

Olanzapine-induced leucopaenia and thrombocytopaenia in an elderly patient: a case report and review of the evidence

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SUMMARY

Haematological adverse effects of antipsychotics are rare but life threatening. Existing literature is limited to case reports, which are mostly reported on second generation antipsychotics (clozapine, olanzapine, risperidone, quetiapine). Elderly individuals are at risk of developing side effects with any psychotropics. Olanzapine is commonly used for the management of psychotic symptoms as well as for the management of behavioural and psychological problems with dementia in the elderly. In this case report, the authors report thrombocytopaenia and leucopaenia in an elderly individual with schizophrenia which developed after initiation of olanzapine and reverted back after stoppage of the drug. This case report highlights that the elderly are susceptible to develop haematological side effects with olanzapine and hence monitoring may be essential.

INTRODUCTION

Blood dyscrasias (leucopaenia—total leucocyte count < 3500/cumm, thrombocytopaenia—total platelet count < 150 000/cumm, pancytopaenia) are rare but life-threatening adverse effects with antipsychotics, mostly reported with second generation antipsychotics. Available literature suggests that antipsychotic induced haematological adverse effects are mostly idiosyncratic. Most of the literature on haematological adverse effects (mostly leucopaenia, neutropaenia and thrombocytopaenia) has been well documented with regard to clozapine.¹⁻³ However, there is also evidence (though limited) for the haematological adverse effects of other second generation antipsychotics like risperidone (oral⁴⁻⁷) as well as in depot long acting preparations,⁸ quetiapine⁹⁻¹² and olanzapine.¹³⁻²² With regard to olanzapine, while some have reported the haematological abnormalities to be reversible,^{18 23 24} others have reported them to be fatal.^{15 25} A recent systematic review on the available literature of the haematological side effects of olanzapine from 1998 to 2015 revealed a total of

38 publications (in the age range of 16–83 years).²⁶ Of all these case reports, to date only seven case reports on the haematological adverse effects of olanzapine have been reported in elderly patients^{13 14 18 23 27-29} and others have been reported in adolescents, youth and middle-aged subjects.²⁶

Though no particular risk factors have been evaluated in this regard, it is a well-known fact that extremes of age (children and elderly, ie, >55–60 years of age) is a risk factor for developing any adverse effect with any psychotropics. In view of this limited literature on the association of olanzapine and blood dyscrasias in the elderly, we report a case of a 62-year-old man with paranoid schizophrenia who developed leucopaenia and thrombocytopaenia while on olanzapine.

CASE DESCRIPTION

Mr G, a 62-year-old married man, retired electrician by occupation was brought by his family members with complaints of hearing of voices over the past 10 years. There was no relevant medical history or family history of mental illness. Detailed exploration of history revealed an illness of insidious onset with a continuous and progressive course which was precipitated by interpersonal problems with office colleagues. Following which initially, the patient started to harbour strong fixed false beliefs that his colleagues wanted to defame him with subsequent anger-outbursts, agitation and suspiciousness towards them. Later on, after few months, he even started to hear voices of his office colleagues in clear consciousness discussing him and commenting on his actions using derogatory language. Due to these events, there was significant socio-occupational dysfunction. He was treated with risperidone (2–4 mg/day) with good compliance for a period



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of 6 months with which there was about 60% improvement but later because of non-compliance and restarting of risperidone he did not show any response. Detailed general physical and systemic examination did not reveal any abnormality and mental status examination was suggestive of auditory hallucinations—third person discussing type, delusions of persecution and reference, low mood and suicidal ideations secondary to psychotic symptoms with absence of insight and intact cognitive functions (Mini mental state examination—28/30). A diagnosis of paranoid schizophrenia as per ICD-10 was considered. After all essential routine haematological (complete blood count) and biochemical investigations (serum electrolytes, liver function tests, lipid profile, renal function tests, serum vitamin B12 and folate), all of which came out to be normal, he was started with Olanzapine 5 mg which was gradually increased to 15 mg over a period of 3 weeks (5 mg increment in dose per week). There was reduction in psychotic symptoms by 40%–50% but on subsequent follow-ups, after 6 weeks of starting Olanzapine, the patient complained of excessive fatigability. On repeat investigations, there was evidence of total leucocyte count of 2600/cumm (baseline—9400/cumm) and total platelet count of 45 000/cumm (baseline—130 000/cumm) without any evidence/history of fever and symptoms suggestive of any local or systemic infection and intake of any other medications. Haematology consultation and detailed autoimmune workup to rule out other possible aetiologies (hepatosplenomegaly, autoimmune antinuclear antibodies and antineutrophil cytoplasmic antibodies) were found to be negative.

Following this, a possibility of Olanzapine induced leucopaenia and thrombocytopaenia was considered and the drug was stopped. The patient was admitted for inpatient serial monitoring of haematological parameters and after stopping of Olanzapine, serial monitoring revealed an increase in total leucocyte count (8900/cumm) and total platelet count back to normal range (156 000/cumm) within a week. Later on, he was started on aripiprazole 2.5 mg with a very slow hiking of dosage (2.5 mg/fortnightly) along with monitoring of haematological parameters and psychopathology. At 10 mg of aripiprazole after a period of 30 days, the patient showed significant improvement in mood and psychotic symptoms by around 75% and his haematological parameters continued to remain stable over the next 4-month follow-up period. The prognosis of the patient was good and there was no relapse of any haematological abnormalities.

DISCUSSION

In the index elderly subject, olanzapine-associated leucopaenia and thrombocytopaenia were detected just after 6 weeks of starting Olanzapine at a dosage of 15 mg/day. After ruling out all possible causes of these haematological abnormalities, olanzapine was considered to have induced these adverse effects. Leucopaenia and thrombocytopaenia have been rarely reported with olanzapine and the exact incidence rate is currently unavailable. In the literature search, seven published case reports on olanzapine-induced blood dyscrasias have been reported with elderly subjects (details mentioned in [table 1](#)).

Table 1 Olanzapine-induced blood dyscrasias in the elderly

Author/year	Patient details	Dose of olanzapine	Detected after days of initiation of olanzapine	Treatment/outcome
Meissner <i>et al</i> , ²⁷ 1999	56-year-old woman with parkinsonism	15 mg	120 days	Reversibility of leucopaenia after stoppage of olanzapine
	58-year-old man with parkinsonism	5 mg	156 days	
Steinwachs <i>et al</i> , ²³ 1999	81-year-old woman with schizophrenia	10 mg	17 days	Reversibility of neutropaenia after stoppage of olanzapine
Teter <i>et al</i> , ²⁹ 2000	60-year-old man with psychosis	20 mg	204 days	Patient had a history of treatment with clozapine and developed neutropaenia subsequent to use of olanzapine which improved after stoppage of the drug
Onofrj and Thomas, ¹⁴ 2001	67-year-old man with Parkinson's disease and psychosis	10 mg	35 days	Stoppage of olanzapine improved pancytopaenia and thrombocytopaenia in 14 days
Carrillo <i>et al</i> , ¹⁵ 2004	78-year-old man with dementia	10 mg	21 days	Death
Mehta and Sanitato, ¹³ 2005	83-year-old woman with dementia and depression	2.5 mg	1 day	Stoppage of olanzapine plus treated with G-CSF led to improvement
Stergiou <i>et al</i> , ²⁸ 2005	69-year-old woman with psychosis	10 mg	17 days	Stoppage of drug

G-CSF, granulocyte colony stimulating factor.

Pancytopenia and neutropenia were also reported with thrombocytopenia in two of these case reports with elderly subjects. Rechallenge with the same drug was not possible due to ethical reasons.

It was also seen that olanzapine-induced haematological abnormalities can be seen at any time of treatment duration ranging from the first day¹³ to 204 days.²⁹ The index case developed leucopenia and neutropenia after around 42 days (6 weeks) of starting of olanzapine. Of the seven case reports, while there was reported fatality in only in one case¹⁵, the others improved with stoppage of olanzapine (though one required granulocyte colony stimulating factor (G-CSF) additionally¹³). Similarly, stoppage of olanzapine led to improvement in haematological parameters within a week, which further ascertains that olanzapine was the definite agent for inducing leucopenia and thrombocytopenia in the index case. The Naranjo probability score³⁰ was 9 indicating a definite association of leucopenia and thrombocytopenia with olanzapine in the index case.

Though the exact mechanism of action of olanzapine induced neutropenia and leucopenia is not known, considering its chemical structure and pharmacological receptor profile are quite similar to clozapine, those mechanisms proposed for clozapine induced haematological abnormalities can be postulated for olanzapine too. Some of these proposed mechanisms are: (1) olanzapine can modulate levels of the G-CSF and can cause subsequent transient granulocytopenia like clozapine³¹ and (2) possibly olanzapine use can also lead to formation of nitrenium cations catalysed by Flavin containing monooxygenase-3 system of leucocytes like clozapine.³² However, both of these hypotheses are not yet proven.

It has been suggested to screen patients as high and low risk for developing olanzapine-induced haematological abnormalities (ie, high risk includes previous history of haematological diseases, family history of blood dyscrasias and any previous history of drug-induced granulocytopenia).²⁶ We further suggest that being an elder be included under high-risk screening for olanzapine-induced haematological abnormalities and a thorough meticulous complete blood count once a month within the first 3 months³³ be carried out so as to detect any haematological abnormality at the earliest time possible.

The index case adds to the extremely limited literature on olanzapine-induced leucopenia and thrombocytopenia in elderly subjects and suggests that whenever an elderly patient receiving olanzapine has objective evidence of any blood dyscrasias, olanzapine must be suspected and stoppage should be considered as early as possible to avoid deleterious results.

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