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Successful rechallenge with paliperidone after clozapine treatment for a patient with dopamine supersensitivity psychosis

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Abstract

We describe the case of a 49-year-old Japanese male patient successfully treated with a paliperidone rechallenge following 2-year treatment with clozapine for treatment-resistant schizophrenia. He had responded well to conventional antipsychotic treatment for the initial psychotic episode but gradually developed dopamine supersensitivity; even treatment with paliperidone and another antipsychotic medication (a total up to 1700 mg in chlorpromazine-equivalent dose) had not improved his psychotic symptoms. Clozapine treatment produced temporary symptomatic relief, but the clozapine dose could not be increased to > 150 mg due to the patient's intolerance. Following low-dose clozapine treatment for 2 years, a rechallenge with paliperidone monotherapy ameliorated his psychotic symptoms. This suggests that clozapine may have the potential to release the dopamine supersensitivity state. Our patient's case indicates that for patients with dopamine supersensitivity psychosis, a rechallenge with a previously ineffective antipsychotic after clozapine treatment may be successful.

Keywords

Dopamine supersensitivity psychosis, clozapine, paliperidone, dopamine D2 receptor, treatment-resistant schizophrenia

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Background

Despite extensive research into the development of antipsychotics over the past five decades, some patients with schizophrenia respond poorly to doses of the drugs that are even higher than the recommended doses; these patients are often considered to have treatment-resistant schizophrenia (TRS). It is estimated that from one-fifth to one-half of patients with schizophrenia eventually develop TRS.[1] While the actual pathophysiology of TRS remains unknown, TRS patients' responses to antipsychotics are roughly divided into two types: initial resistance and resistance that emerges over time. A central theory for the former type of TRS is the "normodopaminergic" hypothesis that includes alteration of the glutamatergic system.[2] Some patients with the latter type of TRS have responded to antipsychotics in the early period of treatment but later became resistant to the drugs, possibly due to a compensatory increase in dopamine D2 receptors (DRD2) induced by a prolonged excessive blockade of DRD2 by antipsychotics.[3–5] This pathology has sometimes been called "dopamine supersensitivity psychosis" (DSP).[4]

The proposed diagnostic criteria of DSP are as follows: (1) remissionable psychotic symptom(s) by antipsychotic treatment at the first episode, (2) tolerance to antipsychotic effects has developed, (3) increased vulnerability to stress, (4) acute recurrence and worsening of psychotic symptoms by the reduction or withdrawal of antipsychotic(s), or (5) the presence of tardive dyskinesia.[3,6] Individuals with DSP initially respond to the appropriate antipsychotic therapy but develop treatment resistance over time. In Japan, patients with DSP account for approximately 72% of the patients who show TRS.[7]

The atypical antipsychotic clozapine (CLZ) is the only medication that has shown confirmed effectiveness against

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TRS. In their study of DSP, Nakata et al.[8] reported that the administration of CLZ to patients with DSP and TRS led to an improvement of symptoms, followed by 2 years with no exacerbation. A recent meta-analysis of 16 studies confirmed that CLZ treatment improved the symptom of antipsychotic-induced tardive dyskinesia.[9] In a basic research study, Kim et al.[10] speculated that the reversal of dopamine supersensitivity is a viable mechanism of action of CLZ, based on unique properties of this drug. Clozapine may thus have the potential to release patients from the DSP state.

Herein we present the case of our patient with DSP for whom the dose of CLZ could not be increased due to his diabetes mellitus (DM) and excessive somnolence. After 2 years of CLZ treatment, his psychotic symptoms were significantly improved by a rechallenge with paliperidone (PAL), which had not worked efficiently before his treatment with CLZ.

Case presentation

Our patient was a 49-year-old Japanese male with schizophrenia and type 2 DM. At the age of 18, after his enrollment in a university, he visited our hospital because he had experienced an auditory hallucination and persecutory delusions. He was diagnosed with schizophrenia and received antipsychotic treatment. He achieved remission and obtained employment after graduating from the university, but he eventually experienced a relapse and quit his job. At the ages of 24–31 years, he was admitted to our hospital several times due to relapses, and his symptoms gradually worsened, although he was under daily treatment with haloperidol 6–9 mg and clocapramine 150 mg (700–800 mg in chlorpromazine-equivalent (CP) dose).

At the ages of 36–40 years, the patient's pathological experiences continued and psychomotor excitement repeated. His medication was then adjusted: haloperidol decanoate was increased to 100 mg and risperidone 5 mg was added in combination (CP: 1200–1400 mg). At the age of 47, the patient repeatedly lost his temper quite easily with only trivial stress, and he stopped going to the hospital. We therefore arranged visiting nursing care for him, and his mother confirmed his adherence to his treatment regimen every day. However, his psychotic state was not improved even by PAL 12 mg and blonanserin 36 mg (CP: 1700 mg). He was then admitted to our hospital, and his symptoms met the above-described diagnostic criteria for DSP (i.e. remissionable psychotic symptoms and tolerance to antipsychotics).

We introduced CLZ despite the patient's DM with the HbA1c value 12.6%, suspecting that its benefits outweighed the risk of hyperglycemia. Nevertheless, it was difficult to raise the CLZ dose to $>$ 150 mg due to the patient's excessive somnolence. He was thus discharged under treatment with CLZ 150 mg, which alleviated his psychotic symptoms to the extent of a minimum requirement. In April 2018, he began to reject regular clinic visits because of a reluctance to undergo frequent blood sampling.

