CASE REPORT

CLOZAPINE RE-CHALLENGE WITH LITHIUM SUPPLEMENTATION FOLLOWING CLOZAPINE-INDUCED NEUTROPENIA

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Abstract

Objectives*: This paper aims to report on a case in which re-challenging with clozapine in combination with lithium in a patient who developed neutropenia was carried out. *Methods*: The patient was treated with clozapine for treatment-resistant schizophrenia. After five weeks he showed much improvement but developed neutropenia. Withdrawal of clozapine brought on a relapse of psychotic symptoms. Subsequently, clozapine was reintroduced along with Lithium. The neutrophil count was monitored closely. *Results*: The neutrophil and white blood cell count were noted to return to normal upon re-challenging, and the patient's clinical condition also improved. *Conclusion*: Simultaneous administration of lithium and clozapine to patients experiencing neutropenia on clozapine is a possible strategy. However, very close monitoring of the white count is needed. *ASEAN Journal of Psychiatry, Vol. 15 (1): January – June 2014: 90-92.

Keywords: Clozapine, Clozapine Re-challenge, Lithium, Neutropenia

Introduction

Clozapine is considered a classic model of an atypical antipsychotic [1]. It has been reserved for the treatment of treatment-resistant schizophrenia (TRS). One of its major disadvantages however, is the occurrence of idiosyncratic blood dyscrasias, namely neutropenia and/or agranulocytosis.

Around 2.7% of patients will develop neutropenia once exposed to clozapine; of these, 50% will develop it in the first 18 weeks of treatment [2]. When patients develop severe neutropenia or agranulocytosis, the guidelines advise the withdrawal of clozapine and advise against re-challenge [3]. However, withdrawal of clozapine usually leads to worsening of the psychotic symptoms. Hence strategies are needed to continue the clozapine, if possible, without any detrimental effect on the granulocyte count. In this paper, we present one such strategy – that of adding lithium which is known to induce leucocytosis, thereby antagonizing the neutropenic effect of clozapine [4].

Case Report

Mr A, is a 32 year-old gentleman, who has suffered from schizophrenia since the age of 23. He has had numerous relapses and 5 admissions in 2 years. He was admitted to the ward due to an acute exacerbation of schizophrenia, with aggressive behaviour, auditory hallucinations commanding him to commit suicide. Throughout the past years, he has been treated with adequate doses of various antipsychotics for adequate duration of time on each drug. Among the medications he was on before were olanzapine, paliperidone and IM fluphenazine depot. Despite adhering to treatment regime, he showed a poor response to all the medications. He was therefore started on clozapine because of the

treatment resistance and persistent suicidal risk due to commanding auditory hallucinations.

His baseline Full Blood Count showed normal results: haemoglobin (Hb) 15.6 g/dL, white blood cell (WBC) count 5.6 x 10^9/L; platelet count 379 x 10^9/L; absolute neutrophil count (ANC) 3.5 x 10^9/L. Renal function and electro-cardiogram (ECG) were normal. He was started on clozapine 12.5 mg nocte and the dose was titrated up gradually following Maudsley Guidelines [5]. At the same time, other drugs were discontinued. By the fourth week, the dose of clozapine was increased to a total of 350 mg daily in divided doses. Apart from sedation and sinus tachycardia, Mr. A did not develop any other adverse effects such as postural hypotension or hypersalivation. The FBC was repeated weekly and yielded normal results. Clinically, the patient made good improvement in his positive and negative symptoms.

As shown in Figure 1, in the fifth week of clozapine treatment, the ANC and WBC started to decrease (WBC ranging between 3.0 to 2.1 x 10^9/L, ANC ranging between 1.3 to 0.9 x 10^9/L). With these low levels, it was decided to withdraw clozapine before the white cell numbers declined further. The patient had no upper respiratory tract symptoms like fever, sore throat, and cough or other signs of infections. Clozapine was tapered off in 2 days before it was completely withheld. Clozapine was substituted with haloperidol reaching a dose of 7.5 mg daily in divided doses.

