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Case Report

Clozapine-Side Effects and Blood Monitoring, how Long to be Done Case report, Review and Discussion

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Abstract

Clozapine 5HT2A/D2 Antagonist is of use in the treatment of Refractory schizophrenia. It is low in causing Extrapyramidal symptoms and can be used in the presence of Tardive Dyskinesia also. Agranulocytosis is a well-known side effect of Clozapine and the manufacturer recommends the risk of Agranulocytosis is high up to 18 weeks on initiation of Treatment and monitoring blood counts for 18 weeks is necessary on a weekly basis for the first 18 weeks on starting Clozapine. can there be a risk of developing after 18 weeks also. The relevant literature reviewed shows the risk is present even after years as the exact mechanism of causation of agranulocytosis is not clearly known, though an immune-allergic, Toxic mediation is suggested. Here with a case report is presented, who developed Agranulocytosis 3 years after staring and continuing Treatment with clozapine.

Keywords: *Clozapine; Agranulocytosis; Risk Factors*

Introduction

Clozapine, a 5HT2A/D2 antagonist, is effective in refractory cases of schizophrenia and in reducing the risk of suicide in schizophrenia, it is low in causing extrapyramidal symptoms and can be given safely in Tardive Dyskinesia. Thus, Clozapine has substantial therapeutic advantage over other neuroleptics [1-4].

Clozapine's use has been limited by its side effects, which include a risk of developing an agranulocytosis and neutropenia, an increased risk of seizures, excessive sedation, salivation, an increased risk of myocarditis along with greatest degree of weight gain. The exact mechanism of Clozapine's ability to cause agranulocytosis, seizures and myocarditis, remain largely unknown [1].

Though there is a suggestion that agranulocytosis may be mediated by immuno-allergic and toxic mechanisms [5-7]. In immune-mediated drug induced agranulocytosis, anti-neutrophil antibodies bind to target cell, usually requiring the presence of causative drug or its metabolite to do so, often consuming the complements. In some cases, antibody can bind to myeloid pro genetic cells and this has been inferred from the inhibition of colony-forming units-granulocytes, macrophage (CFU-GM) derived colony formation by the patient's serum [5-8]. Direct damage to the bone marrow microenvironment or myeloid precursors also may play role in most other cases [5-8]. There are reports substantiating an association between the major histocompatibility complex subtypes and Clozapine induced agranulocytosis have appeared, where in, agranulocytosis patients had a higher frequency of the HLAB38 and HLAB27 antigen [9]. Occurrence of HLA-B35 antigen might prevent this mechanism in certain ethnic groups [10].

Agranulocytosis is said to have occurred when there is a profound decrease in the number of, or an absolute lack of, granulocytes in circulating blood, classically resulting in a Neutrophil count below 0.5 x 10^9/L. These patients may present clinically with fever and or any

sign of infection, at times a life- threatening fatal infection, if neutropenia is severe (Neutrophil count < 0.1 x 10^9/L) [11,12]. The cumulative incidence of this side effect seems to be around 0.8 - 0.91% at 1 - 1 ½ yrs of treatment[2] or in other words around 2.4 - 15.4 cases per million [11].

Risk factors for developing agranulocytosis [2,5,6,8,9,12,14]**:**

- Increased age,
- Being female,
- First 6 months of treatment (especially 6 - 18 weeks of treatment) [2,12],
- Ethnicity of African-Caribbean or Asian origin or Ashkenazi Jewish descent,
- Low baseline white blood count, low baseline hemoglobin level,
- Certain histocompatibility antigens like HLA-B27, HLA-B38, HLACR4, DQW3 and HLA-B35,
- Underlying autoimmune diseases such as rheumatoid arthritis or renal failure,
- Patients receiving other agranulocytosis causing drugs-like captopril, probenecid, antithyroid drugs, ticlopidine, sulphasalazine, gold salts, penicillamine and phenylbutazone.

Studies also have shown that Clozapine induced agranulocytosis or neutropenia is largely not dose dependent, and toxicity may result from a particular ratio of metabolites rather than from a particular dosage [12,16]. Although the risk of agranulocytosis is more [12], in the first 6 - 18 weeks of therapy, with the risk declining during the remainder of the first treatment year, there have been reports of patients developing this dyscrasia even after years of otherwise uncomplicated successful treatment with Clozapine. For example, neutropenia has been documented after 2.5 years of Clozapine treatment [15] and agranulocytosis had been reported after 17 months of treatment [16] or even after 11 years of treatment in one instance [17]. In this context, we present case report of a patient with schizophrenia who developed Clozapine-induced agranulocytosis after 3 years of pharmacotherapy.

Case Report

Mr. D, 43 yrs, single male, educated upto 9th std and working in a fire works factory, was apparently normal until 15 yrs of age. He was brought with history of withdrawn behaviour, poor interaction, irritability, talking to self, claiming to have seen god and been to heaven, of 6 months duration. He was treated initially with Tab haloperidol 15 mgs in divided doses. Though behaviour symptoms were less, he was still withdrawn and was functioning inadequately in his job.

