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Short communication

Clozapine-induced agranulocytosis and leukopenia: Incidence, associated factors, and rate of hematologic adverse-effects monitoring in psychiatric out-patient services in Thailand

Noppawan Tunsirimas[a,b], Pornjira Pariwatcharakul[a], Somrak Choovanichvong[c], Woraphat Ratta-apha[a,*]

[a] Department of Psychiatry, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
[b] Nakorn Ratchasima Rajanagarindra Psychiatric Hospital, Nakorn Ratchasima, Thailand
[c] Srithanya Hospital, Nonthaburi, Thailand

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ABSTRACT

The present study aimed to investigate the incidence of agranulocytosis and leukopenia and its associated factors in Thai schizophrenia patients treated with clozapine and the rate of hematologic adverse events monitored in clinical practice. Data were collected from the medical records of 641 outpatients at two hospitals. The results showed no cases of agranulocytosis and 20 cases of leukopenia (3.1%), 85% of which were observed after 1 year of prescription. The associated factors were female ($p = 0.019$) and duration of clozapine prescription ($p = 0.026$). According to the guideline for safety monitoring, 23.6% of cases had neutrophils count monitoring.

1. Introduction

Clozapine, an atypical antipsychotic drug approved by the FDA for treatment-resistant schizophrenia, has been used with caution due to life-threatening adverse events (AEs), agranulocytosis (neutrophils < 500 cells/mm^3), which is the most severe form of leukopenia. The incidence of agranulocytosis from other studies is approximately 0–3.9% (Balda et al., 2015; Kang et al., 2006; Lee et al., 2015; Sing et al., 2017; Velayudhan and Kakkan, 2014). Other uncommon, but immediately dangerous, AEs are neutropenia (neutrophil count < 1500 cells/mm^3), myocarditis/cardiomyopathy, seizures, and diabetic ketoacidosis (Citrome et al., 2016; Cohen et al., 2012; Sultan et al., 2017). Regarding the guideline for prescribing clozapine, hematologic monitoring has been recommended for the early detection of these serious adverse effects, especially during the first 18 weeks after the initiation of clozapine (Bastiampillai et al., 2016; Cohen et al., 2012). Monitoring of the white cell count with neutrophils count is required weekly for the initial 18 weeks, then fortnightly for up to one year, and then monthly (Kar et al., 2016). The risks of agranulocytosis and neutropenia are highest in the first six months and then gradually decrease over time (Citrome et al., 2016; Drew, 2013; Velayudhan and Kakkan, 2014). Significant and independent factors associated with clozapine-related agranulocytosis are female sex, older age, and use of concomitant medications (Balda et al., 2015; Sing et al., 2017).

According to the incidence of agranulocytosis, the previous studies conducted in Thailand were limited to small sample sizes (95–239 cases/study) or few incidences of the event of agranulocytosis (0–1.1%) and neutropenia (1.5–6.3%) (Maskasame et al., 2007; Ratanajamit et al., 2010; Udomratn, 2000). Thus, the results on the incidence of agranulocytosis and leukopenia or its associating factors for schizophrenic Thai patients treated with clozapine were inconsistent (Maskasame et al., 2007; Ratanajamit et al., 2010; Udomratn, 2000). Nation-wide registry system for clozapine-related hematological monitoring is unavailable in many Asian countries (Ismail et al., 2019; Xiang et al., 2013), including Thailand. Safety advises for white blood cell monitoring has been applied in many psychiatric departments. The present study aimed to investigate the incidence of agranulocytosis and leukopenia and related factors among schizophrenic Thai patients. The secondary objective was to examine the real practice of the frequency of hematologic AEs monitored by the clinicians.

2. Materials and methods

2.1. Participants, study design, and measurements

A retrospective chart review was conducted at a 2221-bed university hospital and a 750-bed psychiatric hospital in Thailand. Schizophrenia patients who were 18 years or older and treated with

* Corresponding author.
E-mail address: woraphat.rat@mahidol.ac.th (W. Ratta-apha).

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clozapine between January 1, 2008 and December 31, 2013 were included. The sample size was calculated by using the incidence of agranulocytosis from a previous study in Thailand (2.6%) with type I error and standard error at 0.05 and 0.015, respectively. This study needed at least 576 subjects to investigate the study's objectives.

