

Clozapine and blood dyscrasia

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Summary Clozapine is an effective antipsychotic medication but is associated with agranulocytosis, neutropenia and leucopenia. The reintroduction of clozapine improved management of treatment-resistant schizophrenia, yet resulted in a paradoxical situation whereby the risk of blood dyscrasias is rigorously managed but other adverse effects (e.g. seizures, cardiovascular complications) are less well monitored. Monitoring of weight, lipids, plasma glucose and other metabolic parameters is recommended. There is also a need to reconsider routine haematological monitoring with other medications associated with blood dyscrasia (e.g. phenothiazines, carbamazepine). In particular, individuals who develop clozapine-induced blood dyscrasia may require haematological monitoring during treatment with other antipsychotics.

Declaration of interest None.

Clozapine was discovered in 1958 and, in 1971, became the first atypical antipsychotic medication introduced in clinical practice in Europe. In 1975, clozapine was withdrawn after blood dyscrasias were apparently linked with deaths in individuals receiving clozapine in Finland.¹ In 1988, a pivotal study suggested that clozapine was more effective than conventional antipsychotics in treatment-resistant schizophrenia² and in 1989 the medication was reintroduced with compulsory haematological monitoring. To start someone on clozapine in the UK or Ireland, the individual must be registered with an approved clozapine patient-monitoring service and have full blood counts performed weekly for the first 18 weeks, fortnightly until 52 weeks and monthly for the duration of treatment. More frequent monitoring is also possible, but the inconvenience and costs of additional phlebotomy requires careful cost–benefit analysis on an individual basis. Monitoring requirements are more stringent in the USA, where people are monitored weekly for the entire duration of treatment.³ In the event that someone develops leucopenia or neutropenia during therapy, further treatment with clozapine is broadly contraindicated.

PsycINFO and MD Consult were used to conduct the literature review.

Incidence of blood dyscrasia

Clozapine-induced suppression of granulocytes can induce three clinically distinct types of blood dyscrasia:^{4,5} mild leucopenia (white blood cells of less than $3.0 \times 10^9/l$ with satisfactory neutrophil count), which occurs in 0.19% of individuals; moderate neutropenia (neutrophil count below $1.5 \times 10^9/l$ but not lower than $0.5 \times 10^9/l$), which occurs in 1.5–2.9% of individuals and when clozapine is discontinued recovery is rapid (2–8 days); and the most severe

neutropenia with a neutrophil count below $0.5 \times 10^9/l$ (agranulocytosis), with an incidence of 0.78% (this type generally lasts for 14–21 days).^{6,7}

The risk of agranulocytosis is greatest in the first 18 weeks of treatment. The risk of all types of blood dyscrasia is significantly reduced after 1 year, with incidence of agranulocytosis falling to 0.07% in the second year.⁶ Overall, the risk of neutropenia decreases from 2.3% to 0.5% to 0.7% in the second to fourth years of treatment. Although risk of agranulocytosis decreases with time, some cases are reported after several years of continued therapy. The incidence of agranulocytosis after 1 year of clozapine is similar to that associated with phenothiazines² and it is reversible in the vast majority of cases, once clozapine is withdrawn promptly.⁷

There is evidence to suggest that the risk of agranulocytosis in Asian individuals is 2.4 times that in White people.⁸ Risk of neutropenia appears higher in African–Caribbean individuals⁶ and it has been suggested that lower normal ranges for white blood cell counts (benign ethnic neutropenia) may account for this, at least in part.⁹ There is an age-related increase in risk of 53% per decade, meaning that adolescents have the lowest risk of agranulocytosis and the greatest likelihood of remaining on clozapine.⁸ The risk of neutropenia or agranulocytosis is not, however, dose-related.

The precise mechanism of clozapine-induced agranulocytosis is not clear.³ The target cells affected are the myeloid precursors, although it appears that the mature neutrophils may also be targeted simultaneously. The reason why only approximately 1% of individuals treated with clozapine are affected by agranulocytosis is not known either, although major histocompatibility-complex antigens and heat-shock protein variants have been implicated in determining individual susceptibility. Theoretically, clozapine toxicity

may be as a result of either the parent compound or one of its stable metabolites. One possible mechanism relates to the fact that clozapine and demethylclozapine are both bioactivated *in vitro* to chemically reactive nitrenium metabolites that may be cytotoxic to polymorphonuclear leukocytes at a drug concentration that can be achieved *in vivo*.¹⁰ Overall, evidence suggests that agranulocytosis associated with clozapine is an idiosyncratic (type B) reaction, is not dose-related and may be immune-mediated or involve a toxic mechanism or both.⁷

