DOI: 10.5455/bcp.20120704065248

Evaluation of the Incidence of Leukopenia and Agranulocytosis in Patients Receiving Combined Clozapine and Other Antipsychotics

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ÖZET:

Klozapin ile birlikte başka bir antipsikotik kullanan hastalarda lökopeni ve agranülositoz sıklığının değerlendirilmesi

Amaç: Bu çalışmada klozapin ile birlikte başka bir antipsikotik kullanan hastalarda lökopeni ve agranülositoz sıklığının klinik pratikte değerlendirilmesi amaçlanmaktadır.
Yöntem: Bu çalışma verileri 2011 yılında Samsun Ruh Sağlığı ve Hastalıkları Hastanesi yataklı tedavi ünitesinde takip edilen şizofreni hastalarının dosya verilerinin geriye dönük incelenmesi ile elde edilmiştir. Klozapin ile birlikte kullanılan antipsikotikler ve dozları, hastaların yaşı, cinsiyeti, tedavinin izlem süresi (hafta), izlemleri sırasındaki lökosit düzeyleri tespit edilmiştir. Klozapin ile birlikte kullanılan farklı antipsikotikler ile lökosit düzeyleri (3500-4000, 3000-3499 ve <2000) arasındaki kategorik sınıflandırılmasının karşılaştırılması değerlendirilmeye alınmıştır.
Bulgular: Bu çalışma 92 hastanın verilerini içermektedir. Çalışma grubunun yaş ortalaması 40.9±10.8 (yaş aralığı: 21-70) idi. Cinsiyetler; 31 (%33.7) kadın, 61 (%66.3) erkek olarak saptanmıştır. Klozapin ile birlikte kullanılan antipsikotiklerin oranları; amilsülpirid 27 (%29.3), risperidon 20 (%21.7), ketiapin 20 (%21.7), olanzapin 10 (%10.3), haloperidol 8 (%8.7), paliperidon 4 (%4.3), aripiprazol 3 (%3.3) olarak saptanmıştır. Bu kombinasyonların ortalama 8.5±9.4 haftalık (2-52 hafta) tedavi izlemi sırasında; lökosit düzeyi 3500-4000 µL aralığında olan 2 (%2.1) (olanzapin: 1 ve haloperidol: 1), 3000-3499 µL aralığında olan 2 (%2.1) (risperdon: 2) ve 2000 µL altında 1 (%1.1) hasta (risperdon: 1) saptanmıştır. Klozapin ile birlikte kullanılan bu farklı antipsikotikler ile lökosit düzeyi 3500-4000 µL, 3000-3499 µL ve <2000 µL düzeyinde olanlar ile >4000 µL olanlar karşılaştırıldığında her iki grup dağılımları arasında istatistiksel anlamlı bir ilişki saptanmamıştır. Lökosit düzeyi <3500 µL düzeyinde saptanan (n=3 (%3.2)) hastalardan; lökosit düzeyi 3000-3499 µL aralığında bulunan hastalar klinik olarak sorunsuz takip edilmiş, bununla birlikte lökosit <2000 olan 1 (1.1%) hasta; agranülositoz ve araya giren infeksiyon sebebiyle fatal seyrettiği saptanmıştır.
Sonuç: Klozapin ile yapılan farklı antipsikotik kombinasyonlarında lökopeni ve agranülositoz oluşturma riski açısından bir farklılık saptanmamıştır. Sonraki çalışmalarla bu bulguların teyit edilmesi gerekir.

Anahtar sözcükler: Klozapin, antipsikotik ilaçlar, lökopeni, agranülositoz

Klinik Psikofarmakoloji Bülteni 2012;22(4):313-9

ABSTRACT:

Evaluation of the incidence of leukopenia and agranulocytosis in patients receiving combined clozapine and other antipsychotics

