The Incidence of Clozapine-Induced Leukopenia in Patients with Schizophrenia at Srinagarind Hospital

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Objective: *Define the incidence of clozapine-induced leukopenia, neutropenia, and agranulocytosis in patients with schizophrenia at Srinagarind Hospital.*
Material and Method: *A descriptive study was done by retrospective reviews of the medical records of schizophrenic outpatients at psychiatric clinic in Srinagarind Hospital who had received clozapine from January 1st, 2003 to December 31st, 2005. The demographic data, incidence rate, and incidence density of leukopenia, neutropenia, and agranulocytosis were collected.*
Results: *One hundred and seventeen medical records were reviewed, 65 patients met the inclusion criteria. One patient developed neutropenia. The incidence rate of neutropenia was 1.5% and the incidence density of neutropenia was 0.01/year. No leukopenia or agranulocytosis was found in the present study. The complete blood counts were not obtained regularly due to the problems of patient's adherence and variations in practice among the physicians.*
Conclusion: *Neutropenia is uncommon. No leukopenia and agranulocytosis were found. According to variations of incidence reports among different studies, the monitoring of white blood count should be continued.*

Keywords: *Clozapine, Leukopenia, Neutropenia, Agranulocytosis, Incidence rate, Incidence density*

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Schizophrenia afflicts approximately 1% of the population and persists throughout life. Several studies have shown that over the 5 to 10 year period after the first psychiatric hospitalization for schizophrenia; only about 10-20% of patients have a good outcome. More than 50% of patients experience repeated hospitalizations, exacerbations of symptoms, episodes of major mood disorders, and suicidal attempts[1].

Since the mid-1950s, a number of different antipsychotic drugs have been used to treat patients with schizophrenic disorders[2,3]. Up to 20% of patients derived little benefit and present major management problems, both with respect to positive symptoms such as hallucinations and hostility, and negative symptoms such as slowness and social withdrawal[2,4]. Clozapine, a serotonin-dopamine antagonist, was identified in 1959 as the first atypical antipsychotic with activity against both positive and negative symptoms of schizophrenia[5]. In Thailand, clozapine was first marketed in 1973 with the brand name of Leponex[R(6)]. It was found to have a distinctive safety profile with minimal extrapyramidal side effects, minimal elevation in plasma prolactin concentrations, and a very low incidence of neuroleptic malignant syndrome[7]. Unfortunately, the development of clozapine was curtailed in 1975 because of a cluster of cases of agranulocytosis in Finland[2]. This led to a withdrawal of clozapine in many countries including Thailand. In 1990, clozapine was approved by the Food and Drug Administration (FDA) of the United States for treatment–resistant schizophrenia and was subsequently reintroduced into clinical practice in many countries. In Thailand, clozapine was approved and reintroduced into the market on March 24th, 1993 and first used at Srinagarind Hospital in 1998.

Although clozapine had unique efficacy in improving 30-60% of treatment-resistant schizophre-

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nia[2,8,9] , the risk of leukopenia (white blood cell count < 3,500/mm^3) and its possible progression to agranulocytosis (absolute neutrophil count < 500 mm^3) was potentially fatal[10]. The incidence of clozapine- induced agranulocytosis occurs at a rate of 1 to 2% and the leukopenia rate was 2.8% of patients treated[11].

It is still unclear on the pathophysiology of clozapine-induced agranulocytosis. Genetic[10,12], Toxic[13,14], and immunologic[14,15] factors have been proposed as causal attributions. Pisciotta et al found that the serum of patients with clozapine-induced agranulocytosis contained a factor that was cytotoxic to peripheral blood granulocytes and at high concentrations (20-40% human allogeneic serum) suppressed hematopoietic progenitor cells called colony forming unit-granulocyte (CFU-GM), implicated the role of immune mechanism[16]. In favor of a toxic mechanism is the long lag time between the onset of re-exposure and re-emergence of agranulocytosis[17]. This is unusual for an autoimmune process, where re-exposure often results in the sudden onset of agranulocytosis. Stanton LG et al found that N-desmethylclozapine, a clozapine metabolite, is toxic to marrow precursors. The possibility that this metabolite is a factor in clozapine-induced agranulocytosis will need to be prospectively assessed[18]. However, there are studies on risk factors associated with agranulocytosis[18,19]. A recent evaluation of the U.S. clozapine database points out an increased risk of agranulocytosis in female patients[19].