To study the incidence of agranulocytosis and leukopenia and related factors among schizophrenic Thai patients, demographic, clinical data, and white blood cell monitoring were obtained from the participants' medical records. Agranulocytosis was defined as neutrophils < 500 cells/mm^3, whereas leukopenia was defined as total white blood cell < 3500 cells/mm^3.

To study the real practice of the frequency of hematologic AEs monitored by clinicians, the frequency of hematologic AEs monitored by the psychiatrists were collected and compared with the clinical practice guideline (as mentioned above) for hematologic AEs monitoring.

2.2. Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics 21 (IBM Corp, Armonk, NY, US). The characteristics were reported as frequency, percentage, mean, and standard deviation (SD). The incidence of agranulocytosis and leukopenia were reported as frequency and percentage by using the definitions above. Factors that relate to agranulocytosis and leukopenia were analyzed using the chi-square test, unpaired *t*-test or Mann-Whitney U test according to the type of data. The statistical significance level was set at $p < 0.05$.

2.3. Ethical consideration

The study was approved by the Siriraj Institutional Review Board, Faculty of Medicine, Siriraj Hospital, Mahidol University (protocol number 728/2557) and the ethical committee of Srithanya Hospital (protocol number Q15/2558). The data were obtained from the case records after the permission of the directors of both institutions.

3. Results

3.1. Demographic and clinical data

The total number of 641 patients (160 from the university hospital, 481 from the psychiatric hospital) consisted of 413 (64.4%) males and 228 (35.6%) females. The average age was 44.56 ± 12.06 years. Most of the patients were single (N = 501, 78.5%), unemployed (N = 423, 66.3%) with no underlying diseases (N = 377, 58.8%) (Table 1).

The average duration of clozapine prescription was 3.82 years. Average maximum and current dosages were 200 and 150 mg/day, respectively. Average baseline leukocytes and neutrophils counts were 7350 and 4618/mm^3, respectively (Table 1).

3.2. Incidence of agranulocytosis, leukopenia, and related factors

No agranulocytosis was found among the patients in this study. The incidence of leukopenia was 3.1%; 0.5% within the first year and 2.6% after the first year of clozapine treatment (Table 2).

Factors related to leukopenia were female gender ($p = 0.026$) and duration of clozapine use ($p = 0.02$). However, the maximum dose, current dose, baseline leukocytes, and neutrophils count were not significant, as shown in Table 2. Further investigation for survival median time of leukopenia by Kaplan-Meier analysis found that 50% of clozapine-use patients had leukopenia at 1053 days (2.89 years) after starting clozapine (95% CI = 521.23–1584.77).

3.3. Hematologic AEs monitoring

According to the guideline for safety monitoring of hematologic AEs of clozapine, 23.6% of cases have neutrophils count monitoring. Sixteen cases (2.5%) were monitored every week for 18 weeks, and 14 cases (2.4%) were monitored every month after 18 weeks as a recommendation.

Table 1
Demographic data of the selected schizophrenic patients treated with clozapine during the time of study.

Characteristics	Number (Percentage), Mean
Demographic characteristics	
Gender (Male: Female)	413:228 (64.4%:356%)
Age (mean ± SD) years	44.56 ± 12.06
Marital status :	
Single	501 (78.5%)
Married	76 (11.9%)
Widow/ divorced	61 (9.6%)
Level of education:	
Primary level or below	155 (26.6%)
Secondary level	295 (50.7%)
Above secondary level	132 (16.3%)
Occupation:	
Employed	208 (32.6%)
Unemployed	423 (66.3%)
Medical and psychiatric condition characteristics	
Comorbidity/ underlying diseases	
Medical conditions	219 (34.2%)
Psychiatric conditions	87 (13.6%)
No underlying diseases	377 (58.8%)
Concurrent psychiatric medications	
Other antipsychotics	489 (76.3%)
Lithium	29 (4.5%)
Anticonvulsants	190 (29.6%)
Antidepressants	424 (66.2%)
Benzodiazepines	36 (56.3%)
Anticholinergic drugs	535 (83.5%)
Clozapine use, duration, dosage, and baseline leukocytes/ neutrophils	
Number of patients continuing clozapine through the period of observation	438 (68.3%)
Number of patients stopping clozapine during the period of observation	88 (17.7%)
The average duration of prescription, years (range)	3.82 (0.01–15.58)
The average maximum/current dosage, mg/day (range)	200/ 150 (12.5–800/ 12.5–800)
The average duration of the temporary holding of clozapine during the period of observation (month)	5 months (0.17–44.0)
The average duration of restarting clozapine (month)	13.2 months (1.0–60)

4. Discussion

The present study is a naturalistic study, which collected the samples from the university hospital and general psychiatric hospital settings. The collected sample size was quite big compared with the previous national studies.

