

Continuing Clozapine Therapy Despite Morning Pseudoneutropenia

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INTRODUCTION

Clozapine is an atypical antipsychotic agent with demonstrated effectiveness for patients with psychoses that are refractory to treatment with other antipsychotic drugs.^{1,2} Clozapine is not recommended as first-line therapy for schizophrenia because of its side effects, which include agranulocytosis (0.5% to 2.0% of patients receiving the drug), seizures, weight gain, glucose and lipid disturbances, sedation, sialorrhea, hypotension, and tachycardia.^{2,3} A trial of clozapine is recommended if there is suboptimal response to adequate trials of antipsychotics from 2 different classes and for patients who cannot tolerate the side effects of other antipsychotic agents.^{1,2}

Clozapine may induce 2 distinct types of neutropenia. The milder form occurs more frequently (in 1.5% to 2% of patients receiving the drug).^{3,4} The exact mechanism of this form of neutropenia is unknown, but it is thought to be due to the premature destruction of neutrophils in the blood or spleen.^{3,4} Recovery from this type occurs rapidly, within 3 to 7 days after drug discontinuation, since myeloid maturation in the bone marrow is unaffected. The second type is more severe, manifesting as agranulocytosis, but occurs less frequently (0.8% cumulative incidence at 3 years of treatment). With this form, there is selective depletion of the granulocyte precursors in the bone marrow, and recovery may take from 14 to 22 days.^{4,5} These patients are at risk of neutropenic sepsis. The risks of morbidity and mortality associated with agranulocytosis necessitate a strict hematologic monitoring program for patients receiving clozapine. Each of the 3 Canadian manufacturers of this drug coordinates a national registry and monitoring program for patients. The risk of agranulocytosis is greatest during the first 6 months of treatment; therefore, weekly assessment of leukocyte count and absolute neutrophil count is essential to ensure that the values

remain above $3.5 \times 10^9/L$ and $2.0 \times 10^9/L$, respectively. After 6 months of therapy, the frequency of monitoring is reduced to every 2 weeks.²

The 3 clozapine monitoring programs generate alerts that are identified by colour: green, yellow, and red. A patient is deemed to be in the green zone, and blood tests are obtained weekly, if the leukocyte and absolute neutrophil counts are above the stated minimum values ($3.5 \times 10^9/L$ and $2.0 \times 10^9/L$, respectively). A patient is deemed to be in the yellow zone if the leukocyte count is between $2.0 \times 10^9/L$ and $3.5 \times 10^9/L$ or the absolute neutrophil count is between $1.5 \times 10^9/L$ and $2.0 \times 10^9/L$, or if a significant decline in either count (i.e., a single decrease or sum of decreases in leukocyte count of at least $3.0 \times 10^9/L$ or in absolute neutrophil count of at least $1.5 \times 10^9/L$) occurs over a 4-week period; for these patients, leukocyte and absolute neutrophil counts must be determined twice weekly until the counts return to green zone values. If neutropenia occurs (defined as leukocyte count below $2.0 \times 10^9/L$ or absolute neutrophil count below $1.5 \times 10^9/L$), the patient is deemed to be in the red zone, and clozapine is discontinued with no opportunity for reinitiation.

“Morning pseudoneutropenia”, or diurnal variation in absolute neutrophil count that necessitates afternoon monitoring of both leukocyte and neutrophil counts, has been reported during clozapine therapy.^{1,6-10} We describe 2 patients for whom multiple antipsychotic trials had failed and clozapine therapy was initiated. In both patients, hematologic monitoring revealed a pattern of diurnal variation in the absolute neutrophil count. Without close monitoring to detect these trends, the patients might have been classified as being in the yellow zone or perhaps the red zone, which would have led to frequent blood sampling or even discontinuation of therapy. By identifying the diurnal variation, we were able to continue therapy for these treatment-refractory patients.



