Clozapine-Induced Fevers and 1-Year Clozapine Discontinuation Rate

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Background: Clozapine-induced fever is a known side effect that can occur during clozapine initiation. This study aims to characterize patients who experience clozapine-induced fever, the nature of the fevers, and rates of clozapine continuation at 1 year in patients who develop fever versus those who do not.

Method: A retrospective chart review of 93 consecutive clozapine initiations (1991–1999) was conducted. Fever was defined as any 1 temperature at or above 38.0ºC (100.4ºF). Demographic information, presence or absence of clozapine-induced fevers, and continuation of clozapine treatment at 1 year were extracted from the charts. These variables were analyzed for significance, and subsample analysis was conducted for those with more severe fevers (at or above 38.5ºC [101.3ºF]).

Results: Of the 93 patients, 20.4% (N = 19) developed clozapine-induced fevers. At 1 year, there was no significant difference in clozapine discontinuation rate between those patients who experienced fever and those who did not. Patients who experienced higher fevers (≥ 38.5ºC [101.3ºF]) tended to be significantly older than those who did not ($p < .027$). The mean fever duration was 3.8 days (range, 1–9 days), with a mean temperature of 39.1ºC (102.4ºF) (range, 38.0–41.0ºC [100.4–105.8ºF]). At 1 year, the patients who experienced fever showed no increased risk of severe reactions such as agranulocytosis. All patients with fevers continued clozapine treatment with good 1-year continuation rate on treatment with this medication.

Conclusion: Clozapine-induced fever is not an indication for discontinuing this effective medication. It is a benign, self-limited phenomenon not predictive of drug discontinuation at 1 year. Older age at time of treatment may be a risk factor for developing clozapine-induced fever.

(J Clin Psychiatry 2002;63:880–884)

Received Sept. 14, 2001; accepted Feb. 14, 2002. From University of British Columbia Hospital, Vancouver (Dr. Tham); and University of Calgary, Calgary (Dr. Dickson), Canada.

Dr. Dickson is currently a clinical research physician with Eli Lilly Canada (the research reported in this article was conducted prior to this employment).

The authors report no financial affiliation or other relationship relevant to the subject matter of this article.

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The tricyclic dibenzodiazepine antipsychotic drug clozapine, reintroduced in North America in 1990,[1] was the first of a new class of "atypical" antipsychotic medications. While other novel antipsychotics followed, clozapine remains the "gold standard" for treatment-resistant patients with schizophrenia who have failed trials of other antipsychotic medications.[2] Therefore, patients will continue to be treated with clozapine despite the known problematic side effects, including agranulocytosis that occurred in approximately 0.38% of patients followed with mandated white blood cell count testing through the Clozaril National Registry.[3] A much less well-studied side effect that appears to be unique to clozapine is the common occurrence of drug-induced fever in the first 3 weeks of treatment.[4,5]

The fevers during clozapine initiation have been described as (1) spiking in nature with temperatures usually below 40ºC (104ºF), (2) lasting an average of 2.5 days, (3) not correlated with dose,[6] (4) sometimes associated with respiratory and gastrointestinal symptoms,[4,7] and (5) sometimes occurring with benign hematologic abnormalities.[5,7] The reported frequency of fever varies widely, from 5% to 55%,[8–10] depending on the study methodology. Because of concerns regarding the development of agranulocytosis in patients treated with clozapine, clinical fears about possible neuroleptic malignant syndrome (NMS),[11] clozapine-induced fever, and its accompanying hematologic changes may deter clinicians from persisting with a treatment that has established efficacy for a substantial number of patients suffering from treatment-resistant schizophrenia.[2] Therefore, understanding these fevers and patient outcomes is clinically useful information.

Anecdotal case observations by staff at a Canadian clinical service who specialized in treating patients with schizophrenia suggested that once the fevers had sub-

sided, patients were able to tolerate a rechallenge with clozapine and were able to achieve good treatment outcome. The current study was initiated to characterize these patients and to document the 1-year medication survival rates in order to compare patients who experienced clozapine-induced fevers early in their treatment and those who did not.

