Ther Adv Psychopharmacol
2016, Vol. 6(1) 33–38
DOI: 10.1177/2045125315624063

Continuing clozapine treatment with lithium in schizophrenic patients with neutropenia or leukopenia: brief review of literature with case reports

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Abstract

Objective: Clozapine is a second-generation antipsychotic used for treatment-resistant schizophrenia. Despite its effectiveness, clozapine is largely underused due to serious side effects such as leukopenia or neutropenia. We aimed to review whether to continue, discontinue or rechallenge clozapine treatment after such haematological side effects.

Methods: We reviewed and summarized the literature on the use of clozapine, how to deal with its side effects, and suitable options in case of any haematological problems. Then, we described several cases successfully treated with clozapine and lithium after development of neutropenia or leukopenia

Results: We present three patients with treatment-resistant schizophrenia. While they had demonstrated poor response to multiple antipsychotic trials, clozapine was started. Clozapine induced neutropenia; or leukopenia developed in some cases that was successfully reversed after lithium onset. Increased serious side effects related with coprescription of lithium and clozapine were not observed.

Conclusion: Lithium increases neutrophil and total white blood cell count as a side effect that may be useful in patients who develop neutropenia or leukopenia while being treated with clozapine.

Keywords: clozapine, leukopenia, lithium, neutropenia, treatment-resistant, schizophrenia

Introduction

Schizophrenia occurs worldwide and is among the most severe devastating mental disorders [Rado and Janicak, 2014]. This severe mental disorder affects 1% of the world population and is characterized by psychotic symptoms such as hallucinations, delusions or disorganized thinking and cognitive, affective and psychosocial impairment [Schultz and Andreasen, 1999]. Antipsychotic medication is the mainstay of pharmacological treatment in the acute phase, in the long-term maintenance therapy and in the prevention of relapse of schizophrenia [Thibaut, 2014]. Despite new-generation antipsychotic medications, one third of schizophrenic patients do not respond well to pharmacological interventions. Such patients are commonly labelled treatment-resistant schizophrenics [Sinclair and Adams, 2014].

Clozapine is known as the first 'atypical' or ' second-generation' antipsychotic drug [Balda *et al.* 2015] that is effective on both the positive and negative symptoms of the disease and effective in 30–60% of schizophrenic patients resistant to common neuroleptics [Balibey *et al.* 2011]. It is mostly used for treatment-resistant schizophrenia [Lewis *et al.* 2006]. It is also effective in reduction of self-harm and suicidal behaviour in schizophrenia [Meltzer *et al.* 2003; Zarzar and McEvoy, 2013]. Despite its effectiveness, clozapine is largely underused for many and serious side effects including haematological (agranulocytosis, neutropenia), cardiac (myocarditis), nervous

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(seizure), metabolic (weight gain, metabolic syndrome, diabetes) and gastrointestinal (ileus, haematemesis, constipation) complications [Raja and Raja, 2014].

Agranulocytosis and neutropenia are life-threatening side effects of clozapine [Abanmy *et al.* 2014]. The incidence of agranulocytosis is about 1%, and of neutropenia about 3%, with the highest risk within the first 6–18 weeks of treatment [Atkin *et al.* 1996]. The neutrophil counts increase or decrease in parallel to leukocyte counts, and the evolution of leukocytes reflects the evolution of neutrophils [Bourin *et al.* 2001]. Mild leukopenia [white blood cell (WBC) count of 3500–3000/mm^3 or absolute neutrophil count (ANC) of 2000–1500/mm^3 of blood], moderate leukopenia (WBC count of 3000–2000/mm^3, ANC 1500–1000/mm^3), or severe leukopenia (WBC count $<$ 2000/mm^3, ANC $<$ 1000/mm^3) are descriptions used for defining the severity of leukopenia. Agranulocytosis is defined as ANC $\leqslant$ 500/mm^3 [Balda *et al.* 2015]. Neutropenia is defined as neutrophil count between 500/mm^3 and 1500/mm^3. If neutropenia occurs during treatment, clozapine use must be interrupted or discontinued [Nykiel *et al.* 2010].

