

CLOZAPINE INDUCED THROMBOCYTOPENIA - A BLOOD DYSCRASIA.

Noel M Isaac^{*}, Mini Johnson Christudas and Dr. Umesh M

Pharmd Intern, Department of Pharmacy Practice, JSS Medical College and Hospital, JSS University, Mysore- 570 004, Karnataka, India.

Article Received on
14 April 2015,

Revised on 08 May 2015,
Accepted on 29 May 2015

***Correspondence for**

Author

Noel M Isaac

Pharmd Intern,
Department of Pharmacy
Practice, JSS Medical
College and Hospital, JSS
University, Mysore- 570
004, Karnataka, India.

ABSTRACT

The term "Blood Dyscrasia" refers to a diseased state of blood which may be induced by either a disease condition or with drug use. It is assumed that drug induced hematologic changes may be due to the interference of the drug with hematopoiesis in the bone marrow affecting one, two or all three major cell lines of hematopoiesis. Antipsychotic class of drugs was primarily found to induce leukopenia as a common blood dyscrasia with clozapine having the highest risk. Although data associating clozapine and leucopenia is available, data regarding that of thrombocytopenia is limited. In our study, thrombocytopenia was observed within 2 weeks of therapy with clozapine at a dose of 150mg/day. Since a reduction in dose did not show any improvements in the platelet count, clozapine was eventually

stopped. Within a month of withdrawing clozapine, the platelet count gradually began to improve. Therefore, an association of the reaction with the drug should be thought of as a possible cause prior to the initiation of therapy with clozapine, and, besides monitoring the leucocyte count of patients receiving clozapine, the platelet count of these patients should also be monitored.

KEYWORDS: Blood dyscrasias, Clozapine, Thrombocytopenia.

INTRODUCTION

The term "Blood Dyscrasia" is defined as a diseased state of the blood; usually refers to abnormal cellular elements of a permanent character.^[1] A variety of blood dyscrasias can be precipitated either with a disease condition and/or drug use; however, the exact mechanisms for a drug to induce hematologic changes are not known. It is assumed that the drug induced

hematologic changes may be due to the interference of the drug with hematopoiesis in the bone marrow affecting one, two or all three major cell lines of hematopoiesis.^[2] General classes of drugs that cause this adverse event include antiparasitic drugs, estrogenic compounds, NSAIDs, antithyroid drugs, anticonvulsants, antibiotics, antifungals, and cardiac drugs.^[3] Although antipsychotic-induced haematological effects are rarely seen, the level of severity of the reaction could be life threatening as it could lead to systemic infections, abnormal bleeding and/or death.^[4]

Antipsychotic (AP) class of drugs are further classified into conventional APs and atypical APs. Both conventional and atypical APs were primarily found to induce leukopenia as a common blood dyscrasia.^[5] The newer generation (atypical) APs were developed with the aim of reducing extrapyramidal side effects. They were considered to be equally efficacious as conventional APs in reducing positive symptoms and could greatly improve negative symptoms.^[6] In patients put on newer APs, agranulocytosis was assumed to be probable or definite drug-related adverse event.^[2] However the risk of leukopenia and agranulocytosis was found to be much greater with clozapine than with other APs, both conventional and atypical.^[7] Roughly 88% of all cases of agranulocytosis occurred within 6 months, and, leukopenia within 3 weeks to 3 months after the initial exposure to clozapine. The onset is usually more rapid and severe if clozapine was restarted subsequently.^[5, 8] However, a blood dyscrasia apart from leukopenia and agranulocytosis induced by clozapine is not well known. Here, we present a case study wherein the patient received clozapine for the treatment of his medical condition following which he developed thrombocytopenia. Also, an assessment of whether withdrawing clozapine could contribute to reaction recovery was made.

