Incidence of Leukopenia and Agranulocytosis in 239 Thai patients treated with Clozapine

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Abstract

Objectives Clozapine was re-introduced again in Thailand on March 24, 1995 with WBC monitoring but there was no report concerning this issue. Therefore, the objectives of this study are: (1) to find out the incidence of clozapine induced neutropenia or agranulocytosis on Thai patients, (2) to compare results with other countries, and (3) to examine the currently monitoring system and propose a better national registry.

Method WBC records of 239 Thai patients receiving clozapine between January 1, 1997 and September 30, 1998 were collected and analysed. The US definitions of mild, moderate, and severe leukopenia were used. Rates of leukopenia, agranulocytosis, and fatalities were reported in number and percentage.

Results No neutropenia or agranulocytosis was found. Only 1.4% of clozapine treated patients at the 6-12 month period and 2.4% at the 12-18 month period had WBC in the range of 3500 - 4000/ mm^3.

Conclusions Although our data did not show the risk of developing clozapine induced leukopenia or agranulocytosis, it does not mean that we do not have such problems. The author recommends development of a centralized national registry for clozapine therapy to ensure safety of using clozapine nationwide and to serve as a tool for quality assurance. **J Psychiatr Assoc Thailand 2000; 45(3): 229-236.**

Key words: clozapine, neutropenia, agranulocytosis, WBC monitoring, Thai patients

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Introduction

Clozapine was identified in 1959 as the first atypical antipsychotic with activity against both positive and negative symptoms of schizophrenia[1]. Clinical studies from the early 1970s indicated that clozapine showed a great promise of becoming the treatment of choice for a broad spectrum of psychotic disorders[1-3]. In addition, clozapine was found to have a distinctive safety profile. Its use was associated with minimal extrapyramidal side effects[4], minimal elevations in plasma prolactin concentrations and a very low incidence of neuroleptic malignant syndrome[5]. However, other side effects were concerned such as sialorrhea and idiopathic agranulocytosis - a condition which can be life-threatening if undetected and it requires more innovative approaches to patient management[6,7].

Clozapine was firstly marketed in Thailand in 1973 with the brand name of Leponex. In the mid-1970s, 17 Finnish patients developed agranulocytosis from a group of 35,000 persons who had received treatment with clozapine[9]. Eight of these patients who took clozapine in conjunction with a variety of other drugs developed severe infections and died[10]. This led to a withdrawal of clozapine in many countries[1], including Thailand in the year 1976.

Subsequently, a number of patients who had previously responded to clozapine experienced relapses. Protests from German psychiatrists led to the reintroduction of clozapine in a few countries under rigorous controlled conditions[1]. The turning point in the history of clozapine came in 1988 with the publication of 2 landmark comparative trials demonstrating the efficacy of clozapine in a significant proportion of treatment-resistant schizophrenic patients[11, 12].

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[1]. In Thailand, clozapine was also approved and reintroduced into the market on March 24, 1995 with the brand name of Clozaril[13].

The 1% to 2% incidence of agranulocytosis observed in early clinical trials, in the absence of a highly structured blood monitoring system, resulted in clozapine's use being limited to therapy for treatment-resistant schizophrenia and necessitated the worldwide development of stringent surveillance procedures to ensure its safe use. Different approaches to monitor the use of clozapine have been developed in different countries to meet the local regulatory requirements. However, a general practice is "no blood, no drug" policy.

In Thailand, all patients who are prescribed clozapine are required to have weekly white blood cell (WBC) monitored during the first 18 weeks and then monthly WBC monitoring for the whole period of clozapine therapy.

Thai psychiatrists who prescribe clozapine are required to fill forms and give a comment whether WBC count is in a normal range (> 3,500/mm^3). Patients then take these forms and the prescriptions to hospital pharmacists to verify with the regulations before dispensing clozapine.

Although clozapine was reintroduced in Thailand in 1995 with the requirement of WBC monitoring systems as described above, but there was no report of the incidence of leukopenia or

agranulocytosis related to the drug. This study therefore aimed at finding results of clozapine-related WBC monitoring in Thailand especially during the first 12 months of the treatment and comparing with findings elsewhere. It also examine currently monitoring systems in order to improve the national registry.

Materials and Methods

All WBC records of patients receiving clozapine in 8 hospitals in Bangkok metropolitan area from January 1, 1997 to September 30, 1998 were collected by the staff of the Novartis (Thailand) and the data were then analysed by the author. Definitions of mild, moderate, and severe leukopenia were used according to the current US definitions (Table 1). Rates of leukopenia, agranulocytosis, and fatalities were reported in number and percentage. Rates were compared to other countries where data were available.