The initiation of clozapine treatment requires WBC count to be $>$3500/mm^3. The treatment decisions are based on normative cutoff WBC values (3600–9500/mm^3) derived from white populations. Normative standards for WBC and ANC measurements do not take into account ethnic differences. Ethnic differences such as benign ethnic neutropenia (BEN) should be considered, either in the initiation of clozapine or in the evaluation of cases of clozapine-related blood dyscrasias [Bray, 2008]. BEN is a familial condition which is prevalent in Afro-Caribbean families and in some Middle Eastern families. Normal WBC levels in Afro-Caribbean families generally range from 2800 to 9500/mm^3. This condition due to ethnic differences becomes important to distinguish between clozapine-induced neutropenia and BEN [Kelly *et al.* 2007].

The mechanism of clozapine-induced agranulocytosis and neutropenia is not clear [Dunk *et al.* 2006; Ng, 2014], but genetic factors, as well as immunological and toxic mechanism may play an important role [Załuska and Gajewska, 1995; Yağcıoğlu *et al.* 2011]. The development of severe neutropenia and agranulocytosis are a substantial hazard in the administration of clozapine, but serious and potentially life-threatening adverse effects can be reduced, or managed, by monitoring the WBC count before the patients began clozapine treatment, weekly for the first 18 weeks, and then monthly throughout the duration of therapy [Alvir *et al.* 1993]. It was reported that the clozapine patient-monitoring system has successfully reduced the death rate by early detection of blood disorders and rapid cessation of clozapine use [Drew, 2013], and has resulted in a lowered incidence of agranulocytosis [Fitzsimons *et al.* 2005].

We present a series of three White inpatients with treatment-resistant schizophrenia who were hospitalized and treated in the mid regions of Turkey. While they had demonstrated poor response to multiple antipsychotic trials, clozapine was started. Clozapine-induced neutropenia or leukopenia developed in some cases that was successfully reversed after lithium onset. We discussed the details of the treatment and obtained written informed consent from the patients and from their first-degree relatives or spouses.

Case reports

Case 1 A 25-year-old woman with a history of schizophrenia for 7 years was referred to the emergency room because of suicide attempts. She had a history of multiple psychiatric hospitalizations: seven times in a 2-year follow-up period and multiple antipsychotic trials including olanzapine, 20 mg/day, paliperidone, 9 mg/day, aripiprazole, 30 mg/day, and risperidone long-acting injections that were unsuccessful in preventing relapses. Eventually, clozapine was considered, to prevent relapse of psychotic episodes and suicide attempts. Baseline laboratory results showed a WBC of 5300/mm^3 count (normal range 4500–10,800/mm^3). After determining baseline WBC results, clozapine was initiated and brought to 400 mg daily with titration according to the guidelines. Leukopenia occurred (WBC count of 3600/mm^3, neutrophil cell count of 1860/mm^3) 3 weeks after starting clozapine treatment. The patient was not taking additional psychotropic medications that carry a risk for blood dyscrasia. Clozapine treatment continued at the dose of 400 mg/day despite the need of a higher dose for symptom control. The patient's haematological parameters showed persistent (mild) leukopenia for the first week without improvement in neutrophil cell count. A week later, a decline in neutrophil cell count (ranging from 1440 to 1750/mm^3) was considered possible progression to neutropenia. Initiation of

lithium treatment was decided, based on the most recent WBC count (3320/mm^3) and neutrophil cell count (1620/mm^3) at the end of first week. Clozapine treatment at a dose of 400 mg daily continued with lithium. The patient's WBC and neutrophil counts began to normalize after 5 days of 300 mg daily lithium administration. Lithium serum level was in the range of 0.5–0.7 mmol/l. Over the course of time, the patient reported significant decrease in frequency and intensity of suicidal thoughts and psychotic symptoms. Time without blood dyscrasia after lithium administration was 24 months. The patient had normal WBC counts in the range of 4250–6360/mm^3 and neutrophil cell counts in the range of 2130–3580/mm^3 in the examinations post hospital discharge.

