

Rhabdomyolysis After the Administration of Clarithromycin in a Japanese Schizophrenic Patient Receiving Aripiprazole: A Possible Impact of CYP2D6 Genotype

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ABSTRACT

The patient was a 67-year-old man. After the patient received a diagnosis of schizophrenia, various antipsychotics were prescribed but did not improve symptoms. However, 18 mg/day aripiprazole (APZ) was found to be highly effective and enabled the patient to continue treatment on an outpatient basis. Two weeks after prescribing clarithromycin for fever and cough, he was readmitted to our psychiatric ward because of anuresis and deterioration of bradykinesia and salivation. Biochemical analysis revealed elevated serum creatine phosphokinase (26060 U/I) and creatinine (2.2 mg/dL). On admission, the patient had a high blood concentration of APZ and its metabolite(s). APZ was therefore discontinued, but the concentration remained elevated until day 8. Hemodialysis was started on day 4 to treat persistent renal dysfunction. The patient's CYP2D6 genotype was *CYP2D6*10/CYP2D6*10*. The elevated APZ levels may have resulted from the inhibitory action of clarithromycin on CYP3A4 combined with the lower inherent CYP2D6 enzymatic activity of the *CYP2D6*10/CYP2D6*10* genotype.

Keywords: *cytochrome P450, drug interaction, aripiprazole, clarithromycin*

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INTRODUCTION

The cytochrome P450 members CYP1A2, CYP2C19, CYP2D6, and CYP3A4 participate in the oxidative metabolism of many psychotropic agents, thereby influencing the clinical response of psychiatric patients to these agents. Allelic variation results in significant individual differences in enzymatic activity, such as the intermediate activity conferred by the *CYP2D6*10* allele. Such variation may increase the risk of adverse events to single agents and drug interactions. The antibiotic clarithromycin is a potent inhibitor of CYP3A4[1] and may influence the response to psychotropic agents. Here we present a case of rhabdomyolysis in a schizophrenia patient

resulting from a clarithromycin-aripiprazole interaction.

CASE PRESENTATION

Case: A 67-year-old man.

Life history: Nothing of note at birth or while growing up. The patient began to work after graduating from high school and continued working until retirement. Medical and family history was unremarkable.

Premorbid personality: Obsessive traits.

Current medical history: In year X-9, the patient started to exhibit symptoms of depression and insomnia, for which he visited the outpatient clinic at

Dokkyo Medical University Hospital. The patient was diagnosed as having depression and was prescribed antidepressants. Remission was not achieved, so the patient was additionally prescribed risperidone, olanzapine, and APZ. Although these medications did not cause adverse events, mild depressive symptoms persisted. In year X-3, the patient was admitted to the psychiatric ward of our university hospital due to slowed thinking and depersonalization. After receiving modified electroconvulsive therapy (m-ECT), his depressive symptoms improved and he was discharged. The patient was readmitted in year X-2 for further evaluation because of strange behaviors caused by thought hearing and auditory hallucinations. The patient was diagnosed as having schizophrenia and prescribed blonanserin. However, as his psychotic symptoms did not improve, m-ECT was re-performed but failed to produce long-lasting clinical effects. Consequently, the patient was readmitted due to recurrence of auditory hallucinations. During the course of the patient's disease, risperidone, olanzapine, quetiapine, perospirone, and zotepine were administered with no effect.

Subsequently, typical antipsychotic drugs such as chlorpromazine, haloperidol, and nemonapride were also administered, but were discontinued due to extrapyramidal symptoms and over-sedation. In July of year X-1, treatment was started with 18 mg/day APZ and was found to be highly effective, enabling the patient to continue treatment on an outpatient basis. The dose of APZ was tapered in July of year X because of side effects such as bradykinesia and salivation. In the middle of the same month, the patient developed fever and cough and was prescribed clarithromycin, a macrolide antibiotic, for 5 days by his primary physician. Immediately after starting clarithromycin, the patient developed dysphagia and worsening of bradykinesia and salivation, as well as of anuresis. In August of year X, 2 weeks after starting clarithromycin, he was readmitted to our psychiatric ward. The APZ dose was decreased to 9 mg/day. Figure 1 shows the clinical course over an approximate one-year period from year X-1 when the patient was first prescribed APZ to August of year X when he was readmitted.

