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REVIEW ARTICLE

Clozapine Usage in Turkish Society: A General Review

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Clozapine Usage In Turkish Society: A General Review

Introduction: *There are many studies carried out on clozapine usage and lots of detailed data have been gathered for these studies. However, there are only a few studies done in Turkey. In this article, we decided to review Turkey's data on clozapine usage.*

Method: *Databases have been scanned in order to have access to the studies on Turkey society's usage of clozapine.*

Results: *Five case reports, three follow-up studies and a case comparison study were found. In follow-up and case comparison studies, clozapine is reported to be an efficient treatment option. In the five case reports where the patient developed clozapine related pericarditis, agranulocytosis, obsessive-compulsive behavior, malign neuroleptic syndrome and myoclonia, the treatments were terminated, except for the one case with the obsessive-compulsive disorder, in which the treatment was continued using an additional medication. While it is reported in one of the studies that the treatment was not terminated due to the results of the case, it is reported that 3 of 29 patients in another study had to be released due to side effects.*

Discussion: *Finally, even though it is a well known fact that clozapine is useful in treatment and results in obtaining well-being in resistant schizophrenia cases, both the number of cases with serious side-effects and non-followed cases are very high both in Turkey and abroad. In order to determine the effective dose, dose-side effects relationship, and the dose effectiveness of clozapine in Turkish society, more case reports and better designed studies are necessary.*

Key Words: *Clozapine, side effects, effectiveness*

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Türk Toplumunda Klozapin Kullanımı: Bir Gözden Geçime

Giriş: *Bu zamana kadar klozapinin kullanımıyla ilgili birçok araştırma yapılmış ve oldukça kapsamlı veri toplanmıştır. Ancak Türkiye'den yapılmış olan az sayıda çalışma mevcuttur. Bu makalede klozapin kullanımı ile ilgili olarak Türkiye verilerinin gözden geçirilmesi amaçlanmıştır.*

Yöntem: *Klozapin kullanımı ile ilgili Türk toplumundan yapılmış olan çalışmalara ulaşabilmek için veri tabanları taranmıştır.*

Bulgular: *Beş vaka sunumu, üç izlem çalışması ve bir vaka karşılaştırma çalışmasına ulaşılmıştır. İzlem ve vaka karşılaştırma çalışmalarında klozapinin etkin bir tedavi seçeneği olduğu bildirilmiştir. Klozapine bağlı perikardit, agranülositoz, obsesif kompulsif belirtiler, malign nöroleptik sendrom, myokloni yan etkileri oluşan hastalarla ilgili olgu bildirimlerini içeren beş adet makaleden; sadece obsesif kompulsif semptomların ortaya çıktığı vakada, ek ilaç eklenip tedaviye devam edilirken diğerlerinin tümünde tedavi sonlandırılmıştır. İki izlem çalışmasından birinde, yan etkiden dolayı tedavinin sonlandırıldığı vakanın bulunmadığı sonucu bildirilmişken, diğerinde 29 hastadan üçünde yan etkiden dolayı tedavinin sonlandırıldığı bildirilmiştir.*

Tartışma: *Sonuç olarak; klozapinin dirençli şizofreni hastalarında belirgin düzelme sağladığı bilinmekle birlikte yan etki görülmesi ve tedaviye devam edememe oranı hem diğer ülkelerde yapılan yayınlarda hem de ülkemizde yapılmış olan yayınlarda yüksektir. Klozapinin Türk toplumundan hasta grubunda etkin dozu, doz yan etki ilişkisi, doz etkinlik ilişkisine ait daha net bilgilere ulaşabilmek için daha çok vaka sunumu ve iyi dizayn edilmiş çalışmaya gereksinim vardır.*

Anahtar Kelimeler: *Klozapin, Yan etki, Etkinlik*

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INTRODUCTION

Clozapine was discovered in 1958 in Bern, Switzerland and was found to be an effective antipsychotic agent without any extrapyramidal side effects in clinical studies. Yet the interest on clozapine declined when the medications hematologic toxicity was discovered (1). About 50 patients globally died of agranulocytosis effect of clozapine. Thus, the medication was withdrawn from the European markets during the 80's. However, John Kane reported that clozapine was more effective than chlorpromazine in 1988 (2). This result is followed by many more study results (3). For this effort, in 1990, it was agreed that clozapine treatment was effective in patients with resistance to other antipsychotics or to the patients that could not tolerate typical antipsychotics because of extrapyramidal side effects or serious tardive dyskinesia.

There are many studies carried out on clozapine usage and lots of detailed data have been gathered for these studies. Yet in Turkey there are only a few studies, the majority of which are case representations.

