



Clozapine Induced Obsessions Treated with Sertraline in an Adolescent with Schizophrenia

Murat Coskun, Salih Zoroglu

ÖZET:
Şizofrenisi olan bir ergende klozapinle ilişkili obsesyonların sertraline ile tedavisi

Şizofrenisi olan hastalarda yüzde 26'ya varan oranlarda obsesif-kompulsif bozukluk bildirilmektedir. Diğer taraftan klozapin başta olmak üzere antipsikotik ilaçlarla tedavinin obsesif kompulsif semptom veya bozukluğun ortaya çıkması ya da kötüleşmesiyle ilişkili olduğu bildirilmiştir. Daha önceden var olan ya da tedaviyle ilişkili olarak ortaya çıkan bu obsesif-kompulsif semptomlar, özellikle obsesyonlar, farkedilmeyebilir ve hastanın işlev bozukluğunu artırıp tedavi uyumunu kötüleştirebilir. Diğer taraftan tedaviyle ilişkili ortaya çıkan obsesif-kompulsif bozukluk ya da semptomlar tedavide önemli bir zorluk yaratabilir. Bu yazıda tedaviye dirençli şizofreni tanısıyla takip edilen ve klozapin tedavisi sırasında doza bağımlı olarak şiddetli dinsel obsesyonları ortaya çıkan ergen bir erkek hasta sunulmuştur. Klozapinle ilişkili obsesif-kompulsif semptomların olası patofizyolojik mekanizmaları, bu yan etkinin klinik önemi ve tedaviye sertralin eklenerek başarıyla tedavi edilmesi tartışılacaktır.

Anahtar sözcükler: Klozapin, obsesyonlar, şizofreni, ergen, sertralin

Klinik Psikofarmakoloji Bülteni 2009;19:155-158

ABSTRACT:
Clozapine induced obsessions treated with sertraline in an adolescent with schizophrenia

Obsessive-compulsive disorder has been reported up to 26 percent in subjects with schizophrenia. Meanwhile treatment with antipsychotic medications, particularly with clozapine, has been reported to be associated with the emergence or exacerbation of obsessive-compulsive symptoms or disorder. These preexisting or treatment-induced obsessive-compulsive symptoms, particularly obsessions, may go unrecognized and result in further functional impairment and poor treatment compliance. Management of this adverse event could be troublesome in the clinical setting. We report an adolescent boy with a diagnosis of schizophrenia who developed severe religious obsessions during clozapine treatment in a dose dependent fashion. We discuss the possible pathophysiological mechanisms of clozapine-induced obsessive-compulsive symptoms, clinical implications, and successful management of this adverse event by adding sertraline to the treatment regimen.

Key words: Clozapine, obsessions, schizophrenia, adolescents, sertraline

Bulletin of Clinical Psychopharmacology 2009;19:155-158

¹Resident, Istanbul University, Istanbul Medical Faculty, Child and Adolescent Psychiatry Department, Istanbul -Türkiye
²Associate Professor, Istanbul University, Istanbul Medical Faculty, Child and Adolescent Psychiatry Department, Istanbul -Türkiye

Yazışma Adresi / Address reprint requests to:
Dr. Murat Coskun, Istanbul Tıp Fakültesi, Çocuk-Ergen Psikiyatrisi Anabilim Dalı, 34093 Çapa, İstanbul -Türkiye

Telefon / Phone: +90-506-541-7128

Elektronik posta adresi / E-mail address:
muratcoskun78@yahoo.com

Kabul tarihi / Date of acceptance:
10 Şubat 2009 / February 10, 2009

Bağıntı beyanı:
M.C., S.Z.: yok.

Declaration of interest:
M.C., S.Z.: none.

INTRODUCTION

The occurrence of obsessive compulsive symptoms (OCS) has been reported to be as high as 10-20 % under clozapine treatment in adult patients with schizophrenia (1,2). Meanwhile, the concurrence of obsessive compulsive disorder (OCD) with schizophrenia was reported as 26 % in adolescent (3) and 15.8 % in adult patients (4). Distinguishing drug-induced OCS from OCS seen as part of the symptomatology of schizophrenia or comorbid OCD is an important yet unresolved issue that needs further investigation.

Here we present a case of early onset schizophrenia (EOS) who developed severe obsessions under clozapine treatment. We plan to discuss clinical implications of this adverse event and the management of these obsessions with adding sertraline to the treatment regimen.

CASE

Clinical Presentation

The subject is a 16.5 year-old male who was consulted to child and adolescent psychiatry department by emergency department. He was admitted to hospital three days ago following a suicide attempt by drinking bleach.

In psychiatric examination he was conscious, cooperative and fully oriented. He was noted to have a blunted affect, some blockage in speech and loose associations. He admitted to hearing voices that command to kill himself and to get rid of his enemies. He claimed that he had enemies that send him messages via headlamps of cars and try to kill him. He also claimed that people were able to read his thoughts.

He did not report any visual or tactile hallucinations

and obsessions at that time and denied use of any substances.