METHOD

The study design is a retrospective chart review of all patients starting clozapine therapy from 1991 to 1999 at a program in Calgary, Canada, specializing in treating schizophrenia patients. Demographic information and DSM-IV chart diagnoses were collected. The patients were either admitted to the inpatient unit of the hospital or closely monitored in our day hospital program. During these admissions, the hospital standard of care included a minimum of daily vital sign (temperature, blood pressure, pulse, and respiratory rate) measurements. In the event of a fever, the patient would be admitted for inpatient management and a minimum of twice-daily vital sign monitoring during the course of the fever. The patients' clozapine-initiation charts were reviewed to determine whether the presence of fevers was noted by the nursing and medical staff. Fever in this study was defined as any 1 reading equal to or greater than 38.0ºC (100.4ºF) with a noncontact infrared tympanic thermometer within the first month of clozapine treatment. Other data collected included whether the fever was noted as a concern by staff, and if so, whether tests were ordered and/or medical consultation(s) obtained. Finally, the charts were reviewed to determine whether the patient remained on clozapine treatment 1 year after the medication was started. Reasons for discontinuation were recorded.

The data were summarized to reflect demographic variables of patients with and without clozapine-related fevers. The clozapine discontinuation rate was calculated for both the group experiencing clozapine-related fever and those free of this side effect, and the difference was assessed for significance using the chi-square method. Also, t test analysis was done to determine significant demographic differences in the 2 groups. Subsample analysis was also done for patients experiencing fevers at or above 38.5ºC (101.3ºF) to determine the presence of significant trends at this higher fever severity.

This study was approved by the local Ethics Committee. No financial support was received for this study.

RESULTS

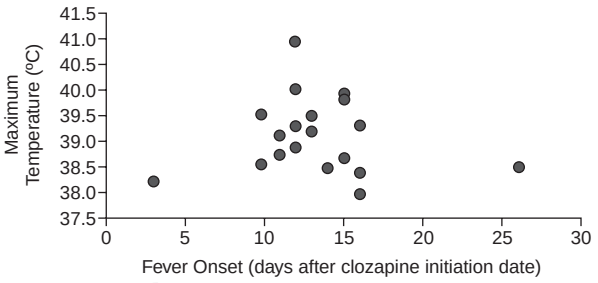
A total of 93 patients from January 1991 to December 1999 were started on clozapine by physicians associated with the clinic. Of these patients, 70% (65/93) were males and 30% (28/93) were females. The patients' mean age at the start of clozapine therapy was 33.9 years (range, 17–60 years). The mean age of the males was younger (32.9 years) than that of the females (36.2 years). The vast majority of the patients were diagnosed with DSM-III-R/DSM-IV schizophrenia (90.3% [84/93]) with a small number classified as having schizoaffective disorder (8.6% [8/93]) and 1 as having psychotic disorder due to a general medical condition. Most patients (87.1% [81/93]) were of white ethnic origin, 7.5% (8/93) were of Asian origin, and the remainder (4/93) were of Middle Eastern or Native American origin.

Table 1. Results of Grouping on the Basis of Clozapine-Induced Fever

Value	No Fever	With Fever
Total, N (%)	74 (79.6)	19 (20.4)
Gender		
Males, N	52	13
Females, N (%)	22 (30)	6 (32)
Age at start of clozapine therapy, y		
Range	17–60	24–53
Mean ± SD	33.0 ± 9.1	37.3 ± 8.6
Males, mean	31.3	36.5
Females, mean	35.4	39.1
Diagnosis, N		
Schizophrenia	67	17
Schizoaffective disorder	6	2
Psychosis due to medical condition	1	0
Discontinuation rate at 1 year, N/N (%)	18/74 (24.3)	4/19 (21.0)
Males, N	16	4
Females, N	2	0
Maximum temperature elevation		
Range	N/A	38.0–41.0ºC (100.4–105.8ºF)
Mean ± SD	N/A	39.1 ± 0.74ºC (102.4 ± 1.33ºF)
Fever onset (no. of days after clozapine initiation)		
Range	N/A	3–26
Mean ± SD	N/A	13.8 ± 5.1
Fever duration, d		
Range	N/A	1–9
Mean ± SD	N/A	3.8 ± 2.6
No. of days clozapine withheld for patients during time of fever		
Range	N/A	0–20
Mean	N/A	3.3

The incidence of clozapine-induced fever during the first month of medication initiation was 20.4% (19/93) (Table 1). In all but 2 cases, the fever was noted as a cause for concern. It was likely that the fever was not noted as a cause for concern in these 2 cases because the patients did not complain of symptoms despite the noted temperature elevation, and the fever was low grade (38.0ºC [100.4ºF] and 38.2ºC [100.8ºF]). In all of the other cases (17/19), complete blood counts were done to rule out hematologic abnormalities. Total white blood cell count elevations were noted in 4 cases (4/19) with the highest elevation up to 15.4×10^9/L (normal range, 4.0–11.0 × 10^9/L). Other abnormalities noted in the cell count differentials included bandemia in 3 cases up to 4.6×10^9/L (normal range, 0.0–1.3 × 10^9/L), eosinophilia in 1 case up to 1.7×10^9/L

Figure 1. Fever Onset and Maximum Temperatures



(normal range, 0.0–0.7 × 10^9/L), neutrophilia in 2 cases up to 12.3 × 10^9/L (normal range, 1.8–7.7 × 10^9/L), and 1 case of elevated monocytes to 1.9 × 10^9/L (normal range, 0.0–1.0 × 10^9/L). Neutropenia and agranulocytosis were not observed in any of these patients.