CASE 1

A 23-year-old white man with chronic treatment-refractory schizophrenia was admitted to the acute care mental health unit. He was experiencing auditory hallucinations, somatic delusions, thought form disorder, and prominent negative symptoms. He had previously undergone trials of therapy with haloperidol, risperidone, olanzapine, and quetiapine, without adequate resolution of symptoms. The patient experienced tardive dyskinesia while taking haloperidol. A hematologist had previously diagnosed idiopathic neutropenia in this patient. In light of his pre-existing neutropenia, and contrary to usual clinical practice, therapy with aripiprazole (through the Special Access Programme of Health Canada) was initiated in an attempt to stabilize the patient's condition without exposing him to clozapine. The patient was receiving aripiprazole 15 mg daily and sertraline 50 mg daily on admission to hospital, without adequate control of his symptoms. A review of the patient's absolute neutrophil counts before initiation of clozapine revealed diurnal variation, with lower values in the morning than in the afternoon (Table 1).

Clozapine therapy was initiated at 12.5 mg orally twice daily and was subsequently increased to 25 mg orally twice daily. On the third day of therapy, the patient's morning absolute neutrophil count was in the red zone ($0.8 \times 10^9/L$). The count was repeated that afternoon to confirm the result, at which time the value was $2.2 \times 10^9/L$ (Table 1). Clozapine therapy was held for 3 days and was then reinitiated according to the guidance of the national monitoring program, since the patient's afternoon absolute neutrophil count was in the green zone (Table 1). Clozapine was then titrated to a total daily dose of 150 mg. Further dose titration was limited by hypotension and sedation. The patient also received concomitant oral therapy with citalopram 20 mg daily and lorazepam 1 mg daily. Because the patient exhibited no flu-like symptoms or fever, it was decided that afternoon monitoring of absolute neutrophil count would continue; it was therefore possible to continue clozapine therapy without any adverse hematologic sequelae. The afternoon values stayed in the green zone for the remainder of the patient's hospital stay.

During outpatient follow-up, a few afternoon values dropped into the yellow zone. In consultation with the hematologist and staff of the monitoring program, lower individualized ranges were developed for this patient, to allow ongoing monitoring without persistent presence in the yellow zone, which would have necessitated twice-weekly monitoring of absolute neutrophil counts.

Fourteen months later, his condition remained stable on clozapine therapy, and his target symptoms were reasonably well controlled.

CASE 2

A 24-year-old white woman with schizophrenia was admitted to the acute care mental health unit with homicidal thoughts and auditory hallucinations secondary to medication nonadherence. She had undergone previous therapeutic trials with risperidone, olanzapine, and loxapine with poor response and intolerance to adverse effects. She was not taking any regularly scheduled medications before admission. A brief trial of quetiapine therapy produced no remittance of symptoms. Clozapine treatment was initiated at a dose of 12.5 mg daily and was titrated to a dose of 275 mg/day over a period of 10 weeks. The pretreatment absolute neutrophil count was $2.2 \times 10^9/L$. During titration of the clozapine dose, the patient experienced significant orthostatic hypotension, which necessitated a conservative titration schedule. Inadvertently, a blood test was not performed until the second week of clozapine therapy; after this time, regular hematologic monitoring was performed (Table 2). The patient's morning absolute neutrophil counts trended downward to the lower limit of the green zone, and she received a yellow zone alert as a result of the sum of decreases in this count over a 4-week period. After 15 weeks of therapy, the morning absolute neutrophil count was $1.8 \times 10^9/L$ (in the yellow zone); on repeat testing during afternoon of the same day, the result was slightly higher, at $2.3 \times 10^9/L$ (in the green zone). Since the patient had no flu-like symptoms or fever, it was decided that monitoring of the absolute neutrophil count would be continued in the afternoon, and clozapine therapy was continued without any adverse hematologic sequelae. Eleven months later, the patient remained on clozapine therapy 275 mg daily; her symptoms were under control, and she was seeking employment.

DISCUSSION

Clozapine is an effective atypical antipsychotic agent that plays a key role in therapy for patients with psychoses that are resistant to treatment with other antipsychotic drugs. However, agranulocytosis is a treatment-limiting adverse effect of clozapine therapy. The exact mechanism of clozapine-induced agranulocytosis remains unclear, although an immune-mediated mechanism has been proposed.^{5,11} Advanced age and female sex have been identified as risk factors for the

