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Neutropenia and Agranulocytosis in Patients Receiving Clozapine in the UK and Ireland

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Background. Clozapine can cause reversible agranulocytosis and neutropenia. This study documents the occurrence of blood dyscrasias and identifies predisposing risk factors.

Method. An analysis was made of the haematological, demographic, and dosage data from a central database on 6316 patients receiving clozapine over four and a half years in the UK and Ireland.

Results. During the study period, 2.9% of the patients developed neutropenia and 0.8% developed agranulocytosis. The peak incidence of both disorders was in the first 6–18 weeks of treatment. Fatal agranulocytosis occurred in 0.03% of patients. After the first year of treatment, the incidence of agranulocytosis significantly decreased to the order noted with some phenothiazines.

Conclusions. The use of a patient monitoring service kept the haematological risks associated with using clozapine within acceptable limits, particularly in view of the benefits of this medication in treatment-resistant schizophrenia.

Clozapine is licensed in the UK for use in people with schizophrenia who are unresponsive to two or more antipsychotics or who are intolerant of their neurological side-effects. It belongs to the dibenzodiazepine class of drugs and has a complex pharmacological mechanism of action (Bruhwyler *et al*, 1990). The multiple receptor types involved may be responsible for both the more favourable extrapyramidal side-effect profile (Lieberman, 1989) and the superior efficacy when compared with conventional neuroleptics (Kane *et al*, 1988, 1994). Clozapine is also unusual in being one of the few medicines that has been relicensed for clinical use after being withdrawn. Although not licensed at the time in the UK, reports of agranulocytosis in Finland in 1975 gave cause for concern. Sixteen patients out of 2260 exposed there (0.7%) developed agranulocytosis and 8 (50%) of these 16 patients subsequently died from secondary infections (details available from author). As a result, clozapine was voluntarily withdrawn from use.

Following pressure from psychiatrists to reintroduce clozapine, trials in patients with treatment-resistant schizophrenia, together with haematological monitoring, were devised, which showed significant improvement in 30% of patients after six weeks (Kane *et al*, 1988). Subsequent studies showed improvement in 61% of patients, if treatment was continued for up to one year (Meltzer *et al*, 1989; Meltzer, 1992). These data, together with a proposal for a nationally coordinated mandatory haematological monitoring service for all patients, enabled clozapine (Clozaril®) to be given a product licence in the UK in January 1990, and in Ireland in August 1993. All patients treated must register with the Clozaril® Patient Monitoring Service (CPMS), ensuring that no patient can receive the drug without a recent satisfactory haematological result. It also helps guarantee that clozapine is stopped immediately if a patient develops a 'red result' (see below) and prevents such patients from receiving clozapine again. The aim of this review was to use the central patient database of the monitoring service to document the incidence of agranulocytosis and neutropenia and to identify any predisposing risk factors.

Method

The CPMS and database

All patients who receive clozapine in the UK and Ireland have been registered on a single database, created to aid patient management by containing a centralised record of all the blood results collected over time. It was, however, not designed for

research purposes. Patients must have a satisfactory (green) pre-treatment blood count before starting clozapine. The monitoring service analyses blood samples to detect falling counts of white blood cells (WBCs), neutrophils and platelets. However, the full range of haematological parameters is also measured and communicated to the patient's psychiatrist. For ease of interpretation, the results are divided into three colour bands: green, amber, and red. These are defined as: *green*, WBC $>3.5\times10^9$/l and neutrophils $>2.0\times10^9$/l; *amber*, WBC 3.0–3.5 $\times10^9$/l and/or neutrophils 1.5–2.0 $\times10^9$/l; *red*, WBC $<3.0\times10^9$/l and/or neutrophils $<1.5\times10^9$/l and/or platelets $<50\times10^9$/l.

For the purpose of this study and for safety reasons, neutropenia is defined as a neutrophil count of 0.5–1.5 $\times10^9$/l, and agranulocytosis as a neutrophil count $<0.5\times10^9$/l; leucopenia as a WBC $<3\times10^9$/l with a satisfactory neutrophil count (i.e. $>1.5\times10^9$/l); and thrombocytopenia as a platelet count $<50\times10^9$/l. In the event of a 'red result', the hospital or other blood sampling venue is contacted immediately to ask for a confirmatory blood sample. The patient's psychiatrist, hospital ward staff and hospital pharmacist are also informed that the patient must stop clozapine immediately and advice is given on the management of neutropenia and agranulocytosis.