Objective: In this study, we aimed to evaluate of the incidence of leukopenia and agranulocytosis in patients receiving a combination of clozapine and other antipsychotics in clinical practice.
Methods: The data for this study were collected by retrospective analysis of the charts of patients with a diagnosis of schizophrenia at the Samsun Mental Health and Diseases Hospital in 2011. The dose of clozapine and the doses of other antipsychotics, the ages and genders of the patients, the duration of follow up (weeks) and leukocyte counts during follow up were recorded. The relationship between the use of clozapine and other antipsychotics and the categorical classification of leukocyte counts (3500-4000/µL, 3000-3499/µL or <2000/µL) was determined.
Results: The study included data for 92 patients. The mean age of the patients was 40.9±10.8 years (range: 21-70). Thirty-one (33.7%) were female and 61 (66.3%) were male. The rate of combinations with other antipsychotics included: amisulpride 27 (29.3%), risperidone 20 (21.7%), quetiapine 20 (21.7%), olanzapine 10 (10%), haloperidol 8 (8.7%), paliperidone 4 (4.3%), and aripiprazole 3 (3.3%). During a mean 8.5±9.4 week (2-52 week) follow up with these combinations, leukocyte counts were between 3500-4000/µL in 2 out of 92 patients (2.1%; olanzapine, n=1, haloperidol, n=1), between 3000-3499/µL in 2 patients (2.1%, risperidone, n=2) and lower than 2000/µL in 1 patient (1.1%, risperidone, n=1). No statistically significant difference was detected in the comparison of patients who had leukocyte counts between 3500-4000/µL, 3000-3499/µL or <2000/µL with those who had counts >4000/µL in patients receiving a combination of these different antipsychotics and clozapine. Leukocyte counts were decreased to lower than 3500/µL in 3 (3.2%) patients. Two (2.1%) of these patients who had leukocyte counts of 3000-3499/ µL were followed without any problem and one patient (1.1%), who had a leukocyte count of < 2000 µL followed a fatal course due to agranulocytosis and complicating infections.
Conclusions: No difference was detected with respect to the risk of leukopenia and agranulocytosis with different antipsychotic combinations with clozapine. These findings must be confirmed by further studies.

Key words: Clozapine, antipsychotic drugs, leukopenia, agranulocytosis

Bulletin of Clinical Psychopharmacology 2012;22(4):313-9

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Gönderme tarihi / Date of submission: 22 Mayıs 2012 / May 22, 2012

Kabul tarihi / Date of acceptance: 4 Temmuz 2012 / July 4, 2012

Bağıntı beyanı:
A.A., O.S.: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

Declaration of interest:
A.A., O.S.: The authors reported no conflict of interest related to this article.

INTRODUCTION

Clozapine is the drug of choice in the treatment of schizophrenia in patients who do not respond to a standard treatment or cannot tolerate other antipsychotics (1-3). Clozapine is also a good choice in schizoaffective disorder and treatment-resistant bipolar disorder (4). Although it has many advantages in clinical use, a limiting factor is the possible occurrence of agranulocytosis resulting in infections that might lead to death (5). There are studies in clinical practice reporting that the incidence of agranulocytosis associated with clozapine is between 0.38% and 0.91% (5-7). With periodic follow-up of white blood cell counts in recent years and the decrease in the incidence of agranulocytosis and mortality as a result, clozapine is still used widely (7-9). There have been recent case reports indicating that other atypical antipsychotic medications also lead to leukopenia and agranulocytosis like clozapine (10-12). In cases where high-dose clozapine cannot be used due to an inadequate response to antipsychotic treatment or its side effects, it has been reported that administration of clozapine with typical and atypical antipsychotics is a method of treatment widely used in clinical practice (13-15). Due to the risk of agranulocytosis, periodic follow-up white blood cell counts should be performed in patients who use clozapine. However, there are no studies investigating the incidence of leukopenia and agranulocytosis when administrating clozapine with other antipsychotics. Our purpose in this study was to evaluate the incidence of leukopenia and agranulocytosis in patients who used clozapine with another antipsychotic in clinical practice and to compare the categorical classification between the levels of leukocytes when administrating clozapine with different antipsychotics.

METHODS

The data for this study were obtained through retrospective analysis of the charts of schizophrenic patients who were followed up between January and December 2011 at the inpatient treatment unit of the Mental Health and Diseases Hospital in Samsun. All patients diagnosed with schizophrenia who were taking clozapine with another antipsychotic were included in the study group. The leukocyte level of all patients was > 4000/μL prior to the onset of treatment with clozapine. The doses of clozapine and other antipsychotics, age and gender of the patients, follow-up period of the treatment (weeks) and leukocyte levels during follow-up were recorded. The value range for leukopenia was considered to be <4000/μL. Only the leukocyte levels of each patient, if determined, that were lower than 4000/μL, 3500/μL or <2000/μL were recorded during follow-up. The clinical follow-up reports were evaluated and the clinical conditions relating to the number of leukocytes were recorded. The comparison of the categorical classification of the leukocyte levels with the co-administration clozapine and other antipsychotics (3500-4000/μL, 3000-3499/μL and <2000/μL) with and >4000/μL was evaluated. The relationship between gender, age and the sub-groups of leukocyte levels was assessed. Our study was approved by the Hospital's Ethics Committee of Clinical Research (05.2012/53).

