

Clozapine associated thrombocytopenia

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ABSTRACT

Although agranulocytosis as a side effect of clozapine is well known, there is scarcity of data with regard to thrombocytopenia associated with clozapine. In this report we describe a case of clozapine induced thrombocytopenia and review the existing literature. A 22 year old female patient developed thrombocytopenia while on clozapine 187.5 mg/day for 17 weeks. Thrombocytopenia persisted for 24 weeks even after reduction in the dose of clozapine and ultimately clozapine had to be stopped, which led to resolution of thrombocytopenia. Clozapine-induced thrombocytopenia is a less well-known, but potentially serious, adverse effect that should be screened for in practice. The case highlights the fact that besides monitoring the leucocyte count, platelet count of patients receiving clozapine should also be monitored.

Key words: Clozapine, thrombocytopenia, platelet

INTRODUCTION

Clozapine has been known to cause haematological side effects like agranulocytosis, neutropenia, leucocytosis, eosinophilia and thrombocytopenia. Although some data is available with regard to leucopenia, data for thrombocytopenia is limited. In this report we present the case of a patient who developed thrombocytopenia with clozapine and review the existing literature.

CASE REPORT

A woman aged 22, suffering from paranoid schizophrenia (as diagnosed by DSM-IV) for the past three years, presented with

an acute episode. She had received adequate trials of olanzapine, risperidone and quetiapine along with electroconvulsive therapy. There was history of severe extrapyramidal side effects with risperidone. Taking this into account she was started on clozapine. Prior to starting of clozapine her hemogram including platelet count did not reveal any abnormality. For the management of acute symptoms in view of the suicidal risk, she was treated with electroconvulsive therapy, lorazepam up to 4 mg/day and was started on clozapine and the dose was gradually increased to 187.5 mg/day over the period of four weeks because of side effects of hypersalivation and constipation. While clozapine was increased, leucocyte count and platelet counts were monitored regularly on weekly basis and serial monitoring did not reveal any abnormality. With this she achieved symptomatic remission following which lorazepam was stopped. While on clozapine 187.5 mg/day, low platelet count (101,000 and 98,000/ μ L on two occasions) was noted for the first time after 17 weeks of continuation of clozapine at the above said dose without reduction in the leucocyte count or haemoglobin levels. Following this monitoring was increased and platelet count kept on fluctuating between 1,20,000/ μ L to 1,35,000/ μ L. Over the period, platelet count started dropping. By another 24 weeks of clozapine therapy, the platelet count

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dropped to 60,000/ μ L without any reduction in the leucocyte count and the haemoglobin levels. The drop occurred despite reduction in the dose of clozapine upto 125 mg/day. Clozapine was stopped completely as a result. Throughout this period she never had any fever, skin rash, purpura, excessive menstrual bleeding or bleeding from any other source, arthritis, arthralgia, muscle pain and muscle weakness. Her investigations in the form of serum electrolytes, liver function test, renal function test, prothrombin time, bleeding time, clotting time and ultrasound abdomen and pelvis did not reveal any abnormality. She was also evaluated by physician and the opinion was that the low platelet count may be related to clozapine.

Within a week of stopping clozapine platelet counts started improving and by six weeks her platelet count was 1,80,000/ μ L. In the meanwhile, with stoppage of clozapine, she had relapse of symptoms and required inpatient care, was treated with electroconvulsive therapy, lorazepam and chlorpromazine, with which she achieved remission. During this period her platelet count remained within the normal range.

DISCUSSION

Thrombocytopenia is defined as platelet count of less than 100×10^9 /L. Only two studies^[1,2] and a small case series^[3]

have reported incidence of thrombocytopenia associated with clozapine and only few case reports have focused on this association.^[4-10] The findings are summarized in Table 1.

Although in most of the literature thrombocytopenia associated with clozapine has been reported to be transitory to at best last for 13 weeks, in a case report thrombocytopenia persisted for 40 months after stopping clozapine.^[11] There are also few case reports of clozapine associated thrombocytosis.^[12,13] In one of this case reports thrombocytosis was seen in a patient treated with granulocyte colony stimulating factor for clozapine associated agranulocytosis.^[13] As with thrombocytopenia, an immunological mechanism is also suggested for development of thrombocytosis.