Case 2 A 51-year-old woman who had been diagnosed with schizophrenia for 26 years. The patient had a history of multiple psychiatric hospitalizations; at least once or twice a year. The patient had disorganized behaviour and responded poorly to multiple antipsychotic trials including zuclopenthixol decanoate depot, risperidone long-acting injection, olanzapine, 20 mg/day, and haloperidol, 15 mg/day. She was started on clozapine and the dose was brought to 300 mg daily according to the guidelines. Before clozapine treatment, the patient had a WBC count of 6200/mm^3. Neutropenia (neutrophil cell count of 1450/mm^3, WBC count of 2950/mm^3) occurred 4 weeks after starting clozapine treatment. The patient's treatment was not including any other potentially bone marrow-suppressing medications. Clozapine treatment continued at the same dose despite neutropenia for a week. The patient's haematological parameters did not improve sufficiently in this period. Next, clozapine treatment was considered, to continue with lithium (300 mg/day), after haematology consultation. As lithium serum level (0.3 mmol/l) was lower than required levels on the fifth day of administration, lithium dose was titrated up to 600 mg/day. The neutrophil count became normal (neutrophil cell count of 2150/mm^3) after 8 days from the first day of lithium administration (lithium serum level 0.7 mmol/l). Lithium treatment continued at a dose of 300 mg daily for maintaining serum level around 0.4 mmol/l. The patient's clozapine treatment was decreased to the dose of 100 mg because of side effects other than haematological problems. Psychotic symptomatology, including disorganized behaviour, responded well to 100 mg daily clozapine treatment. The patient's functioning levels improved significantly. Time without blood dyscrasia after lithium administration was 48 months. She was never hospitalized during this time. During the 48 months of treatment, the patient's WBC and neutrophil counts remained in the range of 4170–9300/mm^3 for WBC and 1900–5620/mm^3 for neutrophils. Clozapine is still used at the same dose (100 mg/day) with lithium (300 mg/day) coprescription.

Case 3 A 44-year-old woman who had been diagnosed with schizophrenia and obsessive–compulsive disorder for 28 years. It was her first psychiatric hospitalization. She presented with a long-standing history of severe obsessive features and psychotic symptoms with agitation. Antipsychotic medications were risperidone, 4 mg/day, chlorpromazine, 100 mg/day, olanzapine, 20 mg/day, risperidone long-acting injection and electroconvulsive therapy (ECT); more than 15 sessions while she was an inpatient and maintenance ECT as an outpatient were not effective in symptom control. After determining a baseline WBC count of 5400/mm^3, clozapine treatment was started and titrated to 400 mg daily according to the guidelines. Around 8 weeks after initiation of treatment with clozapine, neutropenia (neutrophil cell count of 950/mm^3, WBC count of 1800/mm^3) occurred. The patient was taking sertraline, 100 mg daily, due to obsessive features for 3 months. Clozapine and sertraline were discontinued after haematology consultation. Schizophrenia symptoms severely worsened after clozapine withdrawal despite maintenance ECT. After 2 weeks of drug suspension, the patient's haematological parameters improved but the improvement in WBC count (ranging from 3130 to 3350/mm^3) was not sufficient for initiating clozapine treatment. Because of low baseline counts, clozapine treatment was initiated with lithium (300 mg/day, lithium serum level 0.3 mmol/l) and titrated up to 100 mg/day. Symptoms were fairly controlled in the 2 weeks after clozapine rechallenge with lithium (600 mg/day, lithium serum level 0.5 mmol/l) at the dose of 100 mg/day. Lithium treatment continued at a dose of 300 mg daily in order to maintain the required serum level. The neutrophil cell count (2380/mm^3) became normal after administration of lithium. The duration without blood dyscrasia after clozapine rechallenge was 26 months, during which she did not have need of hospitalization. The patient had normal WBC counts in the range of 4190–7250/mm^3 and neutrophil cell counts in the range of 2030–3780/mm^3 in the examinations post hospital discharge.

In all patients, blood tests were repeated at least three or four times on consecutive days after the development of blood dyscrasias while deciding whether to continue or discontinue clozapine treatment. After deciding to continue clozapine treatment, patients' blood parameters were controlled closely and they continued being followed up as outpatients. Any additional episodes of neutropenia were noted during the observation periods of patients.

Discussion

The risk of haematological side effects is still the major limitation of clozapine treatment. To reduce this risk, monitoring WBC count might be useful before initiating clozapine treatment and regularly throughout therapy duration for identifying any haematological abnormalities [Alvir *et al.* 1993; Raveendranathan *et al.* 2013]. The treatment decisions require baseline WBC count to be $>3500/mm^3$. Early administration of growth factors or lithium may be useful for increasing the WBC in patients with low baseline counts who would benefit from treatment with clozapine [Lambertenghi Deliliers, 2000].