Other laboratory tests performed in response to the fever in some of the patients included chest x-rays (5/19), urinalyses (10/19), blood cultures (15/19), and measurements of creatine kinase level (7/19). None of the patients had abnormal findings on the chest x-ray. Trace red and white blood cells were detected in 3 of the patients' urinalyses during the fever. Blood cultures were uniformly negative. Finally, creatine kinase levels were found to be transiently mildly elevated in 2 of the patients (up to 264 U/L [normal range, 0–184 U/L]). An internal medicine consultation was requested for 6 (31.6%) of the 19 patients, and medical problems were not deemed to be the cause of fever in any cases. Furthermore, there was no clear evidence of infectious etiologies in any of these patients. In 1 of the cases, empirical antibiotic treatment was started in response to the fever but was stopped within 24 hours as it was felt that there was no source of infection. Except for the 2 patients with fevers not noted as a concern by the staff, management included withholding clozapine during the course of the fever (17/19), and acetaminophen was used for symptomatic relief with good effect in 14 (82%) of the 17 patients for whom fever was noted as a concern.

Of the 74 patients without clozapine-induced fever, the 1-year drug discontinuation rate was 24.3% (18/74; 16 males, 2 females), whereas in the group with clozapine-induced fever, the rate was 21.0% (4/19; 4 males, 0 females). The female-to-male ratios did not appear to differ markedly in the 2 groups, and the low number of female patients in each group precluded meaningful statistical analysis. Contingency table analysis of these data with the chi-square test revealed no significant difference in the discontinuation rates ($p < 1.0$). The group with clozapine-induced fever had a higher mean age (37.3 years) compared with those who did not display this side effect (33.0 years); Student t test analysis of independent groups showed no significant difference at 95% confidence

Table 2. Reason for Clozapine Discontinuation (N)

Reason	No Clozapine-Induced Fever (N = 74)	Clozapine-Induced Fever (N = 19)
By patient request	8	3
Noncompliance	9	0
Ineffective	0	1
Hematologic abnormality	1[a]	0

[a]Neutropenia.

($t = -1.89$, $p < .062$). For those with fever, the mean maximal temperature was found to be 39.1°C (102.4°F) with 1 instance of fever up to 41.0°C (105.8°F). The patients experienced fever of variable severity for a mean of 3.8 days. As a result of the fever symptoms, the clozapine dose was withheld for a mean of 3.3 days before restarting the medication once the fever subsided. Fever onset ranged from 3 to 26 days after clozapine initiation with the majority of patients experiencing the fever within the second and third weeks (Figure 1). The fever symptoms began a mean of 13.8 days after clozapine was started. In all cases, clozapine was successfully restarted within days after allowing the fever to subside without further fever reoccurrence or reemergence of severe side effects.

Charted reasons for discontinuing clozapine are listed in Table 2. One of the patients who did not experience clozapine-induced fever developed neutropenia with a neutrophil count down to 1.0 × 10^9/L and was discontinued within 2 months of clozapine initiation without associated eosinophil or basophil abnormalities.

Of the patients identified as having fevers, 16 of 19 experienced fevers at or beyond 38.5°C (101.3°F). For all patients in this subsample, the fever was noted as a concern by the staff physician involved and resulted in both temporary suspension of clozapine administration or a workup for organic pathology initiated. Subsample analysis of the data suggested no significant difference regarding discontinuation rates between the fever and nonfever groups ($p < 1.0$). The mean age for those with fevers equal to or greater than 38.5°C (101.3°F) was 38.4 years compared with 32.9 years for those without fevers. This difference is significant by t test analysis ($t = -2.24$, $p < .027$).

DISCUSSION

To our knowledge, this is the first study that examined a large sample of patients taking clozapine to help characterize the clozapine-induced fever side effect and the longer-term outcome of these patients. Importantly, the presence of fever did not predict agranulocytosis or an increased rate of drug discontinuation during the 1-year follow-up period.