In the index case, thrombocytopenia was noted for the first time after 17 weeks of stable dose of clozapine, which kept on worsening with continuation of clozapine, even on the lower dose and subsided only after stoppage of clozapine and normalization of platelet count required six weeks. This clinical picture is consistent with the available literature in many aspects. However, in contrast to some of the reports, in the index case, platelet count kept on falling consistently with continuation of clozapine and improved only after stoppage of clozapine, suggesting that in certain cases the side effects may be transitory and can lead to fatal outcome.

Table 1: Literature reporting clozapine associated thrombocytopenia

Author	Type of study	Findings
Jagadheesan <i>et al.</i> ^[1]	Retrospective study (Sample size=28)	- Thrombocytopenia was seen in 17.8% of cases, with 50-400 mg/day, after 6 to 44 weeks of clozapine therapy. - All episodes of thrombocytopenia resolved over the period of 1-12 weeks without reduction in the dose
Atkin <i>et al.</i> ^[2]	Review of clozaril patient monitoring service of UK and Ireland (Sample size 6316 patients)	0.09% developed thrombocytopenia
Radovčić <i>et al.</i> ^[3]	Case series (Sample size=7)	- Two developed thrombocytopenia with 200-300 mg/day of clozapine - Clinical presentation: Epistaxis and reduction of the platelet count - Discontinuance of clozapine resulted in cessation of epistaxis followed by normalization of the platelet count.
Durst <i>et al.</i> ^[4]	Case report	
Eranti and Chaturvedi ^[5]	Case report	
Rudolf <i>et al.</i> ^[6]	Case report	- Marked fluctuations in the platelet counts with clozapine - Platelet counts varied from 45,450/μL to 7, 07,000/μL during the period of 16th week to 38th week of 200 mg/day of clozapine therapy - Thrombocytopenia along with leucopenia - Treatment with granulocyte colony-stimulating factors (G-CSF) led to normalization of neutrophil count but thrombocytopenia persisted and resolved spontaneously after 14 days
Mahendran ^[7]	Case report	- Thrombocytopenia along with leucopenia with clozapine 50 mg/day - Low platelet count persisted for about 13 weeks after stoppage of clozapine
Henderson and Borba ^[8]	Case report	A patient stabilized on clozapine 375 mg/day developed thrombocytopenia on addition of trimethoprim-sulfamethoxazole
Mihaljević-Peles <i>et al.</i> ^[9]	Case report	Thrombocytopenia was seen after addition of fluphenazine 6 mg/day to clozapine 75 mg/day
Tang <i>et al.</i> ^[10]	Case report	Addition of valproate to clozapine led to development of thrombocytopenia
Gonzales <i>et al.</i> (2000)	Case report	- Thrombocytopenia persisted for 40 months after stopping clozapine - Investigations showed immunological mechanisms for clozapine induced thrombocytopenia

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From the above literature it can be concluded that there is a wide variation in the incidence of thrombocytopenia with clozapine, which possibly is influenced by the sample size studied. There is lack of consensus with regard to resolution, with some reports suggesting that resolution requires stoppage of clozapine, as was seen in the index case too; whereas others suggest that thrombocytopenia resolves on its own. Most of the available literature is silent about the possible mechanism, except for one report which demonstrated underlying immunological mechanism in a case of persistent thrombocytopenia even after stopping clozapine. Other authors have also suggested immunological mechanism for both thrombocytopenia and thrombocytosis with clozapine.^[14]

Considering the fact that the thrombocytopenia may be transitory as suggested in some of the case reports, an informed decision about rechallenge must be made after weighing the risk and benefits.

From the above it can be concluded although rare, clozapine can lead to thrombocytopenia. Hence, besides monitoring the leucocyte count, platelet count of patients receiving clozapine should also be monitored.

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