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CASE REPORT

A Case of Clozapine Toxicity Caused by Infection in a Patient with Treatment-Resistant Schizophrenia

Tetsu Tomita, Sakie Ozawa, Kai Akasaka, Kazuhiko Nakamura

Department of Neuropsychiatry, Graduate School of Medicine, Hirosaki University, Hirosaki, Japan

Correspondence: Tetsu Tomita, Department of Neuropsychiatry, Graduate School of Medicine, Hirosaki University, 5 Zaifu-cho, Hirosaki, 036-8562, Japan, Tel +81-172 39 5066, Fax +81-172 39 5067, Email ttomita1984@yahoo.co.jp

Background: Clozapine is an effective antipsychotic for the treatment of treatment-resistant schizophrenia, but its use is associated with a risk of serious adverse events, especially when plasma levels of the drug exceed the therapeutic reference range. Infections have been reported to contribute to clozapine toxicity, although the underlying mechanisms remain incompletely understood.

Case Presentation: We report the case of a woman in her seventies with treatment-resistant schizophrenia who developed clozapine intoxication, with plasma levels exceeding 3000 ng/mL, following an infectious episode. The patient had been receiving clozapine (300 mg/day) for one year without adverse effects. However, she developed fatigue and severe motor impairment and was found to have elevated levels of inflammatory markers and multiple infectious sources, including a pulmonary abscess, a pelvic abscess, and a decubitus ulcer. Upon admission, her plasma clozapine level was 3085 ng/mL. No changes in concomitant medications were identified, and the electrocardiography (ECG) findings were unremarkable. With antibiotic therapy and a gradual reduction in clozapine dose, her plasma levels reduced, and her symptoms were alleviated. She was discharged after 18 weeks of hospitalization.

Conclusion: This case highlights the potential for infection-induced clozapine intoxication even at relatively moderate doses of the drug. Regular monitoring of clozapine plasma levels is critical for the early identification and prevention of abnormal elevation of clozapine levels, especially.

Keywords: clozapine toxicity, infection

Introduction

Clozapine is widely utilized in Japan and internationally for the management of treatment-resistant schizophrenia, and this drug has demonstrated efficacy in addressing core symptoms such as hallucinations, delusions, and cognitive deficits.[1,2] Despite the clinical importance of clozapine in psychiatric practice, its use is associated with the risk of serious adverse effects.[2–4]

To ensure safe and effective use of clozapine, regular monitoring of plasma levels of the drug is recommended. The therapeutic reference range is between 350 and 600 ng/mL.[5,6] Significant elevations above the upper limit of this range may increase the risk of adverse events and warrant caution, and a level >1000 ng/mL is considered an alert level.[6] However, it is difficult to predict variations in blood levels in individual patients. Mach et al demonstrated that, even when clozapine was administered at recommended daily doses of 200–450 mg, only 37% of patients had serum clozapine concentrations within the therapeutic range, while therapeutic norclozapine levels were observed in 75% of cases.[7]

We recently encountered a case of treatment-resistant schizophrenia in which the patient developed clozapine intoxication, with plasma levels exceeding 3000 ng/mL, following an infectious episode. Clozapine levels gradually decreased as the infection resolved. Here, we report the case of this patient.

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In accordance with the regulations of the Ethics Committee of Hirosaki University Hospital, ethical approval was required for publication of this case report. Approval was therefore obtained from the committee, and written informed consent for publication was obtained from the patient.

Case Presentation

The patient was a woman in her seventies. After four years of psychosomatic treatment for depressive symptoms, the patient began to experience somatic hallucinations and was admitted to a psychiatric hospital. She was diagnosed with schizophrenia and received antipsychotic pharmacotherapy for the next 16 years. However, her symptoms, including somatic hallucinations and disorganized thinking, persisted. She was started on clozapine one year prior to admission to our hospital.

She reported no subjective adverse effects from clozapine use, and routine blood tests revealed no abnormalities. In addition to clozapine, she was taking lorazepam, solifenacin, levothyroxine sodium hydrate, apixaban, lansoprazole, potassium L-aspartate, pantethine and magnesium oxide for anxiety, overactive bladder, hypothyroidism, deep vein thrombosis, chronic gastritis, hypokalaemia and constipation, respectively.

