Case Report
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Successful Management of Clozapine-induced Akathisia with Gabapentin Enacarbil: A Case Report

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The management of clozapine (CLZ)-induced adverse events affects patient prognoses. Akathisia is a relatively rare adverse event related to CLZ administration and thus the management of this syndrome is not well established. Here, we report a case of treatment-resistant schizophrenia wherein CLZ-induced akathisia was successfully managed with gabapentin enacarbil (GE). The patient was a 39-year-old woman who had been treated with atypical antipsychotics other than CLZ for three years with poor tolerability. Initiation of CLZ (400 mg/day) attenuated her psychotic symptoms, but was followed by moderate akathisia. Neither benzodiazepines nor biperiden improved the akathisia; however, akathisia was finally diminished with co-administration of GE. GE facilitated a dosage increase in CLZ (450 mg/day) for the improved management of pyschotic symptoms, and thus indirectly contributed to treatment of the patient's schizophrenia. We suggest that GE is a useful candidate for the management of CLZ-induced akathisia. The improved management of treatment-induced akathisia and other adverse events can extend the potential application of CLZ for treatment-resistant schizophrenia.

KEY WORDS: Akathisia, drug induced; Antipsychotic agents; Clozapine; Gabapentin; Gabapentin enacarbil; Restless legs syndrome.

INTRODUCTION

Evidence suggests that clozapine (CLZ) is highly effective for the management of treatment-resistant schizophrenia.[1] When non-serious side effects result from the use of CLZ, the continuation of therapy depends on the success or failure of side effect management. Therefore, the management of CLZ side effects is an important clinical problem relevant to the prognosis of patients with treatment-resistant schizophrenia.

Akathisia is one of side effects that can arise from the use of antipsychotic medications. Regarding the pharmaceutical treatment of akathisia, the use of conventional beta-blockers and anticholinergic drugs has been proposed; recently, gabapentin has also been proposed as a potential therapeutic agent for akathisia.[2,3] Here, we report a case of schizophrenia with CLZ-induced akathisia wherein therapeutic use of the gabapentin prodrug, gabapentin enacarbil (GE) mitigated akathisia symptoms, and made it possible to increase the dose of CLZ for more complete treatment of schizophrenic symptoms.

CASE

The subject was a 39-year-old female with no significant medical history other than bronchial asthma. At the age of 34 years, the patient presented with auditory hallucinations and paranoia. At the age of 35 years, the patient was referred to our psychiatric hospital and diagnosed with paranoid schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition–text revision (DSM-IV-TR) criteria. In sequence, the patient was prescribed aripiprazole 12 mg/day, paliperidone 12 mg/day, olanzapine 20 mg/day, and finally quetiapine (QTP) 750 mg/day for her schizophrenia; however, due to akathisia, none of these therapies were continued. An attempt to alleviate her treat-

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ment-induced akathisia with biperiden was unsuccessful. At the age of 38, the patient's primary medication was changed from QTP to CLZ. Akathisia temporarily disappeared with the change in medication, but reoccurred when the dose of CLZ was increased to 400 mg/day. Specifically, the patient became aware of an urge to move her limbs and body as well as a sensation of restlessness, accompanied by motor symptoms such as shaking of her hands and feet. She had no pre-existing medical conditions such as iron-deficiency anemia, renal failure, or diabetes that could have secondarily precipitated restless legs syndrome (RLS). Additionally, RLS was ruled out as a diagnosis due to a lack of paresthesia in her limbs, a lack of diurnal variation in symptoms, the fact that the patient's restlessness was not improved by movement, and the presence of only a mild effect on sleep. Instead, medication-induced acute akathisia was diagnosed according to the DSM-5, with a score of 5 on the Barnes Akathisia Scale (BAS). At this point in time, her psychotic symptoms were such severe that a simple reduction in medication dosage was not preferable. The patient's psychotic symptoms were lessened by a combination of diazepam 15 mg/day and clonazepam 1 mg/day and a CLZ dosage increase to 425 mg/day, however her akathisia was worsened (BAS, 9). Informed consent was obtained from the patient and her family before the additional GE 600 mg/day was administered, which made the akathisia subside (BAS, 0). Thereafter, increasing CLZ to 450 mg/day did not cause akathisia to reoccur, and the patient's psychotic symptoms improved. The patient eventually recovered to a level at which her psychotic symptoms no longer significantly hindered her daily life.

DISCUSSION

Akathisia is associated with the exacerbation of psychotic symptoms, poorer treatment outcome, and lower subject well-being in patients with schizophrenia.[4,5] Among antipsychotic drugs, CLZ has the lowest probability of eliciting akathisia as a side effect.[6] However, some cases of CLZ-induced akathisia have been reported and conventional case reports have managed akathisia by reducing or stopping CLZ therapy.[7] In contrast, this report shows that akathisia can be successfully managed with pharmacotherapy. Therefore, our case is expected to improve the availability of CLZ for the treatment of schizophrenia.

Gabapentin is one of the candidates for the pharmaceutical management of akathisia. Additionally, its prodrug GE is used to treat RLS, which has symptoms that are very similar to those of akathisia. To date, there have been some reports of cases in which gabapentin was successfully used to treat akathisia.[2,3] Pfeffer *et al.*[2] reported a case of olanzapine-induced akathisia that was successfully treated with 3,000 mg/day of gabapentin, although the symptoms had never been improved by conventional therapy using diphenhydramine and diazepam. Sullivan also reported two cases of QTP-induced akathisia that were well-managed with 1,200 mg/day of gabapentin, while the two had showed unfavorable response to conventional therapy with timolol, clonazepam and diazepam. However, no study has demonstrated the efficacy of GE for akathisia. In addition to similar clinical symptoms, akathisia and RLS have several similarities, such as the time of appearance after the initiation of antipsychotics[8,9] and their risk factors including iron-deficiency anemia and diabetes.[10-12] Typically, the short half-life of gabapentin necessitates oral administration several times per day. In this case, pronounced daytime sleepiness due to CLZ led us to conclude that the patient was unable to self-administer oral gabapentin during the day, and therefore GE was used. As a result, GE had a marked effect on akathisia. This case is therefore valuable as it demonstrates the potential usefulness of GE as a pharmacotherapy for akathisia.

The mechanism by which gabapentin and GE improve akathisia is still unclear. However, gabapentin likely acts by increasing GABA activity in the brain and managing regions of dopamine dysregulation.[2] Alternatively, no previous research on akathisia has been conducted on GE and therefore no hypotheses regarding its mechanism of action have been proposed. We believe that the activation of dopamine and GABA pathways studied by Pfeffer *et al.*[2] is a plausible hypothesis; however, future research should evaluate and verify this mechanism. A neuroradiological approach using positron emission tomography may be useful in elucidating the mechanism of action of GE in akathisia.

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