Results

During the first period of 21 months of clozapine treatment, there were 239 Thai patients visiting 8 hospitals in Bangkok metropolitan area who had WBC recording forms (Table 2). No patient had leukopenia according to the current US definitions (WBC < 3500 mm^3). Only 1 of 71 patients (1.4 %) at the 6-12 month period and 1 of 42 patients (2.4 %) at the 12-18 month period had WBC in the range of 3500-4000/ mm^3. Overall, about one quarter of patients showed WBC above 8000/mm^3 (Table 3). No patient developed agranulocytosis and no fatalities were reported. In other countries the data are shown in Table 4.

Table 1 Current US definitions for mild, moderate, and severe leukopenia[2]

Mild leukopenia	WBC 3000-3500/mm^3
	ANC > 1500/mm^3
Moderate leukopenia	WBC 2000-3000/mm^3
	ANC 1000-1500/mm^3
Severe leukopenia	WBC < 2000/mm^3
	ANC 500-1000/mm^3

Table 2 Number (percentage) of Thai patients who had WBC count monitoring according to hospital and sex

Hospital	Female	Male	Total
Chulalongkorn	1 (0.9)	5 (3.8)	6(2.6)
Phramongkutklao	39 (36.8)	56 (42.1)	95 (39.7)
Phya Thai 1	9 (8.5)	8 (6.0)	17 (7.1)
Ramathibodi	3 (2.8)	5 (3.8)	8 (3.3)
Siriraj	7 (6.6)	2 (1.5)	9 (3.8)
Somdet Chaopraya	14 (13.2)	18 (13.5)	32 (13.4)
Srithunya	20 (18.9)	25 (18.8)	45 (18.8)
Vajira	13 (12.3)	14 (10.5)	27 (11.3)
Total	**106 (100)**	**133 (100)**	**239 (100)**

Table 3 Number (percentage) of Thai patients who had WBC count monitoring during 21 months period of clozapine treatment

monthly period / WBC (mm^3)	< 6	6-12	12-18	>18	Total
< 3500	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
3500-4000	0 (0)	1 (1.4)	1 (2.4)	0 (0)	2 (0.8)
4000-5000	6 (5.8)	14 (19.7)	7 (16.6)	0 (0)	27 (11.3)
5000-6000	17 (16.5)	15 (21.1)	10 (23.8)	3 (13.0)	45 (18.8)
6000-7000	22 (21.4)	14 (19.7)	9 (21.4)	4 (17.4)	49 (20.5)
7000-8000	26 (25.2)	10 (14.1)	10 (23.8)	7 (30.5)	53 (22.2)
>8000	32 (31.1)	17 (24.0)	5 (12.0)	9 (39.1)	63 (26.4)
Total	**103 (100.0)**	**71 (100.0)**	**42 (100.0)**	**23 (100.0)**	**239 (100.0)**

Table 4 Rates (percentage) of agranulocytosis and fatalities reported with various monitoring systems.

System	Country	No. patients exposed	Agranulocytosis	
			Cases	Fatalities
-	Thailand*	239	0	0
CPMS	Australia	6969	46 (0.7)	0
CSAN	Canada	8414	63 (0.7)	1 (0.01)
CPMS	U.K.	15733	112 (0.7)	2 (0.01)
CNR	U.S.	172938	1856 (1.1)	19 (0.01)

* in Thailand, at the study period there was no centralized national registry system and the available data came from 8 hospitals in Bangkok metropolitan area.

Abbreviations : CPMS = Clozaril Patient Monitoring System
CSAN = Clozaril Support and Assistance Network
CPMS = Clozaril Patient Monitoring Service
CNR = Clozaril National Registry

Discussion

Before clozapine was reintroduced in the US market (pre-commercialization, a period before February 1990), the leukopenia rate was 2.8% and the agranulocytosis rate was estimated at 1% to 2%[14]. After 5-year period between February 1990 and December 1994, a total of 99,502 patients were registered with the Clozaril National Registry (CNR) and treated with clozapine. Of these, 2,931 (2.9 %) developed leukopenia (WBC < 3500 mm^3). An additional 382 patients (0.4 %) developed agranulocytosis[14]. The latest CNR data reported as of early May 1998, there have been 172,938 patients were exposed to clozapine therapy and of whom 1856 (1.1 %) developed agranulocytosis[2].

Although our data in Thailand does not show the risk of developing clozapine-induced leukopenia or agranulocytosis, it does not imply that we are free from problems related to clozapine effects. As there are some limitations from this study. First, fewer WBC recording forms were collected than expected because some hospitals did not keep records as other important documents or perhaps some hospitals did not strictly follow the rule of "no blood, no drug". Second, some forms were not completely recorded. Third, these forms were at first designed to warn doctors for checking WBC before dispensing clozapine and not required too much time from doctors to fill in, so they did not include other data of patients such as age, diagnosis, etc. which may be important for analyse these variables. Fourth, we do not have a systematic centralized and computerized

system, so we can not trace back some data. The author recommends development of a centralized national registry for all patients receiving clozapine treatment. In the United States, the Clozaril National Registry (CNR) has 5 major principles : rechallenge protection, centralized patient registration, weekly WBC monitoring, limited 7-day distribution of the medication, and quality assurance[14].