Without any identifiable precipitating factor, she developed fatigue and severe motor impairment that lasted for approximately one month. She attended a local internal medicine clinic where no abnormalities were found. As her symptoms persisted, she was admitted to the psychiatric unit of our hospital. On admission, her serum clozapine level was found to be significantly elevated, at 3085 ng/mL. Her vital signs were as follows: body temperature, 36.5°C; heart rate, 97 bpm; blood pressure, 100/77 mmHg; and blood oxygen saturation, 96%. Laboratory tests also revealed leukocytosis (white blood cell (WBC) count, 11,100/μL), neutrophilia (neutrophil count, 9630/μL) and elevated C-reactive protein (CRP) levels (19.02 ng/mL), suggesting the presence of a bacterial infection. Further investigations revealed a pulmonary abscess, a decubitus ulcer and a pelvic abscess. Electrocardiography did not reveal any abnormalities.

Treatment was started with antibiotics and a gradual reduction in the dose of clozapine. After that cefazolin sodium of 1–2g/day was used for 3 days, piperacillin/tazobactam of 13.5g/day was used for 14 days. As the infection gradually resolved, the serum clozapine level also decreased (Figures 1 and 2). The patient's symptoms, including fatigue and motor impairment (eg., weakness, gait disturbance, and ataxia), were subsequently alleviated. Clozapine was administered at 300 mg prior to hospitalization but was reduced to 200 mg after admission. Elevated blood levels persisted, leading to a gradual reduction to 100 mg by the second week of hospitalization. Once concentration of clozapine

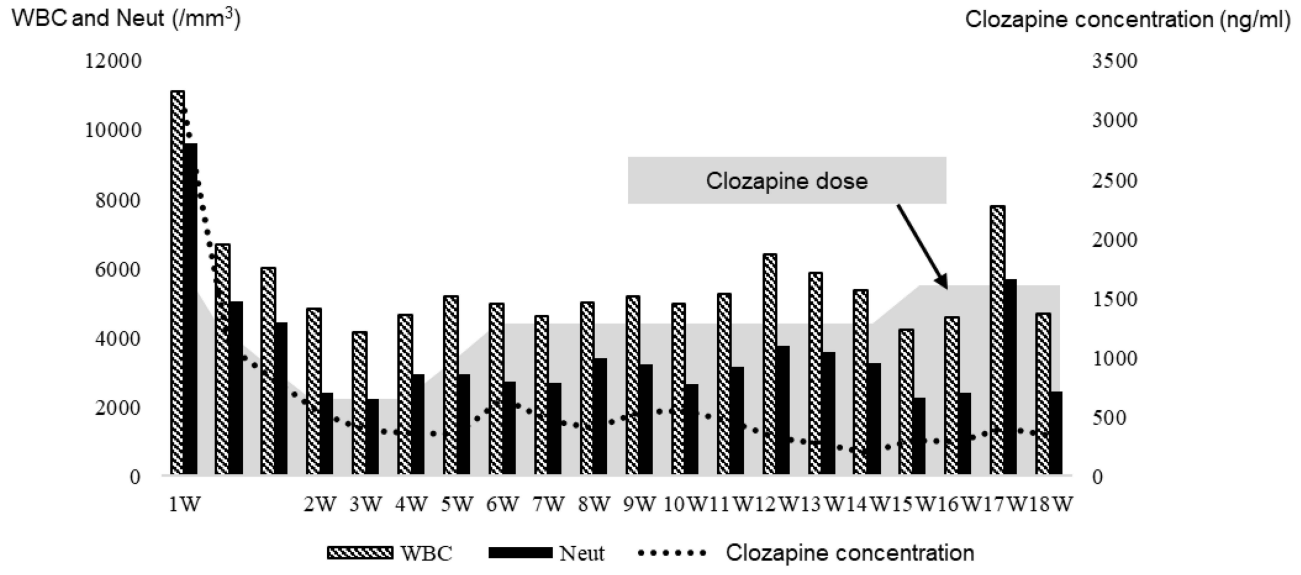

Figure 1 Time course and data of white blood cell, neutrocyte, clozapine dose and concentration.