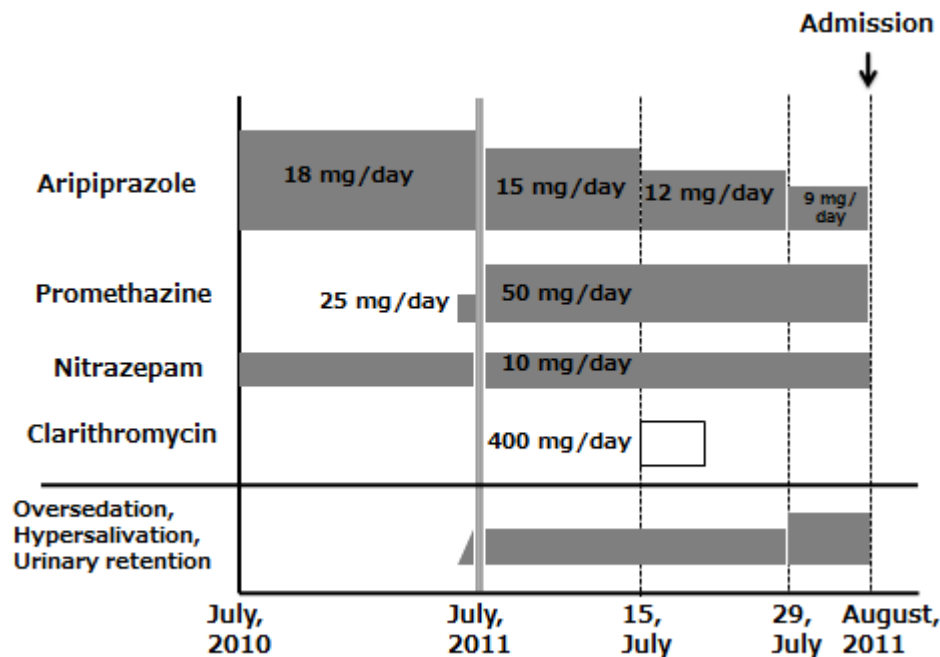


Fig. 1. Clinical course of the patient

Clinical course after latest admission: The patient's speech was slow on admission, but he could communicate and had no apparent impairment of consciousness. The patient's body movements were also slow, but without muscle rigidity. Body temperature was 37.8°C and blood pressure was 87/56 mmHg. Hematological examination revealed an elevated white blood count of 10,300/ μ L, and

biochemical analysis indicated increased creatine phosphokinase (CPK; 26060 U/I) and creatinine (2.2 mg/dL) levels. APZ was discontinued on admission, and the patient was administered drip intravenous infusion of 3000 mL/day of intracellular fluid without potassium. However, hemodialysis was started on day 4 due to exacerbated renal dysfunction, with creatinine reaching 4.9 mg/dL. Hemodialysis improved creati-

nine levels and kidney function. On admission, the patient exhibited high blood levels of APZ and its metabolite, dehydroaripiprazole (see Figure 2), which persisted until day 8. Although negative symptoms such as a flattening of emotional responses and poverty of thought became apparent after physical problems subsided, we did not resume antipsychotic drug administration because of the high risk of further adverse events, and the patient was discharged 121

days after admission. Changes in the blood levels of APZ and its metabolite as well as the changes in serum CPK are shown in Figure 2. Genotyping of CYP2D6 was conducted with approval of the institutional ethics committee and after obtaining informed consent from the patient and his family. Results revealed that the patient carried the CYP2D6 intermediate metabolizer genotype *CYP2D6*10/CYP2D6*10*).

