------------------------|----------------|----------------------|---------------------|-----------------|-----------|-----------------|-------------------|
| 1    | M   | 102T/T | His452His | w/w    | 62                      | RIS 2 mg       | 12 days              | 2237                | 6 days           | 37.2      | -               | -                 |
| 2    | F   | 102T/T | His452His | w/w    | 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 | w/*10  | 32                      | RIS 8 mg       | 14 days              | 4388                | 23 days          | 38.4      | ++              | ++                |
| 5    | M   | 102T/C | His452His | w/*10  | 62                      | RIS 4 mg       | 21 days              | 7120                | 14 days          | 37.4      | -               | -                 |
| 6    | M   | 102T/C | His452His | w/w    | 50                      | RIS 6 mg       | 4 days               | 1259                | 17 days          | 37.8      | -               | ++                |
| 7    | M   | 102T/C | His452His | w/w    | 56                      | RIS 3 mg       | 1 month              | 5276                | 3 months         | -         | -               | -                 |
| 8    | F   | 102T/C | His452His | w/w    | 66                      | QTP 150 mg     | 26 days              | 958                 | 13 days          | 39.2      | +               | ++                |
| 9    | M   | 102T/C | His452His | w/w    | 58                      | QTP 400 mg     | 25 days              | 4450                | 1 month          | -         | -               | -                 |
| 10   | M   | 102T/C | His452His | w/w    | 67                      | RIS 5 mg       | 8 days               | 7120                | 7 days           | 38.5      | -               | ++                |
| 11   | F   | 102C/C | His452His | w/*5   | 48                      | RIS 6 mg       | 56 days              | 877                 | 1 month          | 39.5      | +               | -                 |
| 12   | F   | 102C/C | His452His | w/*5   | 39                      | RIS 6 mg       | 14 days              | 774                 | 7 days           | 39.3      | -               | -                 |
| 13   | F   | 102C/C | His452His | w/w    | 54                      | RIS 8 mg       | 15 days              | 2800                | 9 days           | 39.0      | -               | -                 |
| 14   | M   | 102C/C | His452His | w/w    | 32                      | OLZ 15 mg      | 8 days               | 3033                | 11 days          | 37.0      | ++              | -                 |
| 15   | F   | 102C/C | His452His | w/w    | 48                      | ZTP 75 mg      | 9 days               | 1980                | 5 days           | -         | -               | -                 |

Abbreviations: RIS: risperidone; QTP: quetiapine; OLZ: olanzapine; ZTP: zotepine
1CK level, normal values, 34-190 IU/L for male and 29-135 IU/L for female
2Hypertension, 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   | 99     | 1      | 65 | 31  | 4  |

*Previously reported data in Japanese schizophrenic patients. Values are %.
*Ohara et al: n=119; *Kawanishi el al: n=94; *Suzuki et al: 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

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