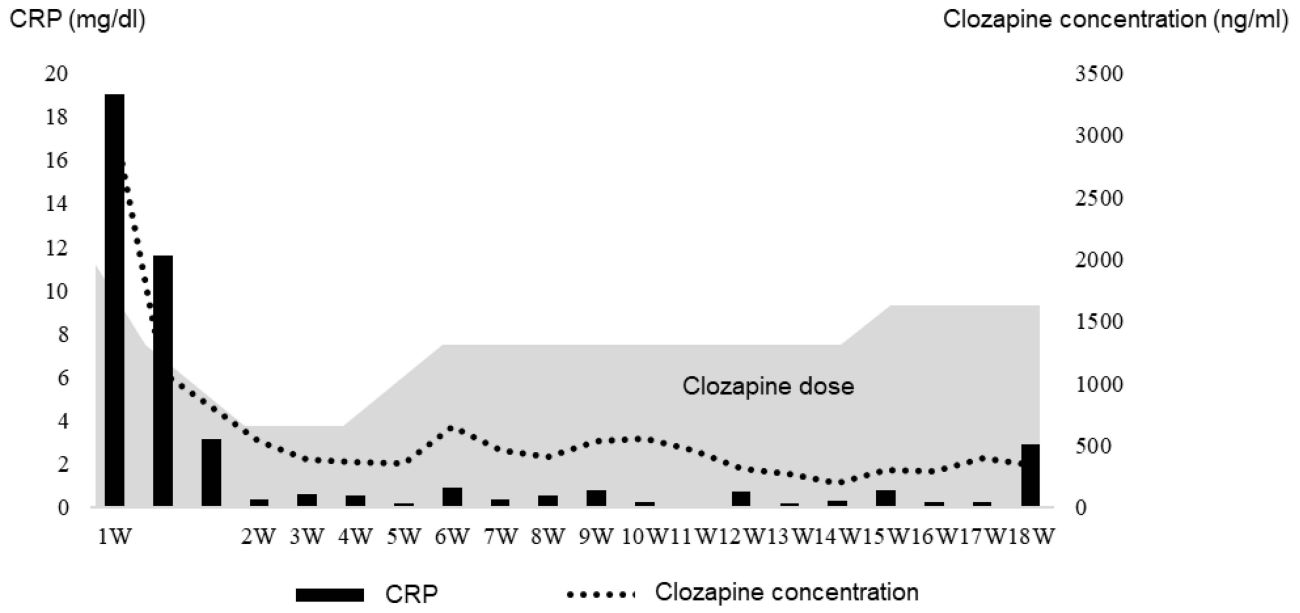

Figure 2 Time course and data of CRP, clozapine dose and concentration.

normalized, the dose was gradually increased to 200 mg between the fourth and sixth weeks due to worsening psychiatric symptoms, ultimately reaching 250 mg. After rehabilitation, she was discharged 18 weeks after admission.

Discussion

We encountered a patient with treatment-resistant schizophrenia who was taking clozapine and developed clozapine intoxication, with plasma levels exceeding 3000 ng/mL, following an infectious episode. The association between elevated levels of clozapine and infections was discussed in a review article; Elevated levels of inflammatory mediators, including IL-6, TNF-α, interferon, and CRP, have been shown to reduce the expression of CYP1A2—the primary enzyme responsible for clozapine metabolism—by as much as 90%, thereby impairing clozapine metabolic capacity.[8] In the present case, clozapine toxicity was also thought to have been triggered by an infection, leading to symptoms such as fatigue and severe motor impairment. The concomitant medications remained unchanged after hospitalization; therefore, drug interactions were not considered the cause of the elevated clozapine levels.

Darling et al and Leung et al reported that the blood levels of clozapine in two patients exceeded 4000 ng/mL because of infection[9,10] In both patients, clozapine was administered at a dose of 700 mg, while the dose for the present patient was 300 mg, resulting in a higher concentration/dose ratio. Factors other than drug interactions and infection-related factors that influence the increase in clozapine blood levels include being female and a nonsmoker.[11] However, these factors did not change before and after admission; therefore, the infection was considered to have caused the abnormal increase in blood clozapine levels.

The optimal blood concentration of clozapine is considered to be between 350 ng/mL and 550 or 600 ng/mL, and concentrations exceeding this range increase the likelihood of adverse events, and levels above 1000 ng/mL may lead to the onset of toxic symptoms.[12,13] Previous reports on clozapine poisoning primarily describe symptoms such as sedation and fatigue, while severe cases involve respiratory depression, coma, and cardiovascular dysfunction. It has also been noted that chronic poisoning may present with nonspecific symptoms.[14–17] Although the hospital did not have a system for measuring blood levels of clozapine until the time of admission, the findings from this case suggest that regular measurement of blood clozapine levels and close monitoring of a patient's symptoms and condition are essential to identify abnormal increases in blood levels of clozapine as early as possible.

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Since no specific antidote exists for clozapine toxicity, supportive care is the primary treatment. The diagnosis of clozapine toxicity is primarily based on medical history, physical examination, and blood concentration monitoring. Therefore, therapeutic drug monitoring including clozapine should be readily available in clinical settings dealing clozapine.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of the Hirosaki University Hospital. Informed consent was obtained from the patient for the publication of this case report.

Consent for Publication

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

Acknowledgment

We are appreciated to the patients of the cases. This paper has been uploaded to Research Square as a preprint: https://www.researchsquare.com/article/rs-6868106/v1.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no potential conflicts of interest in this work.

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