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 In 1975, clozapine was withdrawn after blood dyscrasias were apparently linked with deaths in individuals receiving clozapine in Finland. In 1988, a pivotal study suggested that clozapine was more effective than conventional antipsychotics in treatment-resistant schizophrenia 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. 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. 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is similar to that associated with phenothiazines and it is reversible in the vast majority of cases, once clozapine is withdrawn promptly.

There is evidence to suggest that the risk of agranulocytosis in Asian individuals is 2.4 times that in White people 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. 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. The risk of neutropenia or agranulocytosis is not, however, dose-related.

The precise mechanism of clozapine-induced agranulocytosis is not clear. 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

Incidence of blood dyscrasia

Clozapine-induced suppression of granulocytes can induce three clinically distinct types of blood dyscrasia: mild leucopenia (white blood cells of less than 3.0 × 10⁹/l), moderate neutropenia (neutrophil count below 1.5 × 10⁹/l but not lower than 0.5 × 10⁹/l), and severe neutropenia with a neutrophil count below 0.5 × 10⁹/l (agranulocytosis), with an incidence of 0.78% (this type generally lasts for 14–21 days). 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. 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 phenothiazines and it is reversible in the vast majority of cases, once clozapine is withdrawn promptly.

There is evidence to suggest that the risk of agranulocytosis in Asian individuals is 2.4 times that in White people. Risk of neutropenia appears higher in African–Caribbean individuals 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. 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. The risk of neutropenia or agranulocytosis is not, however, dose-related.
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. 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 al7 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 al7 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 been suggested as a means of preventing neutropenia including chiefly people who were ‘rechallenged’ following 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 for other medications associated with blood dyscrasia, such as phenothiazines and carbamazepine.6

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