History of Present Illness

The parents reported that he first started to display social withdrawal and loss of interest two years ago. He also had difficulties in school and left the school last year. He tried to work in several jobs, but could not continue more than three months in any jobs. According to the report of the parents and the subject, he was judged to have reference and paranoid delusions, commanding auditory hallucinations and bizarre behaviors (such as sitting in his bed in dark for many hours while all windows and curtains are closed) for more than one year. He attempted suicide twice before this last attempt. He refused going outside as he claimed that somebody would kill him and people read his thoughts which were very stressful for him. The parents reported that he also did not take care of his personal hygiene during the last year.

He was admitted to a hospital one year ago after the first suicide attempt. However he did not take his medications regularly after discharge. He had stopped the medications four months prior to his last suicide attempt.

Developmental / Educational and Family History

He was born after a full-term uneventful pregnancy with normal delivery. Despite his early motor development was within normal limits, his language development was moderately delayed with first meaningful words at age two and sentences after three years of age. His academic achievement was usually below normal. There is no history of psychotic disorders in first degree relatives, but a second degree relative had possible schizotypal personality disorder.

Follow up

After detailed psychiatric assessment he was given diagnosis of early onset schizophrenia (EOS). He was started risperidone 2 mg/day treatment, which was titrated up to 5 mg/day, together with a rehabilitation program. However, although he tolerated risperidone generally well, his positive and negative symptoms did not improve

significantly after six weeks of risperidone 5 mg/day treatment. We then gradually tapered off risperidone and started olanzapine 20 mg/day and titrated it up to 30 mg/day. Although he reported a weight increase of more than six kilograms, his positive and negative symptoms showed only a mild improvement after 8 weeks of olanzapine 30 mg/day. Because we considered his symptoms as treatment resistant, we decided to switch to clozapine treatment. We gradually tapered off olanzapine and started clozapine treatment schedule. His positive and negative symptoms scale (PANSS) scores were 31 for positive symptoms (+) and 41 for negative symptoms (-) before clozapine treatment. With 150 mg/day dosage of clozapine he showed some improvement in psychotic symptoms, but started to complain about some recent onset bad and distressing thoughts. He refused to explain these thoughts in details at that time and we interpreted this symptom as a part of psychosis as the family could not give any information on this symptom either. However he was overwhelmed with these thoughts after clozapine was increased to 200 mg/day. He then admitted to having some intrusive and unwanted thoughts about sacrilege and blasphemy (such as swearing to God or prophet) and a fear to say something bad to his beloved people. He stated that he wanted to get rid off these intrusive and extremely disturbing thoughts, but he could not escape from them even for a second. His Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) obsessions subscore was 19 (a maximum of 20 score) and he did not report any other obsessional thoughts or compulsive behaviors at that time. Clozapine was decreased to 150 mg/day and his obsessions decreased significantly within a few days. During subsequent ten days his obsessions were minimally disturbing. Because his psychotic symptoms continued and he was doing well on clozapine, it was re-increased to 200 mg/day. Two days later his obsessions reemerged with previous severity and he insisted to cease medication. However we decided to add sertraline 50 mg/day to his regimen rather than decreasing or ceasing clozapine. His obsessions showed moderate improvement with sertraline 50 mg/day within three weeks. After three weeks we increased sertraline to 100 mg/day and clozapine to 250 mg/day. After two months on this combination the obsessions showed very much improvement (CY-BOCS obsessions subscore: 8), and positive and negative symptoms of psychosis also showed

moderate to much improvement on CGI-Improvement scale (PANSS: +19; - 25). In subsequent weeks we were able to increase clozapine to 325 mg/day without any worsening in OCS. Clozapine was generally tolerated well, with normal blood counts and without significant weight change, except significant day time sedation even in divided dosages which also showed moderate improvement after increasing sertraline to 100 mg/day.

DISCUSSION

Clozapine is an atypical antipsychotic medication that has been reported to effective in young and adult subjects with treatment-resistant schizophrenia (5-8). Clozapine may cause several serious side effects such as agranulocytosis, seizures, and myocarditis (5,6). Besides these medically serious side effects, emergence or exacerbation of OCS or OCD during clozapine treatment has been reported in adult patients with schizophrenia (1,2). Although this is not a medically serious side effect, it should be managed effectively as it may complicate the clinical picture and may cause treatment noncompliance. This is particularly important for adolescent patients as they are reported to have higher frequency of comorbid OCD (3,4) and may have more compliance issues than adult patients. Moreover, given the fact that clozapine is less frequently used in young patients, data regarding its side effects (including obsessive compulsive symptoms) in young subjects are limited in the literature. For instance two recent studies on young patients with schizophrenia did not report OCS related with clozapine treatment (5,6) while the rate of side effects was higher than that typically found in the adult population (5). To our knowledge, there is only one report about clozapine induced OCD or OCS in adolescent patients (9).