In Thailand, a retrospective study of agranulocytosis in clozapine patients at Somdetchaopraya Hospital, Bangkok by Tangtrakul et al[20] found that the rate of agranulocytosis was 0.7%, leukopenia rate was 2.6%, and neutropenia rate was 2.2%. The study of safety and outcomes of clozapine for treatment of schizophrenia at Srithanya Hospital, Nonthaburi found that the incidence of agranulocytosis was 0.95% in the fourteenth weeks of treatment[21]. Despite frequency of blood tests, no agranulocytosis was found in the study of Thiengburanathum T et al[22] and Udomrath P et al[6].

Because of the substantial risk for this potentially fatal adverse reaction, national blood monitoring guideline was required. In the United States, service is known as the Clozaril National Registry (CNR)[10]. The CNR requires that patients have blood checked weekly for the first 6 months after beginning of clozapine treatment, and biweekly thereafter for patients with stable white blood cell counts. In Thailand, all patients using clozapine are required weekly white blood cell monitoring during the first 18 weeks and then monthly checking for the whole period of clozapine therapy[23]. However, the incidence of clozapine induced agranulocytosis has not yet been established, the variations of blood monitoring are still presented. Some physicians monitored clinical signs and symptoms such as common cold, sore throat, and other signs of infection to determine the low white cell count status. If these findings occur, patients will be required to take blood tests immediately[22].

According to outpatient records of Srinagarind Hospital, schizophrenia was common and among the majority of cases during the past few years. The statistics showed as many as 15% of the outpatients of the psychiatric clinic[24]. There is still lack of evidence to show the incidence of clozapine-induced agranulocytosis and other related hematological side effects in Thais especially the northeast populations. Realizing how fatal agranulocytosis is, early detection is necessary. Therefore, the incidence of clozapine-induced leukopenia, neutropenia, and agranulocytosis in patients with schizophrenia and factors associated with leukopenia should be studied.

Material and Method

The present study was a descriptive study where the population came from 117 schizophrenic outpatients at psychiatric clinic in Srinagarind Hospital, Khon Kaen who had received clozapine from January 1st, 2003 to December 31st, 2005. Medical records were abstracted and analyzed by the authors. The demographic data such as sex, age, marital status, education were recorded including the information on clozapine uses. Data on white blood cell count before and after using clozapine, duration, dosages, and continuation of clozapine and other drugs used with clozapine were recorded. Patients with schizophrenia who did not have any white blood cell records during the time of receiving clozapine were excluded. Protocol had been reviewed and approved by the Khon Kaen University Ethics Committee for Human Research.

According to the current US definitions[25], leukopenia is defined as white blood cell count less than 3,500/mm^3, neutropenia as neutrophil count less than 1,500/mm^3, and agranulocytosis as neutrophil count less than 500/mm^3. Descriptive statistics were used to calculate rates of leukopenia, neutropenia, and agranulocytosis in number, incidence rate, and incidence density (incidence rate per patient year). Statistical analysis was done by using SPSS for Windows.

Results

From the medical records from January 1st, 2003 to December 31st, 2005 there were 117 schizophrenic outpatients using clozapine. Sixty-five patients were included. Fifty-two patients were excluded because 48 of them did not have any white blood cell records during the time of receiving clozapine and four were lost to follow up after the first prescription of clozapine. Demographic data are shown in Table 1.

In the present study, 38 patients were male and 27 patients were female. The mean age was 32 (SD = 12.1) years, age range = 13-77 years. The minimum total white blood cell count was 3,500/mm^3 and the maximum was 24,500/mm^3. Neutropenia was found in one blood testing with neutrophils as low as 1,179.5/mm^3 and total white blood cell counts of 3,500/mm^3. The incidence rate was 1.5%. The incidence density was 0.01/year. No leukopenia and agranulocytosis were found. Nineteen patients used clozapine alone and 46 patients used clozapine concomitantly with other drugs such as long acting antipsychotic drugs (haloperidol decanoate, fluphenazine decanoate, flupentixol injection), antidepressant drugs (fluoxetine, amitriptyline), anxiolytic drugs (lorazepam, clonazepam), and mood stabilizers (valproic acid, lithium carbonate).

There was no CBC checks that followed the Thai FDA guideline[23]. There were regular CBC checks in 10.8 %, irregular CBC checks in 78.4 %, and the data couldn't be evaluated in 10.8%. CBC-checks was likely obtained at the early visits and gradually worn-off (Fig. 1).