Table 1. Absolute Neutrophil Counts for Patient 1

Date*	Time of blood sampling		Zonet; Absolute Neutrophil Count		
	Morning	Afternoon	Green	Yellow	Red
T – 455 days	0723			1.6 x 10 ⁹ /L	
T – 449 days		1306	3.3 x 10 ⁹ /L		
T – 365 days	0717			1.8 x 10 ⁹ /L	
T – 40 days	0732		2.3 x 10 ⁹ /L		
T – 8 days		1520	3.4 x 10 ⁹ /L		
T – 4 days		1450	2.5 x 10 ⁹ /L		
T – 1 day		1215	2.1 x 10 ⁹ /L		
T + 2 days	0744				0.8 x 10 ⁹ /L
T + 2 days		1320	2.2 x 10 ⁹ /L		
T + 3 days	0736				1.3 x 10 ⁹ /L
T + 4 days	0715			1.7 x 10 ⁹ /L	
T + 4 days		1330	2.5 x 10 ⁹ /L		
T + 5 days		1345	2.8 x 10 ⁹ /L		
T + 8 days		1700	2.9 x 10 ⁹ /L		
T + 11 days		1341	2.2 x 10 ⁹ /L		
T + 14 days		1646	3.4 x 10 ⁹ /L		
T + 19 days		1405	2.9 x 10 ⁹ /L		
T + 24 days		1405	3.1 x 10 ⁹ /L		
T + 30 days		1355	2.5 x 10 ⁹ /L		
T + 37 days		1540	2.7 x 10 ⁹ /L		
T + 93 days‡		1625	2.7 x 10 ⁹ /L		
T + 104 days‡		1648		1.9 x 10 ⁹ /L	
T + 126 days‡		1810		2.0 x 10 ⁹ /L	
T + 137 days‡		1601		1.2 x 10 ⁹ /L§	
T + 138 days‡		1630	2.7 x 10 ⁹ /L		
T + 155 days‡		1600	3.0 x 10 ⁹ /L		

*T = date of clozapine initiation (marked by solid black line within table).

†Green zone means absolute neutrophil count > 2.0 x 10⁹/L; yellow zone means absolute neutrophil count between 1.5 x 10⁹/L and 2.0 x 10⁹/L or significant decline in absolute neutrophil count (i.e., a single decrease or sum of decreases of at least 1.5 x 10⁹/L over a 4-week period); red zone means absolute neutrophil count below 1.5 x 10⁹/L.

‡Outpatient blood testing.

§Shifted zones were defined at T + 135 days in conjunction with hematologists for the manufacturer's clozapine monitoring program and a local hematologist: green zone means leukocyte count > 3.5 x 10⁹/L and absolute neutrophil count > 1.7 x 10⁹/L; yellow zone means leukocyte count between 2.0 x 10⁹/L and 3.5 x 10⁹/L and absolute neutrophil count between 1.0 x 10⁹/L and 1.7 x 10⁹/L; red zone means leukocyte count < 2.0 x 10⁹/L and absolute neutrophil count < 1.0 x 10⁹/L.

development of clozapine-induced agranulocytosis.³ We have reported here the occurrence of “morning pseudoneutropenia” and diurnal variation in absolute neutrophil counts in 2 patients undergoing treatment with clozapine and the successful continuation of clozapine therapy with afternoon (rather than morning) monitoring of absolute neutrophil count.

Four cases of morning pseudoneutropenia have been reported previously (with some duplication between reports).^{1,6-10} In 3 of these cases,^{6,7,9} the neutropenia developed gradually after 5 to 10 weeks of clozapine therapy, similar to the onset of neutropenia in the second case reported here. In the other previously published case,^{1,10} diurnal variation of neutrophils occurred during 14 weeks of risperidone

therapy; the circadian variation of absolute neutrophil count that persisted during the initial 3 weeks of subsequent clozapine therapy may have been induced by the risperidone, given that a baseline count 15 months earlier had not revealed any abnormalities. In all of these previously reported cases, prior antipsychotic trials (3 trials for each of the 4 patients) had failed, indicating the refractory nature of their disease. These patients were similar to the patients described here. In the previously reported cases, as in the current ones, recognition of the transient nature of the neutropenia and monitoring of afternoon (rather than morning) blood counts allowed continuation of clozapine therapy with positive clinical outcomes and no adverse hematologic effects.



