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CLOZAPINE AND BLOOD DYSCRASIA — A REVIEW

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ABSTRACT

Objectives: The objective of the study was to assess the Heamatological issues related with the use of Clozapine.

Material and Methods: It was a review of articles based on use of Clozapine in schizophrenic patients. Although Clozapine can cause other side effects but in this review article, we assessed different issues of Clozapine induced blood dyscrasia.

Results: Clozapine monitoring has proved to be highly successful in the early detection and has prevented many fatalities. The research into Clozapine induced blood dyscrasia has been ongoing for the past two decades and needs to continue to address unanswered questions regarding mechanism of blood dyscrasia and its prevention.

Conclusion: Clozapine can substantially improve the quality of life of patients with schizophrenia by reducing the presence and severity of symptoms, decreasing the duration of hospitalization.

Key Words: Clozapine, Leucopenia, Neutropenia, Agranulocytosis, Blood dyscrasia, Monitoring.

INTRODUCTION

Clozapine is the archetypal atypical antipsychotic medication which was discovered in the 1950s and first atypical antipsychotic medication introduced in clinical practice in 1971 in Europe. It was withdrawn from the market voluntarily by the manufacturers in 1975 after it was shown to cause deaths in some Clozapine treated patients due to agranulocytosis. The pivotal study by Kane et al proved that Clozapine was more effective than conventional antipsychotics for treating Schizophrenia[1], and it was reintroduced but only for treatment resistant schizophrenia with compulsory haematological monitoring in 1989.

Monitoring

To start someone on Clozapine in UK and Ireland, patient must be registered with an approved Clozapine patient monitoring service (CPMS) and full blood count weekly for first 18 weeks, fortnightly until 52 weeks and then monthly for the duration of the treatment. The current monitoring system is a legal requirement in Ireland and the UK but weekly monitoring can be carried out by the CPMS without any extra cost. This must be weighed up against the increase in blood letting for patients and the potential strain on our already stretched clinical workforce.

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Monitoring requirements are more stringent in the US; patients are monitored weekly for the entire duration of treatment.[2] Further treatment with Clozapine is contraindicated in any patient who has previously experienced Leucopenia or neutropenia during Clozapine therapy, according to manufacturer's guidelines.

Incidence of blood dyscrasia:

Clozapine — induced suppression of the granulocyte can induce three clinically distinct types of blood dyscrasia; the first type is mild Leucopenia (WBC less than $3.0x10^9$/L with satisfactory Neutrophil count), which occurs in 0.19% of Clozapine treated patients.[3] Second type is moderate neutropenia (Neutrophil count below $1.5x10^9$/L but not lower than $0.5x10^9$/L), which occurs in 1.5 – 2.9% of treated patients.[4] When Clozapine is discontinued, recovery is rapid (2-8 days). The third type of neutropenia is more severe with a Neutrophil count below $0.5x10^9$/L (Agranulocytosis) and an incidence of 0.78%. In the third type of patients it generally lasts for 14-21 days.[3] The risk of agranulocytosis is greatest in first 18 weeks. The frequency of all types of blood dyscrasia was significantly less after the first year treatment. The incidence of agranulocytosis decreased to 0.07% in second year. In a similar manner, the frequency of neutropenia significantly decreased from 2.3% to 0.5% to 0.7% in the second to fourth year treatment.[4] Although the risk of agranulocytosis decreases with time, some cases are reported after a number of years of continued therapy. The disorder is reversible in the vast majority of cases if Clozapine is withdrawn

promptly. The incidence of agranulocytosis after 1 year is similar to that associated with phenothiazines.[1] The incidence of agranulocytosis in general population is 0.0003% to 0.002% per year.[4]

Mechanism of blood dyscrasia:

The mechanism of Clozapine – induced agranulocytosis is not clear.[2] The target cells affected are the myeloid precursors, although the mature Neutrophils may also be targeted simultaneously. The reason why only approximately 1% of individuals who are treated with Clozapine are affected by agranulocytosis has not been elucidated. Evidence exists to implicate both the major histocompatibility complex antigens and heat shock protein variants in determining individual susceptibility. Susceptibility to Clozapine induced agranulocytosis is likely to reside at various levels including; bio activation of Clozapine, its detoxification and factors responsible for inducing cell death and tissue injury.[2]

Theoretically, Clozapine toxicity may be due to either the parent compound or one of its stable metabolites.[2] Clozapine and demethyl Clozapine are bio activated in vitro to chemically reactive nitrenium metabolites that cause polymorph nuclear leukocytes cytotoxicity at drug concentration that can be achieved in vivo.[5]

Munro et al[6] analysed cohort of Clozapine Patient Monitoring Service (CPMS) in 1999 and concluded that agranulocytosis associated with Clozapine is an idiosyncratic (type B) reaction and is not dose related. The mechanism of Clozapine induced agranulocytosis could be immune mediated or involve a toxic mechanism or even a combination of both.[3]

Risk factors for blood dyscrasia:

The risk for agranulocytosis in Asians is 2.4 times that in Caucasions. The risk of neutropenia is higher in African – Caribbean subjects[6], it has been suggested that lower normal ranges for white blood cell counts, known as benign ethnic neutropenia may account partially for this.[7] There is an age related increase in risk of 53% per decade with age on starting Clozapine. It means that adolescents have the lowest risk of agranulocytosis and the greatest likelihood of remaining on Clozapine. Higher Clozapine doses do not increase neutropenia or agranulocytosis.[6]

Haematological monitoring for other drugs:

There is a need to reconsider the value of routine haematological monitoring for other medications associated with blood dyscrasia[4] like phenothiazines, and carbamazepines. To the best of our knowledge, there have been two case reports of blood dyscrasia with Clozapine and risperidone who previously developed blood dyscrasia during Clozapine treatment.[8,9] It means that patients, who develop Clozapine induced blood dyscrasia, should have haematological monitoring regularly during treatment with other antipsychotics, even if they have not had any haematological adverse effects with that drug in the past. There is no literature on Clozapine induced neutropenia, it means that there is a possibility that exposure to Clozapine could sensitize the immune system, making it susceptible to other drugs to cause neutropenia.[9]

Rechallenge with Clozapine following blood dyscrasia:

Rechallenge with Clozapine is an off label process undertaken with the assistance of the CPMS but at the discretion and responsibility of the patient's psychiatrist. Dunk et al[3] investigated 53 patients who were rechallenged with Clozapine following blood dyscrasia during previous therapy and found that 33 (62%) did not experience a second episode of blood dyscrasia and were able to continue drug treatment although 20 patients who experienced second dyscrasia; it was more severe in 12 (60%) and occurred more quickly in 17 (85%) patients. In addition, in 65% of the cases in which patients developed a blood dyscrasia on rechallenge, the blood dyscrasia lasted longer after discontinuation of Clozapine following rechallenge than when Clozapine was first discontinued. This result is of considerable clinical relevance because it suggests that some patients with blood dyscrasia may unnecessarily be denied effective Clozapine treatment[10] because trials of other antipsychotics often prove ineffective. The risks of withholding treatment must be weighed against the risks of rechallenge. Lithium's co-administration with Clozapine has been suggested as a means of preventing neutropenia on Clozapine re-challenge but warrants more research. Another means of increasing WBC count in patients taking Clozapine is the use of granulocyte colony stimulating factor, which is believed to both induce Neutrophil maturation and enhance Neutrophil activity.[11]

CONCLUSION

Clozapine monitoring has proved to be highly successful in the early detection of blood dyscrasia and has prevented many fatalities.

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