

# Leucopenia and Thrombocytopenia Induced by Clozapine

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## Abstract

This is a report of a patient with clozapine-induced leucopenia and thrombocytopenia. The latter haematological dysfunction has not been previously reported with clozapine use. The recovery period was also unusually prolonged. Depot injections of zuclopenthixol and flupenthixol, which were given after clozapine was discontinued, could have contributed to the delay in recovery.

**Key words:** Clozapine, Leucopenia, Thrombocytopenia

## Introduction

Clozapine is an atypical antipsychotic agent with proven efficacy for the treatment of refractory schizophrenia. A well known side effect is agranulocytosis, which can occur in 1% to 2% of treated patients.<sup>1,2</sup> Other haematological effects include leucopenia, neutropenia, and eosinophilia.<sup>3-5</sup> Anaemia, leucocytosis, and increased platelet count have been reported in less than 1% of patients receiving clozapine.<sup>6</sup>

Product labelling cites thrombocytopenia as occurring 'very rarely' with clozapine therapy and a MEDLINE search of the English language literature using the terms 'thrombocytopenia' and 'clozapine' yielded 6 citations between 1966 and 1998. Of these, 1 report related the occurrence of agranulocytosis and thrombocytopenia in 2 patients. A second report described lymphocytopenia and thrombocytopenia in a patient treated with risperidone, which continued after switching to clozapine. The third report was of a patient who only had a reduction in platelet count with clozapine and developed epistaxis.

The following is a report of a 41-year-old Chinese man who developed both leucopenia and thrombocytopenia after taking clozapine therapy.

## Case Report

This patient was first diagnosed with schizophrenia in 1981 at the age of 24 years. His condition deteriorated thereafter and he has been unemployed since the age of 27 years. He experienced relapses in 1988 and 1990 and, in 1996, was admitted to a psychiatric hospital after a violent

attack on neighbours during which he chased them with a chopper.

The patient has been treated with various antipsychotic medications, including trifluoperazine up to 60 mg per day, lithium carbonate 750 mg per day, depot injection flupenthixol 40 mg monthly for approximately 1 year, depot injection fluphenazine decanoate 12.5 mg monthly for 6 months, and depot injection zuclopenthixol 200 mg monthly, increased to 400 mg fortnightly for 1 year, and given with depot flupenthixol 20 mg for 4 months. The patient also received electroconvulsive therapy during his first admission to hospital and again in 1996.

As there was little improvement in his mental state and he experienced extrapyramidal side effects, all oral medications were stopped in April 1997 and he was given risperidone titrated to 6 mg per day. A gradual improvement was noted in that he was less withdrawn and was able to start occupational therapy. However, in October 1997, risperidone had to be discontinued because he suddenly became deluded that the medication was 'snake poison' and refused to take it any longer. The patient remained thought disordered, experienced auditory hallucinations, and had bizarre delusions. He was preoccupied and socially isolated in the ward but was able to attend to activities of daily living.

In October 1997, the decision was made to give him clozapine. The physical examination at that time was normal and baseline urea, electrolyte levels, liver and thyroid function tests, and complete blood count were within normal limits. The patient was given clozapine 50 mg at night in October 1997. After 17 days, the total white blood cell count fell to  $3.2 \times 10^9/L$  (normal range,  $4.5-11.0 \times 10^9/L$ ) and platelets were  $122 \times 10^9/L$  (normal range,  $150-450 \times 10^9/L$ ). Clozapine was stopped but the blood monitoring continued. The patient had no fever and no symptoms suggestive of a viral infection or collagen vascular disease. There was no hepatosplenomegaly and investigations revealed normal erythrocyte sedimentation rate. Serology for cytomegalovirus, Epstein Barr virus, Parvovirus B, and hepatitis B and C viruses were negative. The prothrombin/prothromboplastin times were normal. Peripheral blood film showed that the majority of red blood cells were well haemoglobinised normocytes.

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The findings of a bone marrow and trephine examination in December 1997 showed hypocellular marrow with 3 lineages present — granulocytic hypoplasia together with megakaryocytes and normoblastic erythropoiesis were noted, consistent with a drug-induced hypoplasia reaction. The serology for anti-double-stranded DNA antibody and antinuclear antibody were negative.

Twenty days after stopping clozapine, the patient's mental state deteriorated and he was given depot injections of zuclopenthixol 400 mg and flupenthixol 30 mg in November 1997. This was associated with a sharp fall in white blood cell count to  $2.4 \times 10^9/L$  and platelets to  $85 \times 10^9/L$ . The patient was then given oral haloperidol 3 mg per day at the beginning of December 1997. After 3 weeks, the white blood cell count had increased to  $4.7 \times 10^9/L$  and the platelets to  $106 \times 10^9/L$ . When the depot injections were repeated at the same doses, the white blood cell count decreased to  $3.8 \times 10^9/L$  and the platelets to  $90 \times 10^9/L$ . Following this, a decision was made to stop the depot injections and his condition was maintained with oral haloperidol 5 mg per day. It was only 13 weeks after stopping clozapine that the white blood cell count rose to  $4.8 \times 10^9/L$  and platelets to  $147 \times 10^9/L$ .

## Discussion

This case is unusual because of the occurrence of both leucopenia and thrombocytopenia with clozapine use. In addition, recovery from the bicytopenia was prolonged. Generally, the occurrence of neutropenia and eosinophilia are transient and neutrophil recovery occurs after a mean of 9.3 days. The fall in white blood cell count and platelet levels persisted for almost 13 weeks for this patient — prolonged recovery has not been previously reported. The author suspects the depot injections that were given after clozapine was stopped could have contributed to the persistently low white blood cell count and platelet levels. However, there is no documented proof that these compounds could have caused the thrombocytopenia. Furthermore, the patient had been receiving both zuclopenthixol and flupenthixol injections for 4 months without adverse effects. Zuclopenthixol and flupenthixol are also not structurally similar to clozapine.

There is also no indication that the bicytopenia was produced by an immune mediated mechanism as has been suggested in other reports. A repeat bone marrow examination to show recovery after the drug was stopped may be useful, but it was not done as the patient's haematological findings had returned to normal and the clinicians did not feel that a repeat bone marrow was warranted.

It was recently reported that 3 patients had prolonged granulocyte depression when olanzapine was initiated while experiencing decreased granulocyte levels associated with

## Definitions<sup>16</sup>

Leucopenia is a reduction in the circulating total white blood cell count —  $<4.0 \times 10^9/L$ .

Agranulocytosis: granulocyte count  $<0.5 \times 10^9/L$  (neutrophils, basophils, eosinophils).

Thrombocytopenia is a reduction in the blood platelet count to below the lower limit of normal, which is  $150 \times 10^9/L$ .

clozapine use. This is similar to the clinical events for this patient and is a reminder that early institution of other medication for patients with clozapine-induced haematological depression is to be avoided.

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