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Hematological safety of olanzapine

Bezpieczeństwo hematologiczne olanzapiny

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Abstract

Olanzapine is an atypical antipsychotic medication, previously expected to be safe in terms of hematological side effects and considered an alternative choice to clozapine in patients who develop hematotoxicities. However, since olanzapine was introduced to the market many case reports have been published revealing that it could cause hematotoxicity. Some of these reports also indicated that olanzapine induced agranulocytosis. Therefore, we conducted a systemic review to explore and address this issue. Electronic database searches from 1998 to 2015 yielded 35 case reports of olanzapine-induced leukopenia and three related systematic reviews. The onset of leukopenia for the majority of these case reports followed in the first month of administration of olanzapine. Moreover, more than two third of these cases never developed drug-related leukopenia before the use of olanzapine. The ages of affected individuals were 16 to 83 years old and their races were African, Caucasian, Asian, Jewish and Mediterranean. The doses of olanzapine ranged from 2.5 to 30 mg. Interestingly, olanzapine was associated with third highest incidence of neutropenia among antipsychotics. The mechanism of olanzapine-induced neutropenia is still unknown, but could be similar to clozapine because of similar chemical composition. Therefore we recommend that the guidelines regarding olanzapine need to be reconsidered and closely monitored with patients being treated with olanzapine for hematological side effects.

Key words: olanzapine, neutropenia, leukopenia, agranulocytosis

Streszczenie

Olanzapina to nietypowy lek przeciwpsychotyczny, dotychczas uznawany za bezpieczny pod względem hematologicznym i stosowany jako alternatywa dla klozapiny u pacjentów z objawami hemotoksyczności. Jednak od czasu wprowadzenia tego leku na rynek pojawiło się wiele doniesień dotyczących jego hematologicznych działań niepożądanych. Niektóre z tych prac wskazują także, że olanzapina może wywoływać agranulocytozę. Celem przeprowadzonego przeglądu systematycznego było zbadanie tego zagadnienia. W elektronicznych bazach danych z lat 1998–2015 odnaleziono 35 doniesień dotyczących leukopenii indukowanej olanzapiną oraz trzy podobne przeglądy systematyczne. W większości przypadków leukopenia rozwijała się po pierwszym miesiącu stosowania tego leku. Ponadto w ponad dwóch trzecich przypadków leukopenia nie występowała w przeszłości. Pacjenci byli w wieku 16–83 lat i należeli do ras afrykańskiej, kaukaskiej, azjatyckiej, żydowskiej i śródziemnomorskiej. Olanzapinę stosowano w dawkach od 2,5 do 30 mg. Co ciekawe, lek ten był na trzecim miejscu wśród leków przeciwpsychotycznych pod względem wywoływania neutropenii. Mechanizm neutropenii wywołanej olanzapiną pozostaje nieznany, ale może być zbliżony do klozapiny ze względu na podobny skład chemiczny. W związku z powyższym uważamy, że wytyczne dotyczące olanzapiny należy na nowo przemyśleć, a pacjentów stosujących ten lek trzeba obserwować pod kątem występowania hemotoksyczności.

Słowa kluczowe: olanzapina, neutropenia, leukopenia, agranulocytoza

INTRODUCTION

Olanzapine is an atypical antipsychotic medication used to treat schizophrenia and other related psychiatric disorders. Therapy with olanzapine offers some benefits comparing to other atypical antipsychotics. One of them is that olanzapine may be considered the most effective drug among atypical antipsychotics after clozapine for schizophrenia based on Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study and meta-analysis head-to-head comparisons with second generation antipsychotics (Lieberman *et al.*, 2005; Leucht *et al.*, 2009). However, olanzapine and clozapine causes more frequent weight gain than other atypical antipsychotics. In addition to that, there is a potential serious side effect of olanzapine unknown before and related to hematotoxicities such as leukopenia (white blood cell count $<3.5 \times 10^9/L$), neutropenia (absolute neutrophil count $<1.5 \times 10^9/L$), and agranulocytosis (WBC $<1 \times 10^9/L$, and neutrophils $<0.5 \times 10^9/L$).