For this general review, database were scanned and 5 case reports, 1 case comparison study and 3 follow-up studies were found in the literature. In this article, we decided to review Turkey's data on clozapine usage and its side effects.

METHOD

In order to access case representations and follow-up studies on clozapine usage in Turkish society, PubMed, Medline, ProQuest, EBSCOHost and PsycINFO databases as well as the Türk Medline and Psychiatry Index databases were searched for keywords "side effect", "effectiveness", "clozapine" as well as their Turkish meanings in both English and Turkish articles. The search was completed by August 2012 and the articles appropriate for the review were obtained. Although an attempt was made to include all the articles, it cannot be guaranteed that all articles referring to clozapine in various contexts have been included. Five case reports, 3 follow-up studies and a case comparison study on clozapine were found. The articles which did not clearly indicate the relationship between clozapine usage, dosage and side effects were not included in the study.

RESULTS

Güvenç et al. (4) presented a case of a 20-year old male patient which complained about chest pain associated with clozapine usage and diagnosed with acute pericarditis. This side-effect was shown to manifest itself in clozapine usage of 3 days with 50 mg/day dosage.

Tümüklü et al.'s (5) study included 16 patients between 20-56 years with 5 male and 11 females. The time span of the illness was 1-28 years with an average of 13.6 years. Average dose of clozapine was 465 mg/day. This dosage of clozapine was found to reduce HRV (heart rate variability) significantly after 10th week and this was more serious in females and patients under 35 years old.

Sarıçiçek and Gülseren's case report was on a schizophrenic 46-year old male patient. Following the start of clozapine treatment, myoclonia developed in the patient on the 3rd week of 250 mg/day dose, emphasizing that this was a lower dosage than reported in the literature.

Coşkun and Zoroğlu (7) reported obsessive-compulsive symptoms caused by clozapine usage. After increasing the dose to 150 mg/day, the disturbing obsessive thoughts started and with 100 mg/day dosage with additional sertraline, obsession frequency and intensity were reduced.

Herken et al. (8) reported in their study the comparison between sulpride and clozapine and their effectiveness in treatment resistant schizophrenia cases, the most common side effects of clozapine were said to be hypersalivation, tachycardia, weight gain, sedation, increase in sleep and orthostatic hypotension. Yet they did not report the relationship of these side effects with treatment period or dosage.

Kısa et al. (9) case presentation study showed that in a female treatment resistant schizophrenia patient, in the 10th week of treatment with a 300 mg/day clozapine dosage, the treatment was ended because of over increase in liver functions. In the same case, clozapine was started to be

used again, since there were no response to other antipsychotics, however agranulocytosis developed in 500 mg/day dosage.

Erol et al. (10) reported malign neuroleptic syndrome cases during clozapine treatment. In a case of a male patient diagnosed with schizophrenia and after 4 years of using clozapine, when the dosage of clozapine was reduced from 200 mg/day to 150 mg/day, malign neuroleptic syndrome compatible symptoms were seen and the patient was treated using ECT.

Uzun et al. (11) reported in their 3 years of follow-up study, average clozapine dosage of treatment was 326.47 ±75.24 mg/day. One case had heavy sedation and akathisia and another case had heavy sedation, thus they terminated the treatment for those cases. However, they did not report any side effects seen in any week or for which clozapine dosage. In both cases, grand-mal convulsive seizures were seen on the 4th and 14th months in first and the 18th month in second case. In the first patients' first seizure, clozapine dosage was 450 mg/day and in second seizure it was 300 mg/day, where the second patient was taking clozapine 300 mg/day. In both cases, valproic acid in 1000 mg/day doses is added to the treatment and no more seizures were seen during the follow-up study. Weight gain, hypersalivation, sedation and EEG anomalies were reported to be the most common side-effects during the follow-up. The reported results were shown to develop during the sixth month of the treatment yet no information was given on the dosage relationship.

As in Soylu et al. (12) 's 18-months follow-up study on clozapine treatment in schizophrenia patients, 2 cases developed myoclonia in the first and the 5th months, 2 cases developed granulocytopenia the 4th month and a case developed agranulocytosis in the 4th month of the treatment. The most common side-effects of the medication were said to be sedation, hypersalivation and weight gain, yet no information was given on the relationships between the side-effects and the treatment period nor the dosage.

DISCUSSION AND CONCLUSION

This review shows that there are 3 follow-up studies, 5 case representations and a case comparison study in Turkey about clozapine. The literature is only available for 132 patients. There is not a single study reviewing clozapine with a randomized controlled trial.

