Case Report

Late-Onset Clozapine-Induced Agranulocytosis in a Young Woman with Paranoid Schizophrenia

Anuhya Vinayaka, Shubha Sheshadri[1], Sharath P. Madhyastha[1], Ganesh V. Shetty[1], Charan Thej Reddy[1]

Departments of Pharmacology and [1]Medicine, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, India

Abstract

Treatment of schizophrenia has taken so many turns, and adverse effects of the drugs still continue to remain as a hurdle in the management. Clozapine is considered to be the better promising drug in the treatment of paranoid schizophrenia with minimal side effects. Clozapine-induced agranulocytosis is one adverse event that troubles clinicians, and it requires a vigilant eye to look for the signs. In the present study, the authors discuss a case which has developed agranulocytosis in the later stages of clozapine treatment.

Keywords: Agranulocytosis, clozapine, late adverse event, paranoid, schizophrenia

Introduction

Clozapine has been found to be an effective treatment in persons with schizophrenia resistant to treatment with other antipsychotic drugs. In addition, clozapine is an effective treatment for schizophrenia accompanied by persistent suicidal or self-injurious behavior. Clozapine's unique side effect profile, which includes a low rate of life-threatening agranulocytosis, gives rise to numerous considerations in prescribing, monitoring, and side effect management in the use of the drug.[1,2]

Case Report

A 26-year-old female patient, who is a known case of paranoid schizophrenia for 6 years on treatment, came to our tertiary health-care center with the complaints of dry cough and increased fatigue for 1 week. The cough was not associated with fever or dyspnea or throat pain. Her medication history was taken which showed that she was on oral clozapine 600 mg once a day for 18 months. Her attendants revealed that she had similar complaints 2 months prior, for which she was diagnosed as a case of clozapine-induced neutropenia (CIN), and the dose of clozapine was reduced to 200 mg once a day. Her concomitant medications were oral imipramine 25 mg once a day, oral phenytoin 300 mg once a day, and atropine drops 1% sublingual.

Her vital signs were stable. General physical examination and systemic examinations were unremarkable. Psychiatric history was taken which revealed the presence of auditory hallucinations for 2 months, which was more in the morning hours with impaired recent memory. Sleep had increased in the past 4 months with decreased appetite, and bowel and bladder habits were found to be normal. On routine laboratory investigations, she was found to have leukopenia $2.4 \times 10^3/\mu L$ and absolute neutrophil count (ANC) was $0.12 \times 10^3/\mu L$.

Correlating with the past history, the present complaints, and the laboratory investigations, she was diagnosed as a case of clozapine-induced severe agranulocytosis. The causality of the adverse drug reaction was analyzed using the Naranjo algorithm, which gave us a score of 9, denoting "definite" causality.

She was admitted and clozapine was stopped; throat swab revealed a culture of *Staphylococcus aureus* sensitive to cefepime. She was put on subcutaneous filgrastim 300 μg once daily, parenteral cefepime was started with a dose of 2 g intravenous (IV) twice daily, oral phenytoin 200 mg once

Address for correspondence: Sharath P. Madhyastha, Assistant Professor, Department of Medicine, Kasturba Medical College, Manipal Academy of Higher Education, Manipal 576104, Karnataka, India.
E-mail: dr.sharathymc@gmail.com

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a day, betadine gargles thrice a day, and oral pantoprazole 40 mg once a day. Barrier nursing was followed with contact precautions, with the use of N95 mask; consumption of raw foods was avoided and no visitors were allowed. Following which, on day 4 of admission, her ANC returned to $1.2 \times 10^3/\mu L$ and cefepime was stopped. The cough subsided gradually, and she was shifted to oral fixed-dose combination of amoxicillin with clavulanic acid 500/125 mg for 5 days. Five doses of subcutaneous filgrastim 300 μg were given during her stay. Psychiatry consultation was sought for periodic review, and she was advised antipsychotic-free period of 2 weeks.

Discussion

Clozapine remains the single medication approved by the US Food and Drug Administration (FDA) for treatment-resistant schizophrenia. It has a relatively low affinity for D2 receptors and thus is associated with a lower incidence of extrapyramidal side effects when compared with that of typical antipsychotics, but concerns about tolerability and side effects are barriers to treatment. Specifically, treatment with clozapine poses an increased risk of agranulocytosis and requires monitoring through regular blood draws examining white cell counts. Agranulocytosis is one of the most serious clozapine-induced adverse drug events. Agranulocytosis is defined as an ANC $<100/mm^3$ in association with infectious disease.[3] Although the incidence in the Indian population is relatively lesser, the risk of agranulocytosis is 0.38% of all schizophrenia cases treated with clozapine. The risk of agranulocytosis and neutropenia is more in the initial 6–18 months of clozapine treatment.[4] The incidence falls after this period, and there have been very few reports of neutropenia and agranulocytosis in later stages.

The FDA's recently released modified blood monitoring guidelines (i.e., the monitoring of ANC only) not only grant patients access to clozapine treatment but also encourage health-care providers to take the possible side effects of clozapine into consideration.[5] Clozapine-induced agranulocytosis/granulocytopenia (CIAG) may represent two possible phenotypes: CIN (ANC <1500/mL) and clozapine-induced agranulocytosis (CIA) (ANC <500/mL).

The mechanism of CIAG is dose independent, with a significant genetic predisposition and also idiosyncratic. The most recent theory explaining CIAG is that of the immune-mediated response against haptenized neutrophils.[6] The mechanism of delayed-onset agranulocytosis is unclear. Treatment with clozapine generally lasts for months or even years. It is hypothesized that modest growth-inhibiting effects of clozapine on bone marrow may be amplified in patients undergoing long-term therapy with clozapine. N-desmethylclozapine, a metabolite of clozapine at therapeutic drug concentrations (1–3 μM), has been found to be directly cytotoxic to neutrophils or interferes with the turnover of bone marrow precursor cells.[6] The report of delayed-onset agranulocytosis in India is very rare and many cases go undiagnosed as most of the patients do not report the minor adverse effects.

In our case, the ANC levels have shown a drastic fall after the introduction of clozapine and the levels have recovered after stopping clozapine and treatment with granulocyte-stimulating factor. On analyzing the case using Naranjo's algorithm, it was observed that both dechallenge and rechallenge were positive, which gave us a score of 9, hence concluding it to be a "definite" adverse drug reaction.[7]

The patient had previous complaints which were managed with dose reduction, but the adverse effect returned as delayed onset and it was very severe requiring barrier nursing. The risk factors of female sex and young age were also present.[8] It is important to make necessary adjustments in dosage when initiating clozapine, especially in patients who have previous complaints of neutropenia. Furthermore, patients and their attenders should be advised to keep a vigilant eye on the minor adverse effects such as cold, sore throat, fever, or any sort of infection.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initial will not be published, and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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