In addition to haematological data, the following demographic information is also collected from the psychiatrist at the time of patient registration: date of birth, gender, ethnic origin and daily dose of clozapine. The recorded daily dose is that entered on the blood sample request form by the psychiatrist and may not always accurately reflect the actual amount prescribed, particularly during periods of dose decrease or escalation. Information on concomitant medication and reasons for withdrawal were not routinely collected, as the database was designed as a practical tool to aid the management of the blood monitoring results.

This analysis consists of data collected on the 6316 patients registered in the UK and Ireland between 7 January 1990 and 3 July 1994.

Data management

The CPMS data are collected from two sources:

(a) demographic data and occasional local blood count results from the hospital;
(b) routine haematological laboratory data (electronically transferred into the database) from central laboratories.

For the purposes of analysis, the data were transferred from the PC database to SAS datasets (SAS 6.08) on a micro VAX platform, using a VMS system environment. After data validation, a further classification of the patients was made to enable sub-analyses to be performed.

The time to occurrence of agranulocytosis or neutropenia was calculated as that from the date of the first blood test result to the date when clozapine was stopped. However, this may not exactly match the actual duration of treatment, as patients usually start therapy two to three days after the first blood sample has been taken.

Statistical methods

The baseline characteristics and summary statistics were analysed using *t*-tests and χ^2 tests. All demographic results were summarised as means or percentages and, if applicable, 95% confidence intervals were given. Significance tests were set at an alpha level of 5%; no modification of the *P* values was applied, as this was a retrospective investigational analysis.

Results

In the four and a half years covered by the review, 6316 patients were registered and received at least one blood test. While 2858 (45.2%) of these received clozapine for at least one year and 1625 (25.7%) for at least two years, 338 (5.4%) withdrew before starting, or within a week of commencing the medication. Fifty-four per cent of the patients were currently on clozapine.

Pre-treatment results and baseline demographic data

One in 260 patients (0.4%) had a pre-treatment 'red result'. Eighteen of these 24 cases were neutropenias, particularly in patients of African and Afro-Caribbean origin, who were significantly more likely than other ethnic groups to have pre-treatment neutropenia (2.8% *v.* 02%, $P<0.001$).

The mean age of the patient cohort was 37 years (range 9–91 years). The percentage of patients withdrawing from therapy increased with age, particularly over 50 years (Table 2).

Two-thirds of the patients were male (4178 (66.1%) male, 2138 (33.9%) female). Females were significantly more likely to withdraw from treatment (49.3% *v.* 43.6% for males, $P<0.01$).

Of the patients who withdrew from treatment, the majority, 2603 (43.3%), did so for non-haematological reasons such as lack of efficacy,

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poor compliance, or side-effects. However, data were not routinely collected on the reasons for withdrawal. Only 4.3% of patients had to stop clozapine for haematological reasons. There were 182 cases of neutropenia, 48 of agranulocytosis, 38 of leucopenia, and 6 of thrombocytopenia.

The usual recommended daily dose is 150–450 mg/day, and the mean doses for patients were within this range. Only 5.2% of patients received more than the maximum recommended dose of 900 mg/day on one occasion. The mean (s.e.m.) recorded average dose was 313 mg (2.9) mg, while the mean (s.e.m.) last recorded dose was 344 mg (2.6) mg (range 12–1500 mg/day). The mean (s.e.m.) maximum recorded dose was 450 (3.1) mg. Sub-analysis showed that patients taking less than 200 mg/day were significantly more likely to withdraw from therapy ($P<0.0001$).