In the 5 case representations, 4 of them are reported to have been terminated due to side effects. When follow-up studies were read, Uzun et al. (11) had 29 cases yet 4 cases could not be reached, so in the remaining 25 cases, for 3 of them, the treatments were terminated because of side effects or non-compatibility. Soylu et al.'s (12) article reported that in 47 patients, the treatments for 17 patients were terminated because of side effects and non-compatibility. Of the remaining 20 patients, 10 patients completed the study follow-up period of 18 months but their treatments were terminated afterwards. Tümüklü et al.'s (5) study on the effects of clozapine on HRV, follow-up studies showed that clozapine reduced HRV values significantly and the reduction in HRV was related to increased arrhythmic complications and mortality risk. Finally, when the results of clozapine usage of 132 patients in Turkish society are reviewed, it can be seen that 48 of those patients could not continue with their treatments for one reason or another, meaning the percentage of leaving the treatment is 36.36%. In literature, leaving the clozapine treatment percentages are as follows: Hayhurst et al. (13) 44% Tuunainen and Gilbody (14) 31%, Revicki (15) 34.6%, Blieden et al (16) 48%.

When the side effect related doses are reviewed, in acute pericarditis the dose can be as low as 50mg/day, in obsessive compulsive symptoms the dose is 200 mg/day, myoclonia is seen at 250 mg/day, in Uzun et al.'s study, convulsive seizures were seen in 300 mg/day and 450 mg/day doses, yet in other studies there are no clear statements on side effect and dose relationship. Considering the fact that the effective clozapine dose is between 300-450 mg/day, almost all cases represented side effects before the introduction of effective dosage. We see how much the difference on personal responses to psychotropic treatments can be in our clinic practice. Age, sex, comorbid

physical illnesses, genetic factors, diet, coexisting other treatments, alcohol and tobacco consumption and other similar factors seem to effect this response. Race is also one of these factors. For example, the reference dose for clozapine in patients from African-Caribbean background is defined as race-specific. A significant proportion (25–50%) of otherwise healthy Afro-Americans are known to have a persistently lower white blood cell count than the normal range defined for individuals of European ancestry—a condition known as benign ethnic neutropenia (17). For this reason, in order to increase clozapine usage in a group, the clozapine reference values of white blood cell count and neutrophils are defined again. In a study that compares Asian and Caucasian schizophrenia patient groups receiving follow-up doses of clozapine in the parameters of similar clozapine dosage, plasma clozapine and metabolite levels, clinical effect and side effect profiles, Asian patient groups' average effective dosage is 176 mg/day where Caucasian patient groups' effective dosage is 433 mg/day. In both groups, plasma clozapine levels are close and after reviewing the data for sex, BMI, tobacco-alcohol-caffeine consumption, similar values are reached (18). When the literature on the Turkish society is reviewed, it is not possible to make a comment about the relationship with dosage and side effects. That relationship is not clearly stated in the studies. That's why it seems necessary to have case reports that clearly state dosage–side effect relationship or more detailed explanations about this relationship in the studies.

When we look at the patients who can continue the treatment, the average effective clozapine doses are 462.65 mg/day in Tümüklü et al.'s study (5), 326.47 mg/day in Uzun et al.'s study (11), 295, 395, 405, 370 and 368 mg/day in first, 3rd, 6th, 12th and 18th months respectively in Soylu et al.'s follow-up study (12), and 200 mg/day in Coşkun and Zoroğlu's study (7). Even though the low numbers of cases and patients, as Ng et al.'s study (18) defined in Asian and Caucasian patients, no average dose can be defined for Turkish society. That's why it seems necessary to have case reports that clearly state dosage–side effect relationships or more detailed explanations on this relationship in the studies.

The most feared side effect of clozapine is agranulocytosis, only 1 case out of 132 patients is represented in the study done by Kısa et al. (9). In literature, agranulocytosis risk is 0.38 % in clinical application (19). Also in some publications this risk is given as 0.8% on the first and 0.91% for the second year (20). One in 132 may seem to be a high ratio but as noted before, case number is very low.

As a result, even though clozapine is known to be useful in treatment and causes obvious well-being in resistant schizophrenia cases, large number of side-effects and high percentage of non-followed treatments are reported both in local and international studies. In order to the effective dose, dose-side effects relationship, dose effectiveness relationship of clozapine in Turkish society, more case reports and better designed studies are necessary.