Table 1. Demographic data

	Number (n = 65)	Percentage
Sex		
Female	27	41.5
Male	38	58.5
Marital status		
Single	52	80.0
Married	11	16.9
Divorced	2	3.1
Education		
Elementary	3	4.6
Middle school	15	23.1
Highschool	17	26.2
College	4	6.2
University and above	17	24.6
Occupations		
Unemployed	22	33.8
Business	4	6.2
Farmer	7	10.8
Government	9	13.8
Employment	11	16.9

Discussion

In recent evaluation of the U.S. clozapine database, the database points out to an increased risk of agranulocytosis in female patients[19]. In this study, there were more males than females therefore; this might lower the possibility of finding agranulocytosis (Table 1). Furthermore, no leukopenia or agranulocytosis

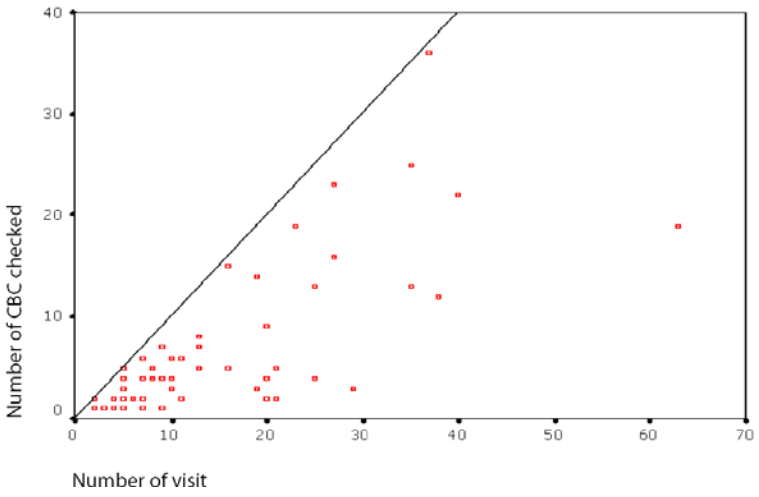

Fig. 1 Relationship of visit and white count checked

was found. Thus, the factors that might associate with leukopenia could not be evaluated. The present results were consistent with previous reports of Thiengburanathum et al[22] and Udomrath P et al[6]. However, these results were different from Tangtrakul et al[20] in which the incidence of leukopenia was 2.6% and the incidence of agranulocytosis was 0.7%. The study of safety and outcomes of clozapine for treatment of schizophrenia at Srithanya Hospital from 1995 to 2000 found that the incidence of agranulocytosis was 0.95%, which occurred at week fourteen after starting treatment with clozapine[21]. In the study of Honigfeld G et al[11], leukopenia rate was 2.8% and agranulocytosis was found 2% in the report of clozapine study group[2]. Alvir JM et al reported 0.8 % of agranulocytosis at 1 year and 0.9% at 1.5 year[19]. Only one patient in the present study showed decrease neutrophils count as low as 1179.5/mm^3, and the incidence of neutropenia rate was 1.5 %, which was lower than the study of Tangtrakul et al (2.2%)[20], Atkin et al (2.9%)[26], and clozapine study group (3.7%)[2].

In the present study, neutropenia was found in one patient at the second visit after receiving clozapine for 5 weeks at the dosage of 25 mg/day. Clozapine was promptly discontinued. There were no previous WBC checks before giving clozapine. No significant clinical signs and symptoms related to neutropenia were found at this second visit. It could be assumed that this patient might have lower white blood cell counts before taking clozapine and therefore would increase the risks of agranulocytosis[27].

Therefore, CBC-checks before using clozapine should be required. Clozapine may also induce transient neutropenia, which had been shown to start as early as the first week of treatment and to subside in spite of ongoing drug therapy, then return to normal within an average of 1.4 weeks[12]. It is important to be aware of this transient phenomenon so as not to be overly cautious and stop clozapine too early in these patients[11]. If neutropenia occurs and patients still respond to clozapine, continuing of clozapine and closely monitoring white blood counts every other day is a good clinical practice. Clozapine should be discontinued immediately if progressive neutropenia occurs. According to the present results, the incidence of neutropenia rarely occurred. The determined incidence density of neutropenia was 0.01/year. This meant that during one year of 100 patients exposed to clozapine, only one patient would have neutropenia.