Of the patients, 89% were Caucasian, 5.0% African and Afro-Caribbean, 3.6% Asian (Indian subcontinent), 0.4% Oriental (China, Japan and South-east Asia) and 1.9% were of mixed race. Patients of African or Afro-Caribbean origin were significantly more likely to withdraw from treatment than other ethnic groups. Although the majority of withdrawals were for non-haematological reasons, African and Afro-Caribbean patients had significantly lower mean pre-treatment WBC (6.33×10^9/l, *v.* 7.57×10^9/l), neutrophil counts (3.67×10^9/l *v.* 4.98×10^9/l) and platelet counts (257×10^9/l *v.* 265.4×10^9/l), than all other racial groups ($P<0.001$, $P=0.0001$ and $P<0.03$, respectively). Figures relating to other ethnic groups were too small to derive any statistically meaningful conclusions. However, reassuringly, Africans and Afro-Caribbeans were not at increased risk of the more serious condition of agranulocytosis.

Agranulocytosis and neutropenia

A clearly defined period of increased risk for developing neutropenia and agranulocytosis was seen in the first 6–18 weeks of therapy (Fig. 1), with 1.2% and 0.7% respectively affected within these 12 weeks. Of the cases of agranulocytosis, 89.6% (43/48) occurred within the first 18 weeks of treatment; this risk then declined during the remainder of the first treatment year. Table 1 shows that the incidence of agranulocytosis in the first year decreased by a factor of 10 from 0.7% to 0.07%, in the second year of treatment ($P<0.05$). Although there were no cases of agranulocytosis in the third treatment year, the upper limit of the 95% confidence interval of 0.22 suggests the risk is no greater in the third year of treatment.

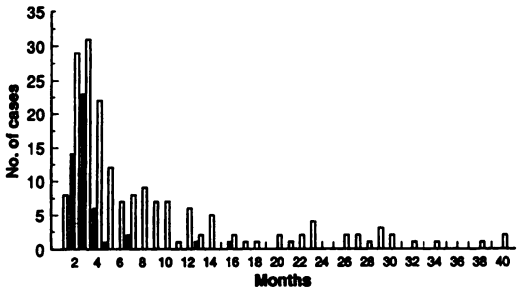

Fig. 1 Frequency of agranulocytosis (■) and neutropenia (□).

Table 1
The risk of clozapine-associated agranulocytosis and neutropenia over time

	First year	Second year	Third year	Fourth year
No. of patients remaining on clozapine	6316	2858	1625	661
Incidence of agranulocytosis				
n	46	2	0	0
%	0.7	0.07	0	0
95% CI	0.53%–0.97%	0%–0.25%	0%–0.22%	0%–0.56%
	1 in 137 patients	1 in 1429 patients	–	–
Incidence of fatal agranulocytosis				
n	2	0	0	0
%	0.03%	0%	0%	0%
95% CI	0.006%–0.12%	0%–0.13%	0%–0.22%	0%–0.056%
	1 in 3158 patients	–	–	–
Incidence of neutropenia				
n	147	20	12	3
%	2.3	0.7	0.7	0.5
95% CI	1.97%–2.73%	0.41%–1.04%	0.39%–1.3%	0.09%–1.3%
	1 in 42 patients	1 in 143 patients	1 in 135 patients	1 in 220 patients
Incidence of fatal neutropenia				
n	0	0	0	0
%	0	0	0	0
95% CI	0%–0.06%	0%–0.13%	0%–0.23%	0%–0.56%

The earliest time to onset of agranulocytosis was five weeks and the last case occurred at 16 months. Only two patients developed agranulocytosis after the first year of treatment and then only just after (Fig. 1). In the first case, agranulocytosis occurred 11 weeks after stopping clozapine, while the patient was taking other neuroleptics, and there is considerable doubt as to whether this represented a true clozapine-associated agranulocytosis, given the exceptional temporal relationship and the absence of literature reports of agranulocytosis occurring

with other medications at a similar time after discontinuation.

Similarly, half of the cases of neutropenia occurred in the first 18 weeks and the incidence significantly decreased, from 2.3% in the first year of treatment to between 0.5% and 0.7% in the second to fourth years ($P<0.005$). The cumulative incidence was found to be 2.9% for neutropenia and 0.8% for agranulocytosis over the four and a half years covered by the study.