REFERENCES

1. Van Kanmen DP, Marder SR. Serotonin–Dopamine antagonists. In: Sadock BJ, Sadock VA, editors. Comprehensive Textbook of Psychiatry. 8 th. pp. 2914–38, 2004.
2. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. Arch Gen Psychiatry 45: 789–96, 1988.
3. Breier A, Buchanan RW, Kirkpatrick B, Davis OR, Irish D, Summerfelt A, et al. Clozapine in schizophrenic outpatients: Effects on positive and negative symptoms. Am J Psychiatry 151: 20–26, 1994.
4. Güvenç TS, Aksoy Ş, Çetin R, Karataş B, İlhan E, Erer HB, Eren M. Nadir bir Göğüs Ağrısı Nedeni: Klozapin Tedavisi ile Akut Perikardit Birlikteliği. Kafkas J Med Sci 1 (1): 30–33, 2011.
5. Tümüklü MN, Alptekin K, Kırımlı Ö, Aslan Ö, Akdede BB, Badak Ö, Akdeniz B, Göldeli Ö, Güneri S. Arrhythmic Markers and Clozapine in Patients with Schizophrenia: Effect of 10 weeks Clozapine Treatment on Heart Rate Variability, Late Potentials and QT Dispersion. Klinik Psikofarmakoloji Bülteni 18: 167-173; 2008.
6. Sarıçiçek A, Gülseren L. Klozapin Kullanımıyla İlişkili Miyokloni: Bir Olgu Sunumu. Klinik Psikiyatri 9: 198-202, 2006.

7. Coşkun M, Zoroğlu S. Clozapine Induced Obsessions Treated with Sertraline in an Adolescent with Schizophrenia. Bulletin of Clinical Psychopharmacology 19: 155-158, 2006.
8. Herken H, Kaya N, Beşiroğlu L, Derman H, Özkan İ. Kronik Şizofreni Hastalarında Klozapin ve Sulpiridin Etkinliğinin Karşılaştırılması. Klinik Psikofarmakoloji Bülteni 9: 148-151, 1999.
9. Kısa C, Süer Yalçın E, Göka E. Atipik Antipsikotiklerin Neden Olduğu Agranülositoz: Olgu Sunumu. Klinik Psikofarmokoloji Bülteni 11: 187-191, 2001.
10. Erol A, Putgül G, Sert E, Mete L. Klozapin Kullanımına Bağlı Nöroleptik Malign Sendrom ve Ardışık Katatoni: Olgu Sunumu. Türk Psikiyatri Dergisi 23: pp, 2012.
11. Uzun Ö, Özşahin A, Özmenler KN, Doruk A, Battal S. Tedaviye Dirençli Şizofrenide Klozapin: Üç Yıllık İzlem. Klinik Psikofarmokoloji Bülteni 10: 74-80, 2000.
12. Soylu C, Bilici M, Bekaroğlu M, Yıldırım F. Tedaviye Dirençli Bir Grup Şizofrenili Hastada Klozapinin Etkinliği. Klinik Psikofarmakoloji Bülteni 9 (1): 34-38, 1999.
13. Hayhurst KP, Brown P, Lewis SW. The cost-effectiveness of clozapine: a controlled, population-based, mirror-image study. Journal of Psychopharmacology 16 (2): 169–175, 2002.
14. Tuunainen, A, Gilbody SM. Newer atypical antipsychotic medication versus clozapine for schizophrenia: The CochraneLibrary. Update Software, Oxford, 2000.
15. Revicki DA, Luce BR, Weschler JM, Brown RE, Adler MA. Cost-effectiveness of clozapine for treatment-resistant schizophrenicpatients. Hosp Commun Psychiatry 41: 850–854, 1990.
16. Blieden N, Flinders S, Hawkins K, Reid M, Alphs LD, Arfken CL. Health status and health care costs for publicly funded patients started on clozapine. Psychiatr Serv 49: 1590–1593, 1998.
17. Kelly DL, Kreyenbuhl J, Dixon L, Love RC, Medoff D, Conley RR. Clozapine underutilization and discontinuation in African Americans due to leucopenia. Schizophr Bull. DOI:10.1093/schbul/sblo68, 2006.
18. Ng C H, Chong S, Lambert T, Fan A, Hackett L P, Mahendran R, Subramaniam M, Schweitzer M. An inter-ethnic comparison study of clozapine dosage, clinical response and plasma levels. Int ClinPsychopharmacol 20: 163–168, 2005.
19. Miller DD. Review and Management of Clozapine Side Effects. J Clin Psychiatry 61 (8): 14-17, 2000.
20. Alvir JM, Lieberman JA, Safferman AZ, Schwimmer JL, Schaaf JA. Clozapine-induced agranulocytosis. Incidence and risk factors in the United States. N Engl J Med 329: 162-167, 1993.