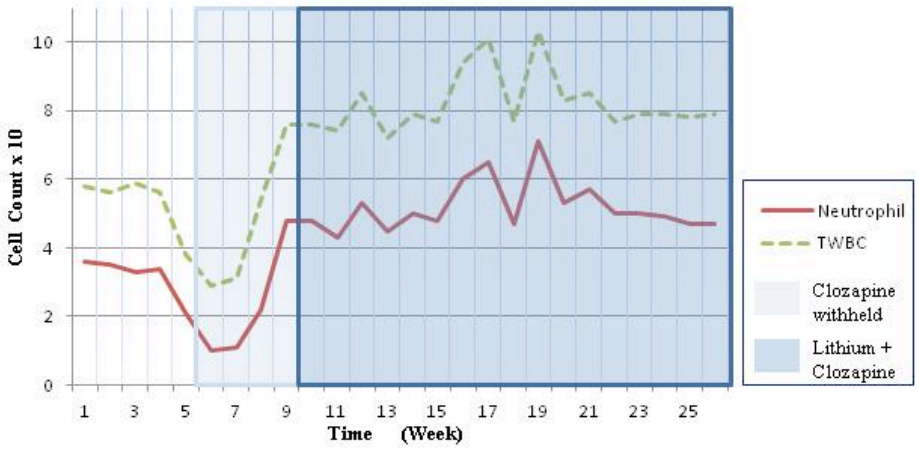

Fig. 1: The trend of patient's total white blood cell (TWBC) and neutrophil count over time (week). Clozapine was withheld at 5th week (light scale) and re-challenge at 9th week along with lithium (dark scale).

The FBC was repeated more closely (i.e every other day) and within two weeks of withdrawing clozapine, the WBC and ANC were noted to stabilize to the pre-neutropenic levels (WBC: 5.4 x 10^9/L and ANC: 2.2 x 10^9/L). The patient, however, began to relapse and his previous psychotic symptoms returned. He became aggressive again and his family was unable to cope with caring for him. It was decided therefore to re-challenge with clozapine together with lithium.

Clozapine was introduced at a slower rate, starting at 6.25 mg nocte, and slowly increased by 6.25 mg every 3-4 days. Lithium was started at the same time at 600 mg a day. It was titrated up to achieve a stable lithium level of about 0.6 mmol/l. The WBC and ANC results have been stable since then (7.6- 10.3x 10^9/L and 4.8-7x 10^9/L respectively) [Fig. 1]. The patient again showed an improvement on clozapine. Lithium level of 0.54 mmol/l was achieved. At this stabilized level, the patient had only minimal psychiatric symptoms, without any suicidal thoughts, intentions and/or acts. He has continued to remain well since.

Discussion

The combination of clozapine and lithium has not been studied extensively [6]. The mechanism behind the occurrence of clozapine-induced neutropenia is thought to be premature peripheral destruction in the blood or spleen whereas the severe form of agranulocytosis is caused by bone marrow suppression [7] via stimulation of granulocyte-macrophage colony stimulating factor (GM-CSF) [6].

This case report revisits the issue whether clozapine should be discontinued when patients develop blood dyscrasias. Nielson J et al. (2013) are of the opinion that re-challenging might be useful in neutropenia but clozapine should be discontinued in the event of agranulocytosis [3]. Dunk et al (2006) showed that the second reaction of agranulocytosis will be more severe and lasts longer [8]. About 20% of patients receiving combination of clozapine-lithium develop neurotoxicity [9].

Conclusion

This case report suggests that clozapine re-challenge may be considered for some patients who would otherwise be left to suffer the disabling effects of treatment-resistant schizophrenia. There is no current consensus on the dosage of lithium to be used in cases of clozapine re-challenge and lithium use is not without risk. Therefore this should be done with close monitoring.

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