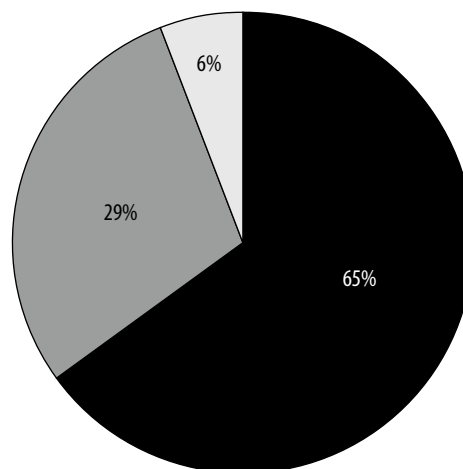
In the past, olanzapine was expected to mitigate the risk of hematotoxicities (Naumann *et al.*, 1999) and was recommended as a safe alternative for patients taking clozapine who had developed hematotoxicity (Oyewumi and Al-Semaan, 2000). However, since olanzapine was introduced on the market several cases reports have been published revealing that it could cause hematotoxicity. Some of them indicated that olanzapine induced agranulocytosis, although during premarketing clinical trials for olanzapine provided no evidence of hematotoxicity (Buchman *et al.*, 2001). Because of that, concerns raised regarding hematological safety of olanzapine. Up to date no review discussed this topic, so we have conducted a systematic review to explore and address this issue.

METHODS

We have searched Medline/PubMed, Google Scholar, OVID and Embase search engines for published articles in English language between 1998 and 2015 for the following search combinations: (olanzapine or Zyprexa) AND (leukopenia OR neutropenia OR agranulocytosis OR white blood cells OR hematotoxicities). Databases search was limited to human studies. Several strings of additional search terms have been used to search for additional papers in all four databases.

RESULTS

Total of 38 publications were identified: three related systematic reviews and 35 case reports (Tab. 1). Case reports of olanzapine-related leukopenia were divided into three groups, as shown in the table: prolongation of clozapine-induced leukopenia with olanzapine use, olanzapine-induced leukopenia after previous hematological toxicity due to antipsychotic use, and olanzapine-induced leukopenia in patients who have never developed drug-related leukopenia (Fig. 1).



■ Group A: PT never developed drug-related leukopenia
 ■ Group B: PT have previous hematological toxicity
 ■ Group C: PT with prolongation of clozapine-induced leukopenia with olanzapine use

Fig. 1. Classification of patients who developed leukopenia after taking olanzapine

The cases included patients aged 16 to 83 years and their races included African, Caucasian, Asian, Jewish and Mediterranean. Doses ranged from 2.5 to 30 mg. Onset of hematotoxicity after treatment beginning varied from the first day to 2–3 years, but most commonly followed within the first month (Fig. 2).

The main diagnoses related to primary psychotic disorders, except 2 cases of systemic lupus erythematosus (Salviati *et al.*, 2012; Su *et al.*, 2007) and Parkinson's-related psychiatric disorders (Meissner *et al.*, 1999). In the majority of cases, management and recovery was limited to discontinuing olanzapine, but a few patients with severe neutropenia received granulocyte-colony stimulating factor (G-CSF) and antibiotics (Stip *et al.*, 2007; Su *et al.*, 2007). Hematotoxicities were reversible in all reported cases except one in which the patient died, possibly because of myelodysplastic syndrome (Stip *et al.*, 2007).