In consistent with the previous reports on the efficacy of clozapine in treatment-resistant schizophrenia, clozapine resulted in a significant improvement in symptoms in our case, too. However he started to report obsessions after we increased clozapine up to 150 mg/day and obsessions worsened significantly at 200 mg/day. The association between the emergence and severity of obsessions and the dosage of clozapine suggested that the obsessions were clozapine induced rather than coincidence. Ertugrul et al. (2005) (2) reported that the severity of OCS was not related to dosage and duration of

clozapine treatment. However Levkovitch et al. (1995) (9) reported that the emergence and severity of OCS was dose related in their two adolescent subjects taking clozapine. The question whether this association could manifest differently in young patients or it was only an individual difference remains unclear at this point. As this patient's obsessive compulsive symptoms were affected by clozapine in a dose dependent fashion, we agree with previous reports (9,10) that it would lead to some interesting speculations about psychopharmacology of clozapine. Clozapine is a potent antagonist of serotonin receptors and it has been suggested that blocking off the serotonergic receptors may result in subsets of schizophrenic patients developing obsessive-compulsive symptoms (9,10,11).

To date there is no consensus in the literature on the treatment of clozapine induced OCS or OCD in subjects with schizophrenia. Some authors reported modest (12) or no significant improvement (2) with adding a serotonin reuptake inhibitor (SSRI) to the treatment regimen. Levkovitch et al. (1995) (9) preferred dosage reduction in their adolescent subjects. However we preferred adding sertraline rather than decreasing clozapine and/or switching to another antipsychotic. If OCS in this subject were the result of blockade of serotonergic receptors by clozapine, pharmacologically, it would have made sense adding a serotonergic agent to treat clozapine induced OCS. His obsessions improved very much at 100 mg/day dosage of sertraline even at higher dosage of clozapine. He tolerated clozapine well even at higher dosage (325 mg/day) and his day time sedation also improved in combination with sertraline.

In conclusion young patients on clozapine treatment deserve a closer attention on emergence or exacerbation of OCS or OCD as these symptoms may go unrecognized or be considered as a part of psychosis and have great impact on patient's compliance and adaptive life. Because clozapine is generally prescribed in treatment resistant cases after other antipsychotics have already been tried, decreasing or ceasing clozapine or switching to another medication may not be possible in the development of clozapine induced OCS. Rather managing these OCS with an SSRI could be a reasonable treatment option. We prefer to interpret this favorable result with caution as more research is warranted on this subject.

References:

1. Baker RW, Chengappa KNR, Baird J, Steingard S, Christ MA, Schooler NR. Emergence of obsessive-compulsive symptoms during treatment with clozapine. *J Clin Psychiatry* 1992;53:439-442
2. Ertugrul A, Yagcioglu EA, Eni N, Yazici KM. Obsessive-compulsive symptoms in clozapine-treated schizophrenic patients. *Psychiatry Clin Neurosci*. 2005;59:219-222
3. Nechmad A, Ratzoni G, Poyurovsky M, Meged S, Avidan G, Fuchs C, Bloch Y, Weizman R. Obsessive-compulsive disorder in adolescent schizophrenia patients. *Am J Psychiatry* 2003;160:1002-1004
4. Kruger S, Braunig P, Hoffler J, Shugar G, Börner I, Langkrär J. Prevalance of obsessive-compulsive disorder in schizophrenia and significance of motor symptoms. *J Neuropsychiatry Clin Neurosci* 2000;12:16-24
5. Sporn AL, Vermani A, Greenstein DK, Bobb AJ, Spencer EP, Clasen LS, Tossell JW, Stayer CC, Gochman PA, Lenane MC, Rapoport JL, Gogtay N. Clozapine treatment of childhood-onset schizophrenia: evaluation of effectiveness, adverse effects, and long-term outcome *J Am Acad Child Adolesc Psychiatry* 2007;46:1349-1356
6. Shaw P, Sporn A, Gogtay N, Overman GP, Greenstein D, Gochman P, Tossell JW, Lenane M, Rapoport JL. Childhood-onset schizophrenia a double-blind, randomized clozapine-olanzapine comparison. *Arch Gen Psychiatry* 2006;63:721-730
7. Akay AP, Dogan Ö, Emiroglu FNİ. Çok erken başlangıçlı şizofreni ve klozapin: olgu sunumu. *Klinik Psikofarmakoloji Bulteni –Bulletin of Clinical Psychopharmacology* 2006;16:47-51
8. Uzun Ö, Özşahin A, Özmenler KN, Doruk A, Battal S: Tedaviye dirençli şizofrenide klozapin: üç yıllık izlem. *Klinik Psikofarmakoloji Bulteni –Bulletin of Clinical Psychopharmacology* 2000;10:74-80.
9. Levkovitch Y, Kronenberg Y, Gaoni B. Can clozapine trigger OCD ? *J Am Acad Child Adolesc Psychiatry* 1995;34:263
10. Patil VJ. Development of transient obsessive-compulsive symptoms during treatment with clozapine (letter). *Am J Psychiatry* 1991;149: 772
11. Kayahan B, Öztürk Ö, Veznedaroğlu B. Şizofrenide Obsesif Kompulsif Belirtiler. *Türk Psikiyatri Derg* 2005;16:205-215
12. Zink M, Knopf U, Anna K. Management of clozapine-induced obsessive-compulsive symptoms in a man with schizophrenia. *Aust N Z J Psychiatry* 2007;41: 293-294