One year later, patient was brought with complaints of muttering to self, claiming a dog was stuck in his throat, frequently opening his mouth and attempting to swallow. He was started on Clozapine, which was later built up to 400 mg/day. He presented 3 months later with persisting complaints and Clozapine was increased to 500 mg/day. Patient showed partial recovery with Clozapine on follow up and after a period of about 3 years, patient was noticed to have fever, sore throat and generalized weakness. On investigation he was found to be having Neutropenia (Total Leucocyte count of 3200/mm^3) with Neutrophils being 42% and agranulocytosis. He had no preexisting haematological disease. Clozapine was withdrawn and he was managed conservatively. Though he was on Clozapine from September 2003 haemotological monitoring was not done for some unknown reason after the 1st 8 weeks. The monitoring done on his physical complaints nearly 3 years after he started taking Clozapine revealed neutropenia. Patient's leucocyte counts returned to normal within 5 weeks of stopping Clozapine and treated conservatively

Discussion

All these reports, though sporadic and scattered, suggest the idiosyncratic nature of Clozapine induced agranulocytosis and neutropenia and thus stress the importance of continued monitoring of complete blood counts in Clozapine-treated patients even after many years of uncomplicated use [17,18].

Clozapine was approved by the FDA in October 1989 and a special surveillance system, in which a weekly white-cell count was to be monitored weekly to receive a further supply of the drug [2]. Clozapine was licensed in UK in 1970s was later withdrawn due to its propensity to cause agranulocytosis. Clozapine was reintroduced for clinical use with a proposal for a nationally coordinated mandatory

hematological monitoring service for all patients known as the CPMS (Clozaril Patient Monitoring Service), which ensures that no patient receives the drug without a recent blood cell monitoring [12,14,18] The purpose of the CPMS is to monitor WBC, Neutrophil and Platelet counts of people prescribed with Clozapine [14]. Results were classified as shown in the table below.

Color code/names of syndrome	Absolute Neutrophil count	WBC count
Green	> 2.0 x 10^9/l	> 3.5 x 10^9/l
Amber	1.5 - 2.0 x 10^9/l	3.0 - 3.5x 10^9/l
Red	< 1.5 x 10^9/l	< 3.0 x 10^9/l

For coding in the above way, blood was required to be sampled on a weekly basis for the first 18 weeks of treatment and fortnightly thereafter [14]. Data from Atkin., *et al* [12], revealed that the sampling frequency after one year could be reduced to once every four weeks in majority of subjects exhibiting stable hematological profile [14]. However, in certain cases, treating physician is to be alerted by the case administrator. This included a white-cell count below 3500 per cumm, a large absolute drop in the white-cell count (even if the count remained above 3500/cumm) or three consecutive drops in the count. Treatment guidelines also specified that a complete blood count with a differential count be determined twice weekly if the white cell count dropped below 3500/cumm. Clozapine treatment should be interrupted if the WBC count fell below 3000/cumm or the absolute Neutrophil count fell below 1500/cumm and daily hematological monitoring was instituted; Treatment could be resumed if the WBC counts and absolute PMN leucocyte count returned to levels above 3000 and 1500/cumm respectively. The guidelines also stipulated that Clozapine be permanently discontinued if leucopenia developed, indicated by a white-cell count below 2000/cumm or an absolute polymorphonuclear leucocyte count below 1000/cumm. Weekly monitoring is to be continued for at least 4 weeks after Clozapine was discontinued for any reason [18]. APA practice guidelines for treatment of psychotic disorders - (Compendium 2004 and Psychotropic drug directly 2001/2) also recommend weekly monitoring upto 6 months and once in 2 weeks thereafter with no instructions as to the duration of monitoring required. It also warns about increased risk of agranulocytosis when other antipsychotics are combined with Clozapine.

However, once Clozapine induced agranulocytosis has been identified, further management of the patient should be prompt and immediate. This includes immediate withdrawal of the causative drug with a careful and thorough drug history, aggressive treatment of any diagnosed or potential sepsis, as well as prevention of secondary infections [5,13]. Therapeutic measures may include empirical broad spectrum antibacterial intravenous therapy, and transfusion of granulocyte concentrations and haematopoietic growth factors like granulocyte and granulocyte-macrophage colony stimulating factors (G-CSF and GM-CSF) at a mean dosage of 300 ug/d, which has been reported to be successful [19,20].

Thus, Hematological monitoring using the CPMS has been shown highly effective in keeping the risk of Clozapine –associated fatal agranulocytosis and neutropenia to a minimum, bearing in mind the potential benefits obtainable from this form of neuroleptic treatment. Further the hematological guidelines can be modified, subtly and conveniently, by treating clinicians so that the drug can be managed in a less burdensome yet safe manner, for e.g. reducing the frequency of monitoring to every 2 weeks or even once a month after the maximal risk period of first 6 months have elapsed. However. attention to patterns of decline in addition to absolute threshold levels are also important.

Though, the future of Clozapine use, may see some modifications in the guidelines of hematological monitoring requirements, past experience and evidence suggest unmistakably the usefulness and inevitability of having a regular blood monitoring as part of Clozapine prescription in order to keep in check the fatal Clozapine–induced agranulocytosis or neutropenia.

Conclusion

Though the recommendation both by the manufacturer of Clozapine and CPMS (Clozaril Patient Monitoring service) is to monitor neutrophil counts every week for 18 weeks as risk of Agranulocytosis is more during the first 18 weeks after initiating treatment, it is necessary and prudent enough to monitor the Neutrophil counts as long as the patient is taking Clozapine at least once in month to detect delayed occurrence of Agranulocytosis as supported in Literature and a case report presented here, for avoiding complications that may occur.

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