The leukocyte level 3500-4000/μL was considered to be mild-temporary leukopenia, 3000-3499/μL was a medium-level leukopenia and <2000/μL was a serious level leukopenia or agranulocytosis. For the first 18 weeks during administration of clozapine, the leukocyte count is recommended to be checked once a week and afterwards once a month. The following steps are recommended in the clinical evaluation of changes in leukocyte numbers such as leukopenia and agranulocytosis developed during treatment with clozapine: If there is a significant decrease in leukocyte numbers but there are no clinical symptoms of an infection, at normal levels the leukocyte count should be performed twice a week and continued treatment with clozapine is advised. If a repeat leukocyte level shows a 3000-3500/μL, a decrease in clozapine dose and monitoring for signs of infection and continued treatment with clozapine are recommended. Even if there is no sign of infection with leukopenia (2000-3000), discontinuing the treatment of clozapine, isolating the patient against infection, performing the leukocyte count twice a week, and restarting clozapine treatment when the leukocyte level returns to normal are recommended. Even though there is no sign of infection in the presence of agranulocytosis (leukocyte < 2000), discontinuing the treatment of clozapine, isolating the patient, examination of bone marrow and not restarting clozapine are recommended (16,17).

Table 1: The average dose (range), average follow-up period (week) and mean age (age range) for the combination of clozapine with other antipsychotics

	N	%	Clozapine	Antipsychotics	Age	Follow-up Period
Clozapine-Amisulpride	27	29.3	440±180(100-700)	637±184(400-800)	40.6±11.5(21-68)	9.3±11.8(2-52)
Clozapine-Risperidone	20	21.7	375±167(100-600)	5.2±1.7(3-8)	39.6±10.7(27-70)	10.2±11.4(3-52)
Clozapine-Quetiapine	20	21.7	320±159(100-600)	425±229(200-900)	40.9±11.1(27-68)	8.4±7.3(3-28)
Clozapine-Olanzapine	10	10.9	235±156(100-500)	16.0±5.1(10-20)	44.9±11.2(22-59)	8.3±7.8(3-25)
Clozapine-Haloperidol	8	8.7	262±118(100-500)	16.3±5.2(10-20)	38.7±9.0(30-51)	5.6±4.3(3-16)
Clozapine-Paliperidone	4	4.3	275±170(100-500)	7.5±1.7(6-9)	45.0±4.7(42-52)	5.0±1.4(4-7)
Clozapine-Aripiprazole	3	3.3	466±57 (400-500)	15.0±5.0(10-20)	39.0±15.6(29-57)	5.0±1.7(4-7)

Statistical Analysis

The Chi square test was performed to compare the data classified categorically. The parametric t-test was applied to compare the sub-groups of age and leukocyte levels. A p value of <0.05 was considered to be significant.

RESULTS

A total of 92 patients who were on clozapine combined with other antipsychotics were the sampling group for this study. The patients were prescribed clozapine and one of the following: amisulpride (27, 29.3%), risperidone (20, 21.7%), quetiapine (20, 21.7%), olanzapine (10, 10.3%), haloperidol (8, 8.7%), paliperidone (4, 4.3%) or aripiprazole (3, 3.3%) (Table 1). The gender distribution was 31 (33.7%) women and 61 (66.3%) men. The mean age was 40.9±10.8 (21-70). The patients were followed up at the inpatient treatment unit for approximately 8.5±9.4 weeks (2-52 weeks). The average dose of clozapine was 355±175 mg/dl (100-700) for all patients.

For the combinations of clozapine-amisulpride (n=27), clozapine-quetiapine (n=20), clozapine-paliperidone (n=4) and clozapine-aripiprazole (n=3), no leukopenia or agranulocytosis were observed in the patients during follow-up period. For the combination of clozapine-olanzapine (n=10), one (10%) patient presented with leukopenia of 3500-4000/µL (leukocytes= 3800/µL) during monitoring and for the combination of clozapine-haloperidol (n=8), one (12.5%) patient developed leukopenia of 3500-4000/µL (leukocytes= 3700/µL) during follow-up. For the combination clozapine-risperidone (n=20), two (10%) patients presented with leukopenia of 3000-3499/µL (leukocytes= 3400 and 3300/µL) during follow up period. These patients were monitored without clinical worsening. One (5%) of the patients had fatal outcome because of an infection associated with agranulocytosis (leukocytes= 900/µL).