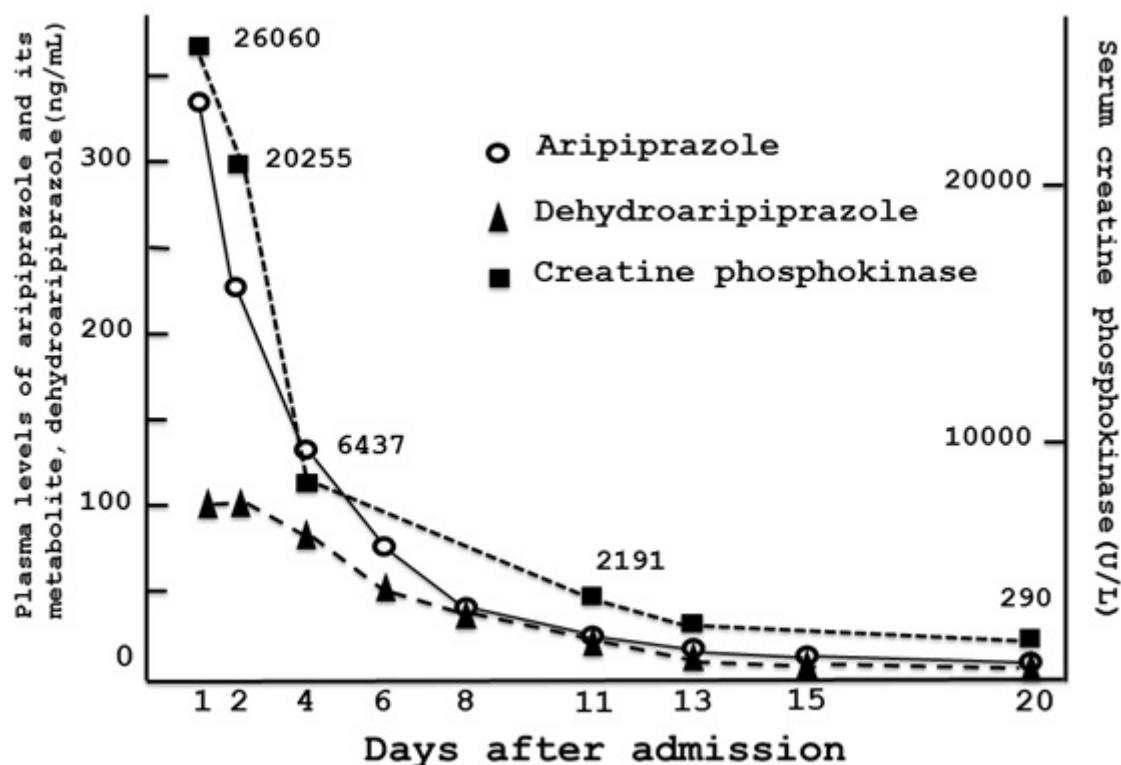


Fig. 2. Changes in plasma aripiprazole, plasma dehydroaripiprazole, and serum creatine phosphokinase during admission

DISCUSSION

Although this treatment-resistant case of schizophrenia finally achieved remission on APZ, the patient developed rhabdomyolysis due to an APZ-clarithromycin interaction. CYP2D6 and CYP3A4 are involved in the metabolism of APZ, and the pharmacological effect of dehydroaripiprazole, the major metabolite of APZ, is similar to that of APZ [2, 3]. The blood concentrations of APZ and its active metabolite dehydroaripiprazole increase when APZ is co-administered with a drug that inhibits CYP2D6 or when it is administered to a patient with impaired CYP2D6 activity [4-6]. Conversely, concomitant use of APZ with a drug that induces CYP3A4 lowers the blood concentration of APZ [6, 7].

A study of Japanese schizophrenia patients found that the blood concentrations of APZ varied depending on

the frequency of CYP2D6 mutant alleles [8]. The plasma APZ level was approximately 123 ng/mL in a CYP2D6 intermediate metabolizer, but only 37 mg/ml in an extensive metabolizer when both were administered the same dose of APZ (3 mg/day for 14 days) [4]. Aripiprazole is most effective when the blood concentration is 150–300 ng/mL, and only mild adverse effects are observed when the concentration reaches 110–249 ng/mL [9]. In the present case, the patient was placed on APZ 9 to 12 mg/day for 14 days prior to his latest admission. Under this regimen, the predicted mean concentration would be in the range of 111–148 ng/mL for a CYP2D6 extensive metabolizer [4]. In this case, however, the plasma concentration was 333 ng/mL on admission, three times higher than expected for a CYP2D6 extensive metabolizer, likely because the patient was homozygous for the *CYP2D6*10* allele. However, the patient was also

taking clarithromycin, which is metabolized by CYP3A4. The metabolite(s) bind irreversibly to CYP3A4 immediately upon generation, resulting in CYP3A4 inactivation. As APZ is also metabolized by CYP3A4, inhibition in a subject with low CYP2D6 activity would result in a substantial elevation in plasma APZ, as observed in the present case.

Rhabdomyolysis is reportedly also caused by the interaction of clarithromycin and statins, the 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors used to treat hyperlipidemia [10]. In addition, concomitant administration of itraconazole, another potent inhibitor of CYP3A4, was shown to reduce the systemic clearance of APZ by approximately 30% in CYP2D6 extensive metabolizers and by 50% in intermediate metabolizers [11]. Thus, inhibition of APZ metabolism due to the co-administration of clarithromycin likely resulted in extremely high plasma levels of APZ, possibly reaching 500-1000 ng/ml in the present case.

The reasons for this elevation in APZ levels may include the inhibitory action of clarithromycin against CYP3A4 and the patient's decreased enzymatic activity of CYP2D6 due to *CYP2D6*10/CYP2D6*10* (i.e., intermediate metabolizer).

CONCLUSIONS

Rhabdomyolysis in the present case likely resulted from elevated APZ levels due to clarithromycin-mediated inhibition of the APZ-metabolizing enzyme CYP3A4. Physicians should be cognizant of the large individual variability in drug efficacy and adverse reactions and provide treatment with potential drug interactions in mind.

CONSENT

Written informed consent was obtained from the patient for publication of this case report.

COMPETING INTERESTS

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AUTHOR CONTRIBUTIONS

TI and TS treated the patient, conducted the literature survey, and wrote the case report. KS conducted a literature survey and helped write the case report. All authors read and approved the final manuscript.

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