Agranulocytosis was reversible in all but two fatal cases, with a median time to neutrophil recovery of 10.5 days (range 0–32 days). The two fatalities were due to complications of agranulocytosis (4.2% of agranulocytosis cases), both of which occurred within the first 12 weeks of treatment, and were a result of at least one week of uncontrolled sepsis, despite antibiotics. Both the patients were over 50 years of age and were taking moderate doses of clozapine (200 mg and 400 mg daily), reinforcing the view that agranulocytosis is not dose related. There were no fatalities due to complications of neutropenia (Table 1).

Predisposing factors for the development of agranulocytosis or neutropenia

Age

The incidence of agranulocytosis increased marginally with increasing age. The mean age of patients developing agranulocytosis was 42 years, compared with 37 years for the entire patient cohort ($P<0.05$). In contrast, there was no increased risk of neutropenia with age (Table 2).

Table 2
Relationship between the development of neutropenia or agranulocytosis and age

	Total no. of patients	No. (%) of patients who developed neutropenia	No. (%) of patients who developed agranulocytosis
<20 years	244	14 (5.7)	0 (0.0)
21–30 years	2066	74 (3.6)	8 (0.4)
31–40 years	1911	46 (2.4)	14 (0.7)
41–50 years	1203	27 (2.2)	16 (1.3)
51–60 years	555	14 (2.5)	9 (1.6)
61–70 years	224	7 (3.1)	1 (0.4)
>70 years	95	0 (0.0)	0 (0.0)
Not known	18	1	0
Mean (s.d.) age	37 (12)	34* (12)	42** (10)
Range	9–91	17–67	21–63

*Total patients *v.* those with neutropenia, $P=0.09$.
**Total patients *v.* those with agranulocytosis, $P<0.05$.

Ethnic origin

No racial group was more susceptible to agranulocytosis, but Africans and Afro-Caribbeans appeared to be at increased risk of developing neutropenia (5.3%) compared with the whole patient population (2.6%) ($P=0.02$).

Dose

No relationship was found between mean average recorded daily dose, mean maximum recorded daily dose, or mean last recorded daily dose and the risk of developing agranulocytosis or neutropenia. The lack of correlation between either neutropenia or agranulocytosis and last daily dose is well illustrated by the symmetrical distribution about the mean (Fig. 2). Indeed, cases of both agranulocytosis and neutropenia occurred at maximum daily doses below 100 mg and above 700 mg.

Gender

Of the cases of agranulocytosis, 45.8% were in females, and although this was more than expected given that only 33.9% of the patients treated were female, the difference was not significant ($P=0.09$). Similarly, there was no increased susceptibility for females to develop neutropenia (32.5% of the cases involved females).

Discussion

Compliance with monitoring

Of those registered, 54% were receiving clozapine at the time of the review. Given the expected efficacy rates of up to 60% (Meltzer, 1992), the results indicate good compliance with the blood

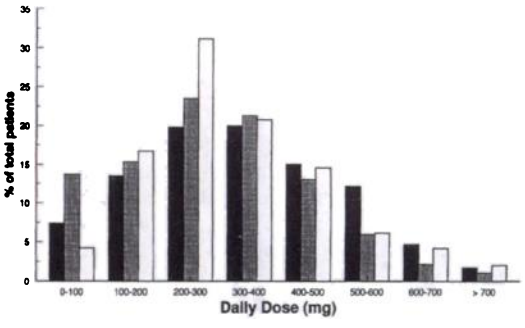

Fig. 2 Relationship between last daily dose (mg) and agranulocytosis or neutropenia (■, 3441 patients currently on clozapine; ■, 182 patients developing neutropenia; □, 48 patients developing agranulocytosis).

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testing required for this oral medication. While compliance with clozapine was not directly measured, 45.3% and 25.7% of patients were still on treatment after two and three years, respectively (Table 1).

More patients withdrew for non-haematological reasons at lower total daily doses (<200 mg/day); such patients were more likely to be in the early stages of treatment, when side-effects and problems with compliance due to lack of efficacy at this dose may arise.