With respect to the comparison of leukocyte levels and categorical classifications for the combination of clozapine with other antipsychotics, in this study, 2 out of 92 patients had 3500-4000/µL (olanzapine (1) and haloperidol (1)), 2 out of 92 patients had 3000-3500/µL (risperidone (2)) and 1 out of 92 patients had a level lower than 2000 µL (risperidone (1)). When comparing those combinations with leukocyte levels 3500-4000/µL, 3000-3499/µL, under 2000/µL and with > 4000/µL, no significantly statistical relationship was observed in the distribution of both groups (p=0.25), (p=0.28), (p=0.72). When comparing the gender with the patients who had leukocyte levels 3500-4000/µL, 3000-3499/µL, under 2000/µL and with >4000/µL, no significant statistical relationship was observed in the distribution of genders (p=0.3, p=0.3, p=0.5).

The average age was 40.9±10.9 in those who had leukocyte levels >4000/µL; it was 43±0.0 for those who had leukocyte levels 3500-4000/µL, 45.0±8.4 for those who had leukocyte levels 3000-3500/µL and 36.0±0 for those who had leukocyte levels under 2000/µL. No significantly statistical difference was observed between all three groups and the ages (p=0.78, 0.50, 0.64). The average dose and numbers of doses, average follow-up period (week), mean age and age range for the combination of clozapine with other antipsychotics are presented in Table 1.

DISCUSSION

Due to the limited or inadequate response to monotherapy with antipsychotics, they are commonly used in combination. In addition to this, depending on clinical monitoring by physicians, the health-care system, the state of the disease, the medication industry, and social

causes, the use of polypharmacy generally occurs in the treatment of schizophrenia (18). It has been reported that the frequency of use of multiple antipsychotics in the treatment of schizophrenia has been 55% in outpatients and up to 90% in inpatients (18-21). The combination treatment has been mentioned to improve the efficacy of the treatment in schizophrenia. On the other hand concomitant use of multiple antipsychotic medications increases the total antipsychotic dose and may result in undesirable side effects (18,22). The data obtained through a ten year-follow-up study showed that mortality rate increased by 2-3 times in cases where multiple antipsychotic medications were used in combination (23).

In cases where high-doses of clozapine cannot be applied due to inadequate response to clozapine or its side effects, combination of clozapine with typical or atypical antipsychotics is generally applied in clinical practice (13-15). The use of clozapine with other antipsychotics (amisulpride, risperidone, quetiapine, olanzapine, haloperidol, paliperidone, aripiprazole) has been reported to improve the efficiency of the treatment (24-27). In this study, clozapine was combined with mostly amisulpride and the other combinations were with risperidone, quetiapine, olanzapine, haloperidol, paliperidone and aripiprazole. The use of clozapine with other antipsychotics has been found to be a common application as much as the use of clozapine alone (28).

The most significant drugs leading to agranulocytosis are chemotherapeutic and antithyroid agents, ticlopyridine, sulfasalazine, dipyrone, trimethoprim/sulfamethoxazole, deferiprone, carbamazepine, and clozapine (29,30). The capacity of clozapine leading to agranulocytosis is considered to be the result of an idiosyncratic reaction, due to the activation of the immune system, an increase in apoptosis of neutrophils, or a direct toxic impact of clozapine on bone marrow (29,31).There are studies reporting that the prevalence of leukopenia associated with clozapine is 0.38-0.91% (5-7). The risk of mortality related to agranulocytosis associated with clozapine is estimated to be 1/10,000. In the 1970's there were deaths that occurred due to agranulocytosis associated with clozapine and then there was a decrease in deaths with required periodic monitoring of leukocyte levels (29,32,33).

In our country, Uzun et al. performed a study with twenty-nine patients who were treated with clozapine for three years and observed no leukopenia or agranulocytosis during their follow-up (8). Furthermore, a study was performed to evaluate the efficacy of clozapine and no leukopenia or agranulocytosis were observed during a two-month follow-up period (34). The data about the contribution of the use of clozapine with other antipsychotics to the risk of agranulocytosis is limited to only one case (35). There is no study in the literature investigating the prevalence of leukopenia and agranulocytosis resulting from the combination of clozapine with other antipsychotics. In this study, during follow-up of inpatient treatment, 2.1% of the patients had leukocyte levels of 3500-4000/μL with the administration of clozapine-antipsychotic combinations for 8.5 weeks. Furthermore, when comparing the different groups of antipsychotics with the patients who had leukocyte levels of 3500-4000/μL and > 4000/μL, no significant statistical difference was found in the distribution of both of the groups. The antipsychotic combined with clozapine was not found to be different from another antipsychotic in terms of producing temporary leukopenia. During the treatment with clozapine, benign and temporary leukopenia was reported to be more common than serious leukopenia and the rate could reach up to 22% (36). In this study, only 2.1% of temporary leukopenia was observed with the combinations of clozapine with antipsychotics. Again in this study, 2.1% of the patients had a leukocyte level of <3000-3499/μL with the combination of clozapine with antipsychotics and those patients were followed up without clinical worsening. One patient (1.1%) had a leukocyte level of <2000/μL and that patient had a fatal outcome due to agranulocytosis and complicating infections during treatment. The patients who had leukocyte levels of 3000-3499/μL and <2000/μL were only administrated the combination of clozapine-risperidone. On the other hand, no significant difference was found between an antipsychotic that was associated with leukopenia or agranulocytosis and other antipsychotics. These findings should be replicated with larger, controlled and prospective studies.