Rechallenge with clozapine following blood dyscrasia

Rechallenge with clozapine is an 'off-label' process undertaken at the discretion of the psychiatrist. Although it is methodologically difficult to study this practice, Dunk *et al*⁷ studied data relating to 53 participants who were rechallenged with clozapine following blood dyscrasia, and found that 33 (62%) did not experience a second episode of blood dyscrasia. Twenty participants (38%) experienced a second episode of blood dyscrasia; this was more severe in 17 (85%) of these, and in 12 (60%) it lasted longer. Of these 20 participants, 5 (25%) received treatment with granulocyte-colony stimulating factor (aimed at inducing neutrophil maturation and enhancing neutrophil activity). There were no fatalities. This study had the limitations of including chiefly people who were 'rechallenged' following mild neutropenia or leucopenia, being retrospective in design, and including just 53 participants. Given the nature of the topic under study, however, these limitations were, in large part, inevitable. Moreover, one of the key principles of evidence-based medicine is the explicit, conscientious and judicious use of current best evidence in making decisions about patient care.¹¹ This means that decisions should be informed by the best available evidence; if that evidence is imperfect, decisions should still be informed by the evidence albeit with an awareness of the limitations of the evidence base.

Notwithstanding its limitations, then, the study by Dunk *et al*⁷ is of considerable clinical relevance because it suggests that some people with blood dyscrasia may unnecessarily be denied effective clozapine treatment, especially if trials of other antipsychotics prove unsuccessful.¹² The risks of withholding treatment must be weighed against the risks of rechallenge in each individual case. Risk-modifying strategies in certain individuals may include the use of granulocyte-colony stimulating factor to both induce neutrophil maturation and enhance neutrophil activity.¹³ Co-administration of lithium with clozapine has also been suggested as a means of preventing neutropenia on clozapine rechallenge but requires further research.^{13,14} The Maudsley guidelines recognise clozapine as the treatment of choice in refractory schizophrenia but at the same time it is also considered a toxic drug. However, the risk can be well managed by the approved clozapine-monitoring systems. The guidelines recommend that the individual's clinical circumstances should be considered. In particular, individuals developing dyscrasia in the earlier phase of treatment (first 18 weeks of treatment) that is severe and prolonged should be considered to be very high

risk if rechallenged with clozapine. The guidelines also suggest that lithium may be used to increase the neutrophil count but this will only be effective if agranulocytosis is not linked with clozapine-induced dyscrasia. Clozapine should be discontinued if the individual is prescribed any other medications that can suppress bone marrow activity. If the white blood count is in the normal range, clozapine can be commenced or rechallenged with close observation and monitoring.¹⁴ Whiskey & Taylor¹⁵ in 2007 suggested that neutropenia could arise because of various factors that might be unrelated to clozapine treatment. In such cases, clozapine may be restarted if non-clozapine causes of neutropenia are identified and treated. Where clozapine is clearly the cause of agranulocytosis, rechallenge should not be considered unless there are exceptional circumstances. In these cases, re-exposure to clozapine may rarely be attempted if the treatment facilities are close and can offer frequent monitoring.¹⁵

Clinical experience with blood dyscrasias associated with clozapine indicate a need to reconsider the potential value of routine haematological monitoring for other medications associated with blood dyscrasia, such as phenothiazines and carbamazepine.⁶ There have been case reports of blood dyscrasias associated with olanzapine and risperidone in individuals who previously developed blood dyscrasia during clozapine treatment.^{16,17} Such reports suggest that people who developed clozapine-induced blood dyscrasia may require haematological monitoring regularly during treatment with other antipsychotics, even if they have not yet had any haematological adverse effects with their new medication. It is possible that exposure to clozapine could sensitise the immune system in some fashion, making individuals susceptible to blood dyscrasias with other drug use in the future.¹⁷

Conclusion

Clozapine can substantially improve the quality of life of people with treatment-resistant schizophrenia by reducing symptoms, decreasing hospital admissions and supporting community living. The re-introduction of clozapine, with mandatory haematological monitoring, has had the welcome effect of making available an effective treatment for treatment-resistant schizophrenia, but has resulted in a paradoxical situation whereby adverse effects other than blood dyscrasia, such as seizures and cardiovascular complications, may be substantially less well managed. Monitoring of weight, lipids, plasma glucose and other selected metabolic parameters is recommended.¹⁴ In addition, clinical experience with blood dyscrasias associated with clozapine indicate a need to reconsider the potential value of routine haematological monitoring in people receiving other medications linked to blood dyscrasia, such as phenothiazines and carbamazepine. In particular, individuals who develop clozapine-induced blood dyscrasia may require haematological monitoring regularly during treatment with other antipsychotics.

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