Agranulocytosis, neutropenia and predisposing risk factors

The cumulative incidence of agranulocytosis over the study period (four and a half years) was found to be 0.8%, a figure similar to the 0.8% incidence over 15 months in the USA (Alvir *et al*, 1993). The frequency of agranulocytosis and neutropenia was highest in the first 6–18 weeks of treatment; the incidence of both was significantly less after the first year. In the second year of treatment, the incidence of agranulocytosis decreased by a factor of 10, from 0.7% to 0.07% ($P<0.05$) (Table 1) and although there were no cases of agranulocytosis in the third treatment year, it is possible to be 95% confident that the risk is as low during the third year of treatment. Such figures are higher than the estimated background incidence of agranulocytosis in the general population, of 0.0003% to 0.002% per year (Bõttiger & Bõttiger, 1981; Kaufman *et al*, 1991). In a similar manner, the frequency of neutropenia significantly decreased, from 2.3% to 0.5% to 0.7% ($P<0.005$) in the second to fourth year of treatment.

The only risk factor identified for the development of agranulocytosis was increasing age, and in particular patients over 50 years; however, this effect was only marginal and does not require greater monitoring frequencies with increasing age. African and Afro-Caribbean patients were significantly more likely than the rest of the cohort to develop both pre-treatment neutropenia and neutropenia during treatment. Reassuringly, they were not at increased risk of the more serious condition of agranulocytosis. This racial group is more likely to have lower baseline counts and may be susceptible to benign ethnic neutropenia (Reed & Diehl, 1991). Several of the mild cases of neutropenia in this group may therefore represent transient fluctuations around low baseline counts, rather than true clozapine-related neutropenia. Increasing daily dose was not found to be a risk factor for either neutropenia or agranulocytosis.

Mortality from agranulocytosis

Agranulocytosis was reversible in all but two cases, with a median time for neutrophil recovery of 10.5 days (range 0–32 days). The low mortality rate from agranulocytosis (4.2% of the cases of agranulocytosis) supports the continued existence of the CPMS as a mechanism to aid early withdrawal of clozapine in the event of a neutropenia, rather than waiting until the patient develops sepsis, when the prognosis would clearly be worse. This mortality rate compares favourably both with the pre-monitoring statistic of 62% fatality in Scandinavia in the 1970s (Hippius, 1989) and the mortality seen with agranulocytosis associated with other drugs that are not subject to mandatory haematological monitoring (Medicines Control Agency, 1993).

Drug-induced agranulocytosis and neutropenia

Accurate estimation of the incidence of agranulocytosis and neutropenia has been obtained for only a few drugs. When weekly blood tests were carried out in 6300 patients between the second and tenth weeks of treatment with phenothiazines, the incidence of agranulocytosis was found to be 0.08% and mild transient neutropenias occurred in 8.9% (Pisciotta, 1978; Mandel & Gross, 1986). Although such studies are not directly comparable, the incidence of agranulocytosis (0.07%) and neutropenia (0.7%) in the second year of clozapine therapy were of the same order of magnitude as those found with the phenothiazines. Given the higher mortality from agranulocytosis in drugs without mandatory blood monitoring (Medicines Control Agency, 1993) there is a need to reconsider the value of routine haematological monitoring for other medications associated with agranulocytosis.

Conclusions

Haematological monitoring using the CPMS has been shown to be 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.

This survey showed that the risk of agranulocytosis and neutropenia significantly decreases after the first year of treatment. Thereafter, the risk of agranulocytosis was similar to that seen with some phenothiazines not subject to regular blood testing. The risks of developing reversible haematological dyscrasias while on clozapine are well defined and are reassuringly low after the first year of therapy.

Clinical implications

- Mandatory haematological monitoring via the CPMS has resulted in significant reductions in the mortality of clozapine-associated agranulocytosis and neutropenia.
- After clozapine has been taken for one year, the incidence of agranulocytosis with monitoring decreases to the order of that seen with phenothiazines.
- Neutropenia and agranulocytosis are not dose related side-effects.

Limitations

- Although adherence to the blood monitoring schedule is an indicator of compliance with clozapine this cannot be verified directly.
- No data are kept on the influence of concomitant medications.
- The dosage and demographic data have not been verified at source.

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