The relationships between the number of outpatients visits and CBC checks showed that white blood cell counts were not taken at every visit and gradually decreased as the number of visits increased. Even when the authors brought up the term regularity and irregularity white blood cell monitoring in the present study, most patients did not have regular interval of white blood cell monitoring and no CBC checks followed the Thai FDA guideline[23]. There are variations in practice among physicians and limitations of patients. Taking every week of white blood cell counts would be inconvenient for patients living in rural areas far away from tertiary care hospitals. There are also patients who were afraid of needles or pain and refuse to have frequent blood drawn. Concerning the patient's right is still an important issue, the practice should be balanced with the patients' compliance. Before the more confirming evidence about the rarity of leukopenia in Thais, the physicians need to comply with the guideline. However, there is still controversy in opinions among physicians towards the necessity for frequent monitoring of white blood cell counts of those receiving clozapine.

There are certain limitations in the present study. Even though the authors included every case that matched the inclusion criteria, the sample size was small and might not represent the whole population. Since the data are retrospective, there are some missing data and some cannot be evaluated. The patient who had neutropenia in the present study had total white blood cell counts of 3,500/mm^3 which was marginal to the term leukopenia and made the present result seemed not correlated in the finding of neutropenia and leukopenia. The results of leukopenia and neutropenia may be underestimated in this study due to the irregularity monitoring of white blood cell counts. Re-white blood cell check should be obtained when an abnormal result is found and does not correlate with clinical symptoms. This might be due to laboratory error or in the period of transient neutropenia. The prospective studies requires baseline white blood cell counts before receiving clozapine and should focus on regular white blood cells monitoring for a longer period of time in order to define the course of clozapine induced blood dyscrasias.

Conclusion

No leukopenia and agranulocytosis were found in the present study. The incidence rate of neutropenia was 1.5% and incidence density of neutropenia was 0.01/year. There were no CBC checks that followed Thai FDA guideline. Despite the fatality of agranulocytosis, CBC was mostly obtained irregularly because of certain variations and limitations in practice.

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อุบัติการณ์การเกิดภาวะเม็ดเลือดขาวต่ำจากการใช้ยาโคลซาปีนในผู้ป่วยจิตเภทในโรงพยาบาลศรีนครินทร์

ศรินทร์ มาศเกษม, ธวัชชัย กฤษณะประกรกิจ, จิราพร เขียวอยู่

วัตถุประสงค์*: การวิจัยนี้มีวัตถุประสงค์เพื่อศึกษาถึงอุบัติการณ์การเกิด leukopenia, neutropenia, และ agranulocytosis จากการใช้ยาโคลซาปีนในผู้ป่วยจิตเภท โรงพยาบาลศรีนครินทร์*

วัสดุและวิธีการ*: เป็นการศึกษาเชิงพรรณนา ซึ่งเก็บข้อมูลย้อนหลังจากเวชระเบียนผู้ป่วยนอก แผนกจิตเวช โรงพยาบาลศรีนครินทร์ เป็นผู้ป่วยจิตเภทที่ได้รับยาโคลซาปีนตั้งแต่วันที่ 1 มกราคม พ.ศ. 2546 - 31 ธันวาคม พ.ศ. 2548*

ผลการศึกษา*: รวบรวมเวชระเบียนได้ทั้งหมด 117 ฉบับ พบว่ามีผู้ป่วยที่ตรงตามเกณฑ์คัดเข้าจำนวน 65 คน ผู้ป่วย 1 คนเกิด neutropenia อุบัติการณ์การเกิด neutropenia คือ 1.5 % incidence density ของ neutropenia พบเป็น 0.01/ปี จากการศึกษานี้ไม่พบภาวะ leukopenia และ agranulocytosis การเจาะดูระดับเม็ดเลือดขาว ไม่สามารถทำตามแนวปฏิบัติของกองอาหารและยา กระทรวงสาธารณสุขได้ เนื่องจากปัญหาความพร้อมของผู้ป่วย และความแตกต่างในการปฏิบัติของแพทย์แต่ละคน*

สรุป*: จากผลการศึกษาพบว่าภาวะ neutropenia ไม่ได้เกิดขึ้นบ่อยและไม่พบภาวะ leukopenia และ agranulocytosis อย่างไรก็ตาม ยังมีการวิจัยอื่นๆ ที่พบภาวะดังกล่าวในค่าอุบัติการณ์ที่แตกต่างกันไป การเจาะเลือดเพื่อดูระดับเม็ดเลือดขาวต่ำยังถือว่าเป็นสิ่งที่จำเป็น*