In May 2018, the patient showed irrational speech and behavior, and he refused medical treatment. He was involuntarily admitted to our hospital with his mother's consent. The side effects of clozapine 150 mg such as somnolence and vertigo in addition to his DM made it inadvisable to increase the CLZ dose. We speculated that the patient's 2-year treatment with CLZ might have released DSP, and we thus administered a rechallenge with PAL. After his admission, he was managed in segregation. On the 7th day of his stay, we introduced PAL 6 mg/day by cross-titration after an assessment of his condition with CLZ.

The PAL dose was gradually increased, and the CLZ dose was gradually decreased. On the 19th day of admission, the PAL dose was 12 mg/day and the CLZ was discontinued. On the 7th, 27th, and 72nd days after the patient's admission, his Positive and Negative Syndrome Scale (PANSS)[11] scores were 33, 28, and 21 points on the positive scale; 39, 35, and 34 points on the negative scale; and 65, 54, and 48 points on the general psychopathology scale. In clinical assessments, the patient stopped shouting at staff members and stopped showing reluctance to take a shower. Since the PAL 12 mg improved his psychotic symptoms, we switched from the PAL extended-release tablet to a 150 mg long-acting injection that could counteract the patient's lack of adherence to oral administration and reduce the frequency of his hospital visits as an outpatient. When he was discharged on the 75th day post-admission, his Global Assessment of Functioning (GAF)[12] score had improved to 50 points from 25 points at admission. Over 18 months have passed since his discharge, and he has maintained remission as an outpatient.

Discussion

In our patient's case, a rechallenge with PAL — which had not been effective for him before the CLZ administration — ameliorated his psychotic symptoms, suggesting that his 2-year CLZ treatment improved his dopamine supersensitivity state. To our knowledge, this is the first published report describing a successful rechallenge with an antipsychotic after CLZ treatment.

Iyo et al.[4] proposed the following therapeutic principles for DSP in terms of both prevention and treatment: (1) second-generation antipsychotics should be selected in order to avoid the development of TD, (2) the therapeutic dose that does not induce extrapyramidal symptoms or dysphoria should be determined, (3) antipsychotics or a depot form that stabilizes the brain concentration of the drugs should be selected, and (4) antipsychotics that possess higher affinity for DRD2 should be used. We therefore selected a rechallenge with PAL instead of haloperidol or clocapramine. Before his CLZ regimen, our patient was treated with PAL and blonanserin, both of which have a long elimination time from the body and bind strongly to DRD2. These antipsychotics had little effect.

Interestingly, it was reported that the effectiveness of the above treatment strategy was rarely different from that of

CLZ for patients under treatment with a CP dose < 1000 mg, whereas CLZ is more effective for patients with a CP dose > 1000 mg.[13] In our patient's case, the PAL may have had little effect before his CLZ treatment because he had been treated with antipsychotics amounting to CP 1700 mg.

Clozapine has multiple pharmacological functions and has shown significantly greater effects than other antipsychotics. There are several reports that in contrast to typical antipsychotics, repeated treatment with CLZ or other atypical antipsychotics induced an increase in the level of dopamine in the substantia nigra, and it was noted that treatment with the atypical antipsychotics was less likely to result in extrapyramidal symptoms.[14,15] In light of these reports suggesting that CLZ augments dopamine signaling, we speculate that a moderate stimulation of DRD2 might prevent the development of DSP. However, atypical antipsychotics other than CLZ at their optimal dose provide substantial DRD2 occupancy, and this implies that endogenous dopamine cannot adequately stimulate up-regulated DRD2 under the administration of these drugs, and it cannot down-regulate DRD2 — in contrast to CLZ.

In fact, it was reported that a large number of typical and atypical antipsychotics (other than CLZ and aripiprazole) induce the upregulation of cell-surface DRD2,[16] whereas Tadokoro et al.[5] demonstrated that the DRD2 partial agonist aripiprazole can ameliorate the dopamine supersensitivity state due to DRD2 stimulation. Charron et al.[17] reported that the blockade of 5-HT2A receptor suppressed amphetamine-induced hyperlocomotion in rats with dopamine supersensitivity. Given that CLZ has high affinity for 5-HT2A,[18] the blockade of 5-HT2A by CLZ may also contribute to the amelioration of DSP. Taken together, the past and present findings indicate that it is likely that clozapine's low affinity, occupancy rate, and rapid dissociation for DRD2, its high affinity for 5-HT2A, and other unique properties may make it easy for increased endogenous dopamine to combine with DRD2, which leads to a down-regulation of DRD2 and a release from DSP. In our patient's case, the PAL may therefore have become effective after CLZ treatment, enabling the introduction of the PAL long-acting injection.

A limitation of the present report concerns the patient's adherence to his treatment regimens. We did not examine the serum/plasma levels of antipsychotics in this case because we could not do so in accord with the health insurance system in Japan. However, we received documentation of the patient's adherence. We thus consider the phenomena and outcome of this patient as not so much the natural course of schizophrenia or potential non-adherence to treatment as a release from DSP.

Conclusion

We treated a patient with schizophrenia in whom an ineffective antipsychotic medication became effective after the release of DSP by treatment with CLZ. Since CLZ has the potential to release a patient with schizophrenia from the DSP state, it is worthwhile to consider a rechallenge with a previously ineffective antipsychotic for a patient with DSP who has responded to CLZ but experienced severe side effects after prolonged treatment with CLZ.

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Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

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Informed consent

Written informed consent was obtained from the patient for their anonymized information to be published in this article. The patient had decisional capacity to provide consent.

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