

Venlafaxine-Induced Acute Dystonia: a Case Report

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ABSTRACT

Venlafaxine-induced acute dystonia: a case report

Although mechanisms underlying neuroleptic-induced extrapyramidal symptoms have been well researched, extrapyramidal symptoms associated with antidepressants are understudied. Research conducted to date is more concerned with selective serotonin reuptake inhibitors. Recognized risk factors for extrapyramidal symptoms associated with antidepressants are advancing age, female sex, and pharmacokinetic interaction of concurrently used drugs with CYP2D6 inhibition effect. This case is presented to emphasize that the occurrence of extrapyramidal symptoms, which are clinically important side effects requiring intervention, may be related with venlafaxine, a serotonin noradrenaline reuptake inhibitor.

Keywords: Dystonia, extrapyramidal syndrome, venlafaxine



ÖZET

Venlafaksin kullanımına bağlı akut distoni: Olgu sunumu

Antipsikotiklere bağlı ekstrapiramidal sendromlar iyi araştırılmış olmasına rağmen, antidepresanlara bağlı ekstrapiramidal sendromlar yeterince incelenmemiştir. Bugüne kadar yapılan araştırmalar daha çok Seçici Serotonin Gerilim İnhibitörleri ile ilgilidir. Antidepresan kullanımına bağlı ekstrapiramidal sendrom gelişimi için tanımlanmış risk faktörleri ileri yaş, kadın cinsiyet ve eş zamanlı kullanılan ilaçların CYP2D6 inhibisyonu etkileşimidir. Bu olgu klinik olarak son derece önemli ve müdahale gerektiren bir yan etki olan ekstrapiramidal sendromun, venlafaksin gibi bir Serotonin Noradrenalin Gerilim İnhibitörüne bağlı olarak da gelişebileceğini vurgulamak amacıyla sunulmuştur.

Anahtar kelimeler: Distoni, ekstrapiramidal sendrom, venlafaksin

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Date of receipt / Geliş tarihi:
February 9, 2015 / 9 Şubat 2015

Date of acceptance / Kabul tarihi:
March 7, 2015 / 7 Mart 2015

INTRODUCTION

While antipsychotic-related extrapyramidal syndromes (EPS) have been extensively studied from neuroanatomical, neurophysiological, and neurochemical perspectives, antidepressant-induced EPS have not been researched sufficiently (1). The first report about antidepressant-induced EPS was published in 1959 (2), but by the time that selective serotonin reuptake inhibitors (SSRI) came into wider use in the 1980s, no significant studies were made in the field. In many cases of antidepressant use, extrapyramidal symptoms such as parkinsonism, dystonia, akathisia, and dyskinesia have been reported (3). Studies carried out till now are mainly focused on SSRIs. A number of SSRIs can cause movement disorders; in addition to fluoxetine, this is the case with paroxetine, fluvoxamine, escitalopram, citalopram, and sertraline (1). A study done in the Netherