

Very Late-Onset Neutropenia in a Japanese Schizophrenia Patient Treated with Clozapine

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Abstract

We here reported a chronic schizophrenia patient who occurred neutropenia 13 years after starting clozapine. Thus, once clozapine is administered, the lifelong regular monitoring of the patient's total WBC count should be done.

Keywords: Clozapine; Neutropenia; Late-onset

Case Report

The patient was a 46-year-old Japanese man who had met the DSM-IV diagnosis of schizophrenia, disorganized-type, for the prior 30 years. He had been on antipsychotic regimens since being diagnosed when he was 16 years old. He had been treated with therapeutic doses of sulpiride, haloperidol, levomepromazine, risperidone, olanzapine, aripiprazole, or lithium on several occasions, after which the treatments were stopped due to inadequate treatment response. After that, clozapine was started during his eighth hospitalization in 33-year-old in which he was brought to the hospital for persistent auditory hallucinations, monologias, persecutory delusion aggressiveness, and psychomotor excitement.

After this admission, the clozapine dosage was titrated gradually up to 600 mg/day. The patient's total leucocyte count at baseline was 10,000/mm³. After discharge from the hospital, he showed a prominent improvement in his clinical status, with no apparent psychotic symptoms, and he attended a day-care service. During the long follow-up period, his total leucocyte count range was between 5,380 and 11,290/mm³ with a daily 600 mg clozapine dosage. Twelve years after the start of that clozapine treatment, the patient's total leucocyte count had gradually decreased to 2,255 mm³. We therefore added lithium carbonate (600 mg/day) to increase the leucocyte count. However, the total leucocyte count did not recover after the addition of lithium carbonate (2,460 mm³, 1,663 mm³, 1,584 mm³, 1,526 mm³). In 46-year-old (13 years later), the patient's total leucocyte count had gradually declined to 1,330/mm³, and the 600 mg/day clozapine was stopped at the same time. His auditory hallucination, persecutory delusion, irritability, psychomotor excitement were exacerbated after stopping clozapine. Olanzapine (20 mg/day) and levomepromazine (150 mg/day) were re-started; those symptoms were however not ameliorated. Physical symptoms associated with neutropenia including fever, anemia, bleeding, irritability, and hot flashes were not seen. Four weeks after the clozapine was discontinued, the patient's total leucocyte count had recovered to 8,915/mm³. Written informed consent to have his case published was obtained from the patient.

Results and Discussion

We have reported the case of a patient who developed neutropenia a very long time after starting clozapine treatment, i.e., 13 years. The patient was asymptomatic when the neutropenia occurred. The problematic factor limiting the use of clozapine as a first-line agent in mentally ill patients is the risk of agranulocytosis. Clinicians should monitor a patient for neutropenia during the entire period of clozapine treatment. Although the greatest risk of developing this adverse reaction is during the initial 6-month exposure, clozapine-induced neutropenia may pose a risk after years of exposure [1-3]. The current product

labeling for clozapine recommends the weekly determination of a patient's total leucocyte count and granulocyte monitoring for the first 6 months of treatment, which may be decreased to biweekly monitoring based on the sudden and late onset of agranulocytosis in our patient in Japan according to the regulation of Clozaril Patient Monitoring Service. Several prior studies also found that neutropenia can occur many years after the start of clozapine treatment. Nongpiur et al. [2] reported a case of leucopenia that emerged after 11 years of continuous clozapine monotherapy. Taking these findings into account, it appears that the agranulocytosis occurs the lifelong for clozapine treatment. Our patient's case indicates the necessity of the lifelong monitoring of the WBC count [4-7]. The mechanism responsible for neutrophil toxicity of clozapine is not fully elucidated. Genetic factors, as well as immunological and toxic mechanism may play an important role [8,9]. N-Desmethylclozapine and clozapine N-oxide are the known major metabolites of clozapine. *In vitro* studies demonstrated that those major metabolites, but not clozapine itself is toxic to neutrophils [10].

Most guidelines recommend stopping clozapine treatment when the level of neutrophils falls below 1500/mm³. In cases of neutropenia, the co-prescribing of lithium is supported by several reports [2,7]. The evidence regarding the efficacy of lithium for increasing the total leucocyte count is not robust. In the present case, the total leucocyte count was not recovered.

Conclusion

In conclusion, we treated a patient with very late-onset neutropenia induced by clozapine. Clinicians should pay attention to the risk of neutropenia even when a patient's total leucocyte count remains constant over a long term. When clozapine is administered, the lifelong regular monitoring of the patient's total WBC count should be done.

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