There was no significant statistical difference between gender and age and categorical distribution of leukocyte levels. Also, no significant statistical difference was found between all three groups and the age. Female gender and advanced age are stated to be risk factors for agranulocytosis when applying clozapine (37,38). In this study, there was no relationship determined between the prevalence of

leukopenia or agranulocytosis and gender and age.

In this study, the combination of clozapine-amisulpride was determined to be the most frequently used antipsychotic combination. There are no cases in the literature indicating that amisulpride monotherapy has produced leukopenia or agranulocytosis. In addition, there was no prolonged leukopenia resulting from amisulpride that was applied after agranulocytosis which was produced by clozapine (39). In this study 27 patients did not develop leukopenia or agranulocytosis who used clozapine combined with amisulpride. The use of clozapine and quetiapine was determined to be the most frequently applied combination in this study. There are some cases reported showing that leukopenia has been associated with quetiapine. In addition, leukopenia is reported to be a side effect in the package insert for quetiapine and if it is used with other drugs that might produce leukopenia, the risk will be increased (12,39,40). In this study none of the 20 patients presented with leukopenia or agranulocytosis were on combination of clozapine-quetiapine during follow-up. There has been one case reported that leukopenia was associated with paliperidone and aripiprazole (41,42). On the other hand, the leukopenia that developed with the use of quetiapine resolved after administration of aripiprazole (43). In this study, there was no leukopenia or agranulocytosis that was associated with the use of clozapine combined with both paliperidone and aripiprazole. However, due to the insufficient number of combinations, they should be investigated further in future studies. In this study, 10% of the patients had a mild leukopenia with clozapine-olanzapine and 12.5% of the patients had a mild leukopenia with clozapine-haloperidol and those patients did not show clinical worsening during the follow-up period. There are some case reports stating that olanzapine might produce agranulocytosis or neutropenia (10,39). Furthermore, 33% of the patients presented with prolonged leukopenia during their follow-up period on olanzapine, which was administrated after agranulocytosis caused by clozapine (39).

Ten percent (2) of the patients on combination of clozapine-risperidone developed mild leukopenia and those patients did not present with clinical worsening during their follow-up. Five percent (1) of those patients had a fatal outcome with the use of clozapine-risperidone combination due to agranulocytosis and complicating infections. Risperidone which is a strong D2 blocker has been reported to be the most frequently tried combination with clozapine (1,2,14). Also, risperidone has been determined to raise the blood levels of clozapine (44). There is one agranulocytosis case which presented after administration of risperidone combined with clozapine (35). In addition, there is a placebo-controlled study that investigated the treatment efficiency of clozapine-risperidone with 40 patients. In this study, and during a 12-week follow-up period, there was no difference between risperidone and placebo in terms of agranulocytosis (45). It is quite explicit that there is a risk of agranulocytosis when clozapine is applied alone. An agranulocytosis case associated by risperidone (11) and another agranulocytosis case, that developed after risperidone was added to clozapine, has been reported (35). In this study, there was no statistical difference determined in terms of development of mild or medium leukopenia and the risk of agranulocytosis and mortality with the different combinations of antipsychotics with clozapine. On the other hand, there were cases in this study that showed medium leukopenia and agranulocytosis (fatal course) with only the use of clozapine combined with risperidone. However larger, controlled studies with longer follow-up periods should be performed in order to determine whether these combinations create extra risk or not.

The limitations of this study includes being a retrospective study and the follow-up period was not planned. In addition the sample size was small and the combinations could not be compared due to the insufficient number of inpatients who took only clozapine. Even so, it is valuable in clinical practice because the inpatients represented their inherent data.

CONCLUSIONS

According to the results of this study, no difference was found in terms of the risk of developing leukopenia or agranulocytosis when using clozapine combined with different antipsychotics. Large-scale, randomized, and controlled studies are required to further examine this area.

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