Table 2. Absolute Neutrophil Counts for Patient 2

Date*	Time of Blood Sampling		Zonet; Absolute Neutrophil Count		
	Morning	Afternoon	Green	Yellow	Red
T – 3 days	0700		2.2 x 10 ⁹ /L		
T + 13 days		1636	6.2 x 10 ⁹ /L		
T + 17 days		1915	6.8 x 10 ⁹ /L		
T + 20 days	0735		4.0 x 10 ⁹ /L		
T + 26 days	0719		2.8 x 10 ⁹ /L		
T + 33 days	0727		2.7 x 10 ⁹ /L		
T + 40 days	0720		2.2 x 10 ⁹ /L		
T + 47 days	0732		2.2 x 10 ⁹ /L		
T + 53 days	0722			2.1 x 10 ⁹ /L‡	
T + 60 days	0741			2.1 x 10 ⁹ /L‡	
T + 63 days		1400	4.5 x 10 ⁹ /L		
T + 68 days		1430	5.3 x 10 ⁹ /L		
T + 75 days		1405	3.8 x 10 ⁹ /L		
T + 82 days	0845		3.0 x 10 ⁹ /L		
T + 89 days	0752		2.2 x 10 ⁹ /L§		
T + 96 days	0740		2.3 x 10 ⁹ /L§		
T + 103 days	0719			1.8 x 10 ⁹ /L	
T + 103 days		1520	2.3 x 10 ⁹ /L		
T + 110 days		1350	3.7 x 10 ⁹ /L		

*T = date of clozapine initiation (marked by solid black line within table).

†Green zone means absolute neutrophil count > 2.0 x 10⁹/L; yellow zone means absolute neutrophil count between 1.5 x 10⁹/L and 2.0 x 10⁹/L or significant decline in absolute neutrophil count (i.e., a single decrease or sum of decreases of at least 1.5 x 10⁹/L over a 4-week period); red zone means absolute neutrophil count below 1.5 x 10⁹/L.

‡Classified as “yellow” because of the sum of declines in the previous 4 weeks.

§Could have been classified as “yellow” because of sum of declines in previous 4 weeks, but no notification was received by the monitoring program.

In another report, clozapine therapy was continued for 5 patients despite red zone alerts.¹² During over 600 days of follow-up for each patient, 3 of these 5 patients experienced chronic oscillation of neutrophil counts within or just above the yellow zone, whereas the other 2 patients had no further episodes of neutropenia.

Diurnal variation in circulating neutrophil counts has been demonstrated in healthy subjects.¹³ Sequential blood samples from 12 healthy individuals revealed diurnal changes in concentrations of plasma cortisol and granulocyte colony-stimulating factor and in neutrophil counts. In particular, plasma granulocyte colony-stimulating factor increased by about 15% during the period from morning to early afternoon (0800 to 1400), and neutrophil count increased by 17% over the same period. In addition, transient neutropenia was identified in 15 (22%) of 68 patients receiving clozapine therapy for the first time, as recorded in a national Austrian database.¹⁴ It has been hypothesized that transient neutropenia may be amplified by clozapine therapy and that patients may exhibit successful compensatory mechanisms, such as the production of granulocyte

colony-stimulating factor, which can stimulate granulopoiesis to overcome the transient mild neutropenia.¹⁵

Various strategies have been attempted for continuation of clozapine therapy despite the development of clozapine-induced neutropenia. Murry and Laurent¹⁶ reported use of a hydrocortisone stimulation test to distinguish between benign transient neutropenia and underlying malignant neutropenia in 3 patients receiving clozapine; a bone marrow response, with increased circulating neutrophil counts, was demonstrated following administration of hydrocortisone. Adjunctive therapy with lithium and granulocyte-colony stimulating factor has been used to promote leukocytosis in patients with clozapine-induced neutropenia, to allow continuation of clozapine therapy.^{17,18}

In certain patient populations, “benign ethnic neutropenia” has been described; therefore, provisional green, yellow, and red neutrophil ranges, with lower values than those described above, are used by monitoring programs in the United Kingdom.¹¹

Morning pseudoneutropenia does not necessarily predispose patients to agranulocytosis; therefore,

patients who exhibit morning pseudoneutropenia should not routinely be denied clozapine treatment.¹⁰ Given the possibility of transient neutropenia and morning pseudoneutropenia, we recommend that if a morning absolute neutrophil count is below the target range, a complete blood count should be repeated in the afternoon to confirm the presence of neutropenia before clozapine therapy is discontinued, to avoid unnecessary discontinuation of an effective antipsychotic agent.

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