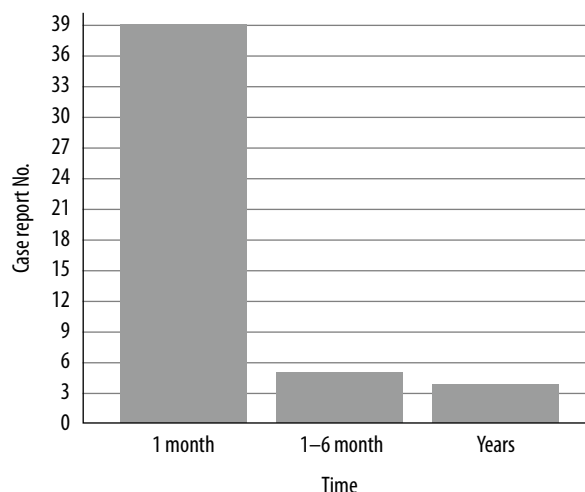


Fig. 2. Onset of leukopenia in patients taking olanzapine

Author, year	Age/Sex/Ethnicity	Dose/Time	Side effect/History of drug-related hematotoxicity
Abdullah <i>et al.</i> , 2003	21/M/African American	30 mg/5 days	Leukopenia, neutropenia
Benedetti <i>et al.</i> , 1999	31/F/White	15 mg/within 1 st week	Neutropenia/Clozapine
Buchman <i>et al.</i> , 2001	46/M/N/A	10 mg/3 weeks	Symptomatic, leukopenia
Cordes <i>et al.</i> , 2004	16/F/White 68/M/N/A 35/M/N/A	20 mg/6 weeks Up to 40 mg/1.5 year 10 mg/single dose	Neutropenia Neutropenia/Haloperidol, levomepromazine Neutropenia
Delieu <i>et al.</i> , 2006	22/F/N/A	20 mg/few weeks	Neutropenia
Dettling <i>et al.</i> , 1999	24/F/Caucasian 27/F/Caucasian	15 mg/5 days 5–7.5 mg/5 weeks	Leukopenia Leukopenia, neutropenia
Duggal <i>et al.</i> , 2004	17/ F/African	25 mg/12 days	Neutropenia
Freedman <i>et al.</i> , 2011	16/M/N/A	15 mg/10 days	Symptomatic agranulocytosis
Gajwani and Tesar, 2000	20/M/African	10 mg/5 days	About neutropenia/Risperidone
Grover <i>et al.</i> , 2012	23/M/N/A	7.5 mg/2 weeks	Leukopenia/Clozapine
Hong and Wang, 2001	19/F/N/A	5 mg/17 days	Agranulocytosis/Clozapine, perphenazine
Jagadheesan and Mehrstens, 2007	32/F/N/A	20 mg/8 days	Prolongation of leukopenia after cessation of clozapine/Clozapine
Kodesh <i>et al.</i> , 2001	42/F/N/A 18/F/N/A 22/F/N/A	10 mg/2 weeks 20 mg/3 weeks 20 mg/2 weeks	Leukopenia, neutropenia Leukopenia, neutropenia Leukopenia, neutropenia
Konakanchi <i>et al.</i> , 2000	39/W/African American	10 mg/14 days	Neutropenia/Clozapine
Lander and Bastiampillai, 2011	59/F/Caucasian	10 mg/2 days	Neutropenia/Quetiapine and aripiprazole
Lin and Chien, 2012	27/F/Asian	20 mg/19 days	Symptomatic leukopenia, neutropenia, thrombocytopenia
Malhotra <i>et al.</i> , 2015	27/M/Caucasian	15–20 mg/N/A	Neutropenia
Mehta and Sanitato, 2005	83/F/Italian	2.5 mg/1 st day	Symptomatic pancytopenia
Meissner <i>et al.</i> , 1999	56/F/N/A 58/M/N/A	15 mg/4 months 5 mg/13 months	Leukopenia Leukopenia/Clozapine
Montgomery, 2006	19/F/African	20 mg/8 days	Leukopenia, neutropenia
Naumann <i>et al.</i> , 1999	27/M/N/A	40 mg/9–10 days	Symptomatic leukopenia, agranulocytosis
Salviati <i>et al.</i> , 2012	25/F/Chinese	20 mg/2 days	Leukopenia, agranulocytosis
Sayin and Cosar, 2006	21/M/N/A	10 mg/during 2–3 years	Leukopenia, neutropenia/Clozapine
Schuld <i>et al.</i> , 2000	26/F/N/A	5–10 mg/14 days	Neutropenia/Clozapine
Steinwachs <i>et al.</i> , 1999	81/F/N/A 44/M/N/A	10 mg/17 days 20 mg/5 months	Leukopenia, neutropenia Neutropenia
Stergiou <i>et al.</i> , 2005	69/F/Caucasian	10 mg/17 days	Leukopenia, neutropenia
Stip <i>et al.</i> , 2007	30/M/Caucasian	15–20 mg/6 months	Agranulocytosis
Stübner <i>et al.</i> , 2004	5 patients/N/A	N/A	Neutropenia
Su <i>et al.</i> , 2007	44/F/N/A	5 mg/12 days	Symptomatic, leukopenia, agranulocytosis
Teter <i>et al.</i> , 2000	48/M/Black 60/M/Black	30 mg/1–2 weeks 20 mg/17 months	Neutropenia/Clozapine Leukopenia, neutropenia
Thangadurai <i>et al.</i> , 2006	31/M/Asian	N/A/3 rd week	Leukopenia/Clozapine
Thinn <i>et al.</i> , 2007	45/F/Chinese	15 mg/13 months	Leukopenia, neutropenia
Tolosa-Vilella <i>et al.</i> , 2002	46/M/N/A	5 mg/15 days	Symptomatic agranulocytosis
Wray and Sztuke-Fournier, 1998	N/A	N/A N/A N/A N/A N/A 20 mg	Granulocytopenia Leukopenia Pancytopenia Leukopenia/Clozapine Leukopenia/Clozapine Unknown
Wu <i>et al.</i> , 2008	40/F/Taiwanese	10 mg/5 days	Prolongation of leukopenia after discontinuation of clozapine/Clozapine therapy