In our sample, with the criterion of a single measurement of 38.0°C (100.4°F) or above constituting fever, a total of 20% of patients were identified as having clozapine-

induced fever. This finding is similar to Blum and Mauruschat's report[12] of 25% in their retrospective group. In our study group, 1 individual experienced a fever of 41.0ºC (105.8ºF), although the majority of fevers tended to be below 40ºC (104ºF). Although the mean age for the patients experiencing this side effect was higher, statistical methods did not show significance using the 38.0ºC (100.4ºF) criterion for fever. The mean time of fever onset in our sample was 13.8 days after starting clozapine, with fevers in the majority of patients (14/19; 74%) starting during the period of days 10 to 15; these findings correlate with previous observations that this side effect peaks within the first 2 weeks of clozapine initiation.[12] Finally, patients' temperatures were noted to wax and wane over the course of their fevers, which lasted a mean of 3.8 days, somewhat longer than the 2.5-day duration previously reported by Hinze-Selch et al.[6] It is important to note that acetaminophen was given to a majority of the patients for symptomatic relief. As a result, the observed duration and severity of the fever may have been modified.

Although we chose 38.0ºC (100.4ºF) as our threshold to maintain comparability with previous studies,[9,12] we felt that, clinically, one would rarely be concerned unless a patient's temperature was to elevate to 38.5ºC (101.3ºF) or beyond. Although the data still showed no difference in clozapine discontinuation rates at 1 year when 38.5ºC (101.3ºF) was used as the cutoff for fever, there was a significant difference in mean age of the patients at the start of clozapine therapy. This would suggest that older individuals are at greater risk of having the fever side effect and experiencing greater severity.

In a recent review of NMS in patients treated with atypical antipsychotics including clozapine,[11] it was suggested that NMS is a possible side effect of clozapine treatment. In our study, despite the temperature elevations and mild creatine kinase elevations, none of the cases displayed adequate signs and symptoms consistent with a clear picture of NMS (DSM-IV research criteria) and none were diagnosed or treated as such. Another possible explanation would be that of an infectious process causing fever in these patients. Although physical examination and tests did not show clear evidence of infection, the possibility of mild viral gastrointestinal or upper respiratory tract infections cannot be completely ruled out.

Recent reports have suggested a role for the immune system in the pathology of schizophrenia,[13] and immunomodulatory effects of antipsychotics have been studied.[14,15] Although the exact cause of clozapine-induced fevers is unclear, in vivo studies have correlated cytokine system changes such as alterations in levels of IL-6, sIL-2,[16] and TNF-α[17] during the second week of treatment. Pollmächer et al.[17] hypothesized that the immunomodulatory effects of clozapine may be related to agranulocytosis development. This study suggests that at least with regard to the symptom of clozapine-induced fever, there is no evidence that this side effect heralds the future development of agranulocytosis. In our study, 1 of the nonfever patients developed neutropenia (1/74) and was discontinued from clozapine, whereas neutropenia was not observed in any of the fever patients (0/19) over the 1-year follow-up.

Overall, the 1-year clozapine discontinuation rate was slightly lower for the fever group (21.0%) compared with the nonfever group (24.3%), but this was not a significant difference. The close monitoring of clozapine-treated patients in our clinic adds validity to our findings that the fever patients did not experience severe side effects, tolerability issues, or poor treatment response requiring early discontinuation of the drug. Nonetheless, various factors such as a small sample size as well as methodological issues may have affected the outcome of this study. The fact that ours is a retrospective study with data polled from observations made over 9 years clearly limited the ability to have consistent protocols for monitoring patients' side effects and the accuracy to which fever measurements were made. Although the tympanic thermometer is a convenient, easily available, and noninvasive way to assess body temperatures, its accuracy is not without question. A recent study measured a 98% accuracy rate in a controlled setting with trained personnel.[18] Accuracy has been found to change depending on patient factors such as ear obstruction and the presence of cerumen[18,19] and operator factors such as the nurse's experience with the machine,[18,19] as well as the calibration and manufacturer of the thermometer.[20] Again, given the nature of this study, these variables could not be accurately accounted for.

In summary, our study supports the belief that fevers during clozapine initiation are common and are benign in that no life-threatening states appeared as a consequence of this side effect once infectious and other medical causes for fever were ruled out. There was no evidence of an increased risk of agranulocytosis developing within the first year of clozapine treatment for these patients. Gender of the patients did not appear to significantly predispose to experiencing fever. There was, however, a significant association of higher grade (≥ 38.5ºC [≥ 101.3ºF]) clozapine-initiation fever and older age at the start of clozapine therapy. Finally, for all patients who developed clozapine-induced fever, clozapine was restarted usually within 3 or 4 days after normalization of the body temperature with no recurrence of this side effect and with a 1-year clozapine continuation rate comparable to that of patients who did not experience clozapine-induced fever.

Drug name: clozapine (Clozaril and others).

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