According to the guidelines, discontinuation of clozapine is required when WBC count falls below $3000/mm^3$ and ANC falls below $1500/mm^3$ [Dunk *et al.* 2006]. However, some treatment options must be considered when leukopenia or neutropenia occur: drug suspension until WBC counts return to normal and then drug reintroduction [Silvestrini and Arcangeli, 2000; Ghaznavi *et al.* 2008]; add-on filgrastim, a granulocyte-colony stimulating factor (G-CSF) during clozapine rechallenge [Hägg *et al.* 2003; Huguet *et al.* 2013; Khan *et al.* 2013]; or utilization of lithium in conjunction with clozapine [Pinninti *et al.* 2010; Suraweera *et al.* 2014]. If the WBC count continues to fall despite growth factors or lithium treatment, consideration should be given to discontinuing clozapine. When agranulocytosis occurs, consultation with a haematologist is required.

Rechallenge with clozapine is an off-label process when haematological side effects occur. However, rechallenge is sometimes considered when clozapine is the only effective treatment and drug discontinuation may lead to psychotic exacerbation [Ahn *et al.* 2004]. Patients who are unresponsive to other antipsychotics and remain significantly distressed with poor quality of life and psychotic symptoms should be considered for clozapine usage in combination with any suitable offered agent when neutropenia or leukopenia occur. The outcome of rechallenge was considered favourable when the risks and benefits of rechallenge with clozapine was assessed carefully [Dunk *et al.* 2006; Manu *et al.* 2012]. Although add-on G-CSF or lithium are favourable therapeutic options when clozapine is rechallenged, physicians should be aware of the potential dangers of recurrent blood dyscrasias [Hazewinkel *et al.* 2013].

In case of neutropenia, coprescribing of lithium is supported by published reports [Ghaznavi *et al.* 2008; Kanaan and Kerwin, 2006]. A retrospective case analysis that presented all patients who had a clozapine rechallenge with lithium coprescribed reported the utility and safety of lithium in clozapine rechallenge. The rate (4%) of a second neutropenic episode or agranulocytosis while undergoing the rechallenge with lithium coprescription was reported as significantly lower than the rate (21.2%) of a second neutropenic episode or agranulocytosis while undergoing the rechallenge without lithium coprescription [Kanaan and Kerwin, 2006].

Some limitations regarding lithium use should be considered. First, there are concerns that lithium might mask impending agranulocytosis, making the combination potentially dangerous [Whiskey and Taylor, 2007]. Second, clozapine–lithium combination might be associated with an increased risk of neurological symptoms, weight gain and metabolic abnormalities [Brunoni *et al.* 2008].

The mechanism by which lithium raises the WBC count is not completely understood [Palominao *et al.* 2010]. Direct stem-cell stimulation, an increase in granulocyte production, stimulation of cytokines, redistribution of demarginated leukocytes, and increased cortisol production have all been suggested as putative theories [Whiskey and Taylor, 2007]. There is no defined serum level for neutrophilia, but a minimum lithium serum level of 0.4 mmol/l may be required [Blier *et al.* 1998]. In most of the literature, the combination of clozapine and lithium treatment is reported as well tolerated and effective when administered within an optimal lithium dose range (300–900 mg/day) with lithium serum levels between 0.4 and 0.9 mmol/l [Bender *et al.* 2004; Kanaan and Kerwin, 2006; Pinninti *et al.* 2010].

In our own experience, the patients responded well to clozapine treatment, in terms of clinical

improvements in psychotic symptoms and reduction of suicide. However, over the course of treatment with those taking clozapine, neutropenia or leukopenia occurred. We considered continuing the clozapine treatment of two patients in conjunction with lithium, while their blood neutrophil cell counts were in the range of 1450–1860/mm^3 (mild–moderate leukopenia), and stopping clozapine treatment of the other due to a neutrophil cell count of 950/mm^3 (severe leukopenia). Lithium treatment was added for increasing WBC counts to all. We chose not to use G-CSF because of potential side-effect limitations: bone pain, autoimmune disorders, allergic reactions, and the possible relationship between the use of G-CSF and the development of acute myeloid leukaemia [Tigue *et al*. 2007], as well as its high cost. G-CSF should be administered within 48 h with an optimal indication (ANC $<$ 500/mm^3). Requirement of daily or weekly subcutaneous injections restricts prescription of G-CSF [Hägg *et al.* 2003].

The three patients presented in this report support previous reports about lithium coprescription with clozapine as a well-tolerated and successful strategy when neutropenia and leukopenia occur. We did not observe any increase in serious adverse effects related with coprescription of lithium and clozapine.

The evidence is limited to retrospective case-analysis reports. Further studies are required to investigate continuing, discontinuing and rechallenging clozapine treatment after neutropenia or leukopenia occur.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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