Tab. 1. Review of case reports regarding olanzapine induced hematological toxicity

The criteria for determining the causal relationship between a drug and hematological abnormalities (e.g. neutropenia) that have to be applied included: 1) necessary administration of drug within 10 days prior to hematological reaction; 2) recovery of the patient after discontinuation of therapy; 3) no immunosuppressive agents or radiotherapy administered during 6 weeks prior to onset of hematological abnormalities; 4) no systematic disease could cause leukopenia; 5) there has to be only one

possible cause of hematological abnormalities (Freedman *et al.*, 2011).

DISCUSSION

Neutropenia and agranulocytosis are the most important drug-related blood dyscrasias (Flanagan and Dunk, 2008). Benign leukopenia occurred in 10% of patients treated with antipsychotic medication (Gajwani and Tesar,

2000), and agranulocytosis occurred in 0.5% of patients treated with first-generation antipsychotic medications (Su *et al.*, 2007). The incidence of clozapine-induced agranulocytosis was between 0.5 and 2%. New atypical antipsychotic medications, such as risperidone, olanzapine, quetiapine, aripiprazole and ziprasidone, were associated with leukopenia. Overall, among antipsychotic medications, olanzapine was associated with third highest incidence of neutropenia (Flanagan and Dunk, 2008) and the second after clozapine among atypical antipsychotic medications. The mechanism of olanzapine inducing granulocytopenia is still unknown. However, since the chemical structure of olanzapine has some similarities to clozapine, several studies hypothesized that they may have common mechanisms that cause neutropenia.

Studies have hypothesized that clozapine and olanzapine-induced granulocytopenia are caused by genetic, toxic and immunological factors. Genetic predisposition such as some human leukocyte antigens subtypes (e.g. HLA-DQB*05) are linked to clozapine and olanzapine induced agranulocytosis (Dettling *et al.*, 1999).

Some investigators suggested that metabolites of clozapine and olanzapine are toxic to neutrophils. They caused rise of nitrenium ions based on oxidative metabolism. These ions were usually detoxified by reducing glutathione. In case of neutropenia, bond of the nitrenium ions and neutrophils resulted in cell death (Fig. 3). Another possible mechanism related to an immune reaction, such as the formation of antineutrophil antibodies due to the reaction of nitrenium ions with neutrophil protein, resulting in hapten formation (Flanagan and Dunk, 2008).