The incidence of agranulocytosis and leukopenia was similar to previous studies. In comparison with the first year of clozapine prescription, the incidence of leukopenia was higher after the first year of clozapine use. There are some limitations to this interpretation. First, there was no clinical registry for recording the physical conditions and treatments that link psychiatric and general hospitals. Second, some patients might have other medications or medical conditions that affect the number of leukocytes. Third, clozapine adherence was not objectively confirmed because monitoring clozapine levels is not the standard practice recommendation in Thailand. Furthermore, the analysis was based on the guideline used at the time of clozapine prescribing, which has now been revised by the FDA, that is, the threshold of the neutrophil count has been lowered to 1000 cell/mm^3 for treatment interruption (Sultan et al., 2017). Further study with the new

Table 2
Selected severe adverse reactions, incidence of agranulocytosis and leukopenia and related factors.

Severe adverse reactions, agranulocytosis and leukopenia	Number of cases (%)
Diabetic ketoacidosis	1 (0.2%)
Seizure	8 (1.2%)
Others (hepatitis, rash, abnormal electrocardiography)	5 (0.8%)
Agranulocytosis	0 (0)
Leukopenia	20 (3.1%)
Within the first year	3 (0.5%)
After the first year	17 (2.7%)

Factor-related leukopenia

Factor	Leukopenia Number or mean	No leukopenia Number or mean	Odds ratio, 95% confidence interval	p-value
Gender				
Male	8	405	0.36 (0.14–0.88)	0.026
Female	12	216		
Age				
40 and less than 40 years	10	254	1.00 (0.96–1.04)	0.921
More than 40 years	10	367		
Duration of clozapine use (year), mean (min.–max.)	5.67 (0.17–14.27)	3.75 (0.01–15.58)	0.87 (0.78–0.98)	0.019
Maximum dosage of clozapine prescription (mg/day), mean (min.–max.)	275 (100–700)	200 (12.5–800)	0.99 (0.99–1.00)	0.051
Baselined white blood count (cell/mm^3), mean (min.–max.)	8180 (3730–12500)	7325 (4000–16000)	1.00 (1.00– .00)	0.596
Baselined neutrophil count (cell/mm^3), mean (min.–max.)	4690 (1850–8700)	4617 (1032–12450)	1.00 (1.00–1.00)	0.942

monitoring algorithm is required to examine the incidence of hematologic AEs of clozapine in Thai patients with schizophrenia.

Next, the rate of completed monitoring of neutrophil count in real clinical practice compared with the recommended guideline was quite low. The possible causes might be (1) the physicians' aspects: the physician might not have strictly followed the guideline, referring their patients to have blood tests done in other hospitals near their residences; and (2) the patients' aspects: the inconvenience for the patients in getting their blood sampling done, referrals for treatment at other hospitals, and lost follow-up due to their physical conditions. Further exploration of the reasons for not following the guideline for both clinicians and patients might be helpful to examine these hypotheses more extensively. Regarding the low incidence of agranulocytosis and leukopenia in Thai patients, we do not suggest that less frequency of blood monitoring can be applied in these settings. Due to the lack of a registry and linked database, we cannot verify the safety of not following the recommended guideline. Based on the available clinical evidence of various potentially life-threatening AEs and the risk of cardiovascular and metabolic disorders, there is a need to broaden drug-safety monitoring, that is, body weight, body mass index (BMI), blood sugar, lipids, and electrocardiography (Kar et al., 2016).

In conclusion, the incidence of agranulocytosis and leukopenia were low in the present study. Leukopenia was associated with the female gender and the duration of clozapine prescription. The rate of hematologic AEs monitoring is low compared with the recommended guideline. Further study is required to investigate both the incidence and the rate of monitoring of AEs of clozapine to provide more understanding and improvement of clinical application.

Declaration of interest statement

The authors have no conflicts of interest to disclose.

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