CASE HISTORY

A 37 year old male patient visited the psychiatry OPD on a regular follow up basis. He was a known case of schizophrenia receiving treatment with T. risperidone 4mg 0-0-1 and T. clonazepam 1mg 0-0-1 for the past 2 years. During his current visit, T. clozapine 150mg 0-0-1 was added to the therapy as the patient was not showing any signs of improvements in his mental status. On initiating clozapine, the laboratory investigation of monitoring the complete blood count was observed in which the platelet count was noted to be 2.4Lakhcells/cumm and the remaining parameters were observed to be within the normal limits. The patient was then asked to continue with his regular monthly follow up. On his 3rd follow up (i.e follow up after 3 months) of initiation with clozapine therapy, the patient's routine laboratory

investigation was repeated in which the patient complete blood count report showed a significant decline in platelet count which was noted as 1.1Lakhcells/cumm, with neither agranulocytosis nor anemia. Clozapine was thought to be the offending agent therefore the dose of clozapine was reduced from 150mg 0-0-1 to 100mg 0-0-1 and the therapy was continued. The patient was again asked to continue with his monthly follow up. After a month of follow up, the routine laboratory investigations were repeated in which the platelet count was noted to be 84300 cells/cumm. Since there was no improvement in platelet count inspite of reducing the dose of clozapine, clozapine was withdrawn and the therapy was switched to T. Iloperidone 4mg. After a month of stopping clozapine, platelet count was found to have significantly improved to 1.9Lakhcells/cumm.

DISCUSSION

Unlike the various atypical antipsychotics available, clozapine is usually reserved for its use in cases of treatment resistant schizophrenia. And, much like any other atypical antipsychotics clozapine is known for its relative absence of extrapyramidal side effects.^[9,10] However, clozapine- induced haematological effects remain to be poorly characterized as there are only few studies that have reported the incidence of blood dyscrasias associated with an antipsychotic. Although some data is available with regard to leucopenia, data for thrombocytopenia is limited.^[4,9]

Thrombocytopenia is defined as a condition wherein the platelet count drops below 1.5Lakh cells/cumm.^[11] Several studies that aimed in finding an association between clozapine use and thrombocytopenia have been conducted overtime, however, each concluded with varying results.^[12,13,14, 15, 16, 17] In our study, a reduction in platelet count was noted for the first time after 14 weeks of stable dose of clozapine at 150mg/day. This finding was consistent with the findings from a study conducted by Jagadheesan et al that concluded the onset of thrombocytopenia associated with clozapine use to occur between 6-44 weeks of clozapine therapy at dose ranging from 50-400mg/day.^[18] Since, the time-temporal relationship between the initiation of clozapine to the patients therapy and the decline of the platelet count was consistent with the findings of the above mentioned study, we suspected clozapine to be the offending drug to cause this reaction in our patient rather than T. risperidone or T. olanzapine that he was receiving for the past 2 years. Therefore, the dose of clozapine was reduced from 150mg/day to 100mg/day and continued for 4 more weeks. However, as the

reduction in dose did not show any improvements in the platelet count. T. clozapine was eventually stopped.

Within a month of withdrawing clozapine, the patient platelet count started to gradually improve. This finding was however contrary to the findings from a case report that observed thrombocytopenia to persist for 40 months even after stopping clozapine.^[19] Despite the duration of the therapy, a common factor connecting our observations with the results from other studies were that the platelet dysfunction and thrombocytopenia rarely occurs during clozapine therapy.^[18, 20, 21] However, certain studies have observed the platelet count to gradually improve by itself without a reduction in dose, over a period of 1-12 weeks.^[18] However, in our study, clozapine at 100mg 0-0-1 was continued for 4 weeks after the initial detection of thrombocytopenia, the period during which no gradual improvements were observed, rather, a decline in platelet count was seen that mandated the withdrawal of therapy with clozapine. Data regarding the association between clozapine and thrombocytopenia is limited and still remains unclear. Although rare an association of the reaction with the drug should be thought of as a possible cause prior to the initiation of therapy with clozapine.

CONCLUSION

From our study we conclude that thrombocytopenia, although rare, can be induced by clozapine, which could improve over a month of stopping the drug. Therefore besides monitoring the leucocyte count of patients receiving clozapine, the platelet count of these patients must also be monitored.

ACKNOWLEDGEMENT

The authors would like to thank the support from JSS University and JSS College of Pharmacy for their constant encouragement. We would also like to extend our heartfelt thanks to Dr. Irene Ann, Physician, Trivandrum Medical College Hospital, India, for her valuable suggestions and constant support throughout the study.

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