Flexibility is needed if we want to adopt a CNR-like system in Thailand. A 1-week supply of medication may not be suitable for patients living in rural areas far away from the tertiary care hospitals. Patients may receive a 2-to-4 week supply of medication but should be instructed on the importance of having blood test performed weekly during the first 18 weeks at the nearby district health office or community hospital. Compliance is a key factor overseen by the registry. Compliance is much more than simply the patient taking his or her medication. In addition, the patient must complete regularly scheduled blood draws and the physician must ensure that the results are reported to the registry. Only effective WBC monitoring system in Thailand can ensure that clozapine be used safely and patients can benefit from the drug despite its association with the serious, and sometimes life-threatening, risk of agranulocytosis.

Conclusion

During the first period of 21 months of the clozapine treatment, no neutropenia or agranulocytosis developed among 239 Thai patients. The author recommends development of a centralized national registry for clozapine therapy to ensure the safety of using clozapine nationwide and to serve as a tool for quality assurance.

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อุบัติการณ์ของ leukopenia และ agranulocytosis ในผู้ป่วยไทย 239 ราย ที่ได้รับยาโคลซาปีน

*พิเชฐ อุดมรัตน์ พบ.**

บทคัดย่อ

วัตถุประสงค์ โคลซาปีนถูกนำเข้ามาจำหน่ายในประเทศไทยอีกครั้งเมื่อวันที่ 24 มีนาคม 2538 โดยมีข้อแม้ว่า ผู้ป่วยจะต้องรับการตรวจเลือดเพื่อตรวจนับจำนวนเม็ดเลือดขาวก่อนว่ามีจำนวนมากกว่า 3500 มม^3 ขึ้นไป จึงจะได้รับยาโคลซาปีน แต่นับจนถึงปัจจุบันยังไม่มีผู้ใดได้รายงานถึงอุบัติการณ์ของการเกิด neutropenia หรือ agranulocytosis จากยาโคลซาปีนในผู้ป่วยไทยมาก่อน รายงานนี้จึงมีวัตถุประสงค์เพื่อ : (1) หาอุบัติการณ์ของการเกิด leukopenia หรือ agranulocytosis จากยาโคลซาปีนในผู้ป่วยไทย (2) เปรียบเทียบอุบัติการณ์ดังกล่าวกับข้อมูลจากประเทศอื่น และ (3) นำเสนอการปรับปรุงวิธีเก็บบันทึกผลการตรวจนับเม็ดเลือดขาว (monitoring system) ในผู้ป่วยไทยที่ได้ยาโคลซาปีน

วิธีการศึกษา ได้วิเคราะห์แบบบันทึกการตรวจนับเม็ดเลือดขาวในผู้ป่วยที่ได้รับยาโคลซาปีนในช่วงวันที่ 1 มกราคม 2540 ถึง 30 กันยายน 2541 โดยแบ่งความรุนแรงของ leukopenia ตามคำจำกัดความที่ใช้ในประเทศสหรัฐอเมริกา และรายงานผลอัตราการเกิด leukopenia, agranulocytosis และ fatality เป็นจำนวนและร้อยละ

ผลการศึกษา ไม่พบว่ามีอุบัติการณ์ของการเกิด neutropenia หรือ agranulocytosis ในผู้ป่วยจำนวน 239 ราย ที่ได้รับยาโคลซาปีนในช่วงดังกล่าว โดยพบมีเม็ดเลือดขาวน้อยที่สุดอยู่ในช่วง 3,500-4,000 มม^3 เพียงร้อยละ 1.4 และร้อยละ 2.4 ในผู้ป่วยที่ได้รับยาไปแล้ว 6-12 เดือน กับ 12-18 เดือนตามลำดับ

สรุป แม้การศึกษานี้จะไม่พบความเสี่ยงของการเกิด leukopenia หรือ agranulocytosis จากยาโคลซาปีน แต่ไม่ได้หมายความว่าจะไม่มีปัญหานี้เกิดขึ้นในประเทศไทย เพราะมีข้อจำกัดในการศึกษาบางประการ รวมทั้งข้อจำกัดจากแบบบันทึกการตรวจนับเม็ดเลือดขาวที่ใช้อยู่ในปัจจุบัน ผู้รายงานจึงเสนอให้มีการบันทึกและเก็บข้อมูลการตรวจนับเม็ดเลือดขาวในผู้ป่วยไทยที่ได้ยาโคลซาปีนอย่างเป็นระบบ โดยรวบรวมไว้เป็นข้อมูลส่วนกลางของประเทศ และมีการตรวจสอบความสมบูรณ์ของการบันทึกอยู่เสมอ **วารสารสมาคมจิตแพทย์แห่งประเทศไทย 2543; 45(2): 229-236.**

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