Schuld suggested that clozapine and olanzapine could compromise granulocytopenia by common mechanism, interfering with the G-CSF. He measured the plasma level of G-CSF of a schizophrenic patient took clozapine. In the last 4 weeks of clozapine, G-CSF parallely declined with decreasing granulocyte counts. The study confirmed that the level of G-CSF was undetected at the lowest level of granulocyte counts. After discontinuation of therapy with clozapine, both the G-CSF level and granulocyte increased and decreased again, once olanzapine was administered. Moreover, the level of G-CSF was undetected at the lowest level of granulocyte counts. The study concluded that hematopoietic growth factor (G-CSF) could play a significant

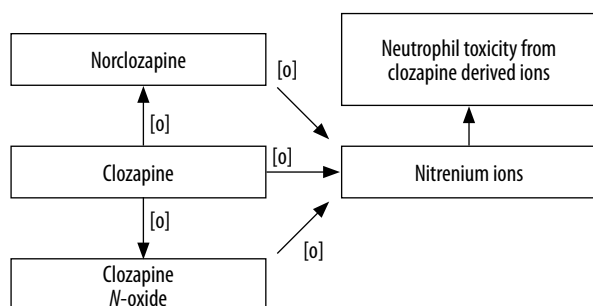


Fig. 3. Metabolism of clozapine (Flanagan and Dunk, 2008)

role in pathophysiology of clozapine and olanzapine, inducing granulocytopenia (Schuld *et al.*, 2000).

The mortality rate of agranulocytosis before the use of antibiotics was up to 80% in the past (Flanagan and Dunk, 2008). However, with early detection of these cases and appropriate management, including use of antibiotics, the mortality rate from drug-induced agranulocytosis is at present below 10%. Therefore, it is crucial to perform a close hematological surveillance for a patient taking medication-induced agranulocytosis, such as clozapine and olanzapine.

Current guidelines, such as those issued by the National Institute for Health and Care Excellence, recommended that patients on antipsychotics, including olanzapine, should perform a full blood count at a baseline and a year thereafter to monitor the hematological effect of antipsychotics (Taylor *et al.*, 2012). Nevertheless, with the increasing incidence of olanzapine-induced leukopenia, several authors have recommended to change the current guidelines regarding monitoring of hematological adverse effects and hence earlier detect agranulocytosis cases (Benedetti *et al.*, 1999; Freedman *et al.*, 2011; Thinn *et al.*, 2007).

Some studies suggested screening for risk factors related to olanzapine induced-agranulocytosis in patients who are going to take olanzapine. Based on screening, patients should be divided into high and low risk to develop granulocytopenia. High-risk patients shall include anyone with identified following risk factors: a history of hematological diseases, previous or family history (genetic determination) of drug-induced granulocytopenia. With regard to the high-risk group, some authors have recommended to perform complete blood count (CBC) once a month within the first three months (Freedman *et al.*, 2011). Having said that, the onset of leukopenia for the most of the case reports occurred in the first four weeks, so it is wisely to perform CBC frequently, on a weekly basis during the first month of treatment, then at 6 months, and once a year thereafter. For low-risk patients who do not have any risk factors of granulocytopenia, we suggest to monitor WBC (white blood cells)/ANC (absolute neutrophil counts) after the first month of treatment, at 6 months, and at 1 year. In cases of patients who develop signs of infection, such as fever, evaluation of WBC/ANC should be considered.

CONCLUSION

Because olanzapine is associated with the third highest incidence of neutropenia among neuroleptics, we want to raise a concern about the hematological side-effect of olanzapine and recommend careful monitoring of patients taking this medication. Those patients have to be screened for risk factors of olanzapine-induced neutropenia. The frequency of WBC/ANC is determined based on presence (high risk patient) or absence of risk factors (low risk patient). Finally, because of the small body of literature regarding the hematotoxic side effects of olanzapine, we encourage further research to understand the mechanism by which olanzapine

causes granulocytopenia. The identification of risk factors could facilitate the development of new surveillance guidelines for patients taking olanzapine.

Conflict of interest

The authors do not report any financial or personal relationships with other persons or organizations that could adversely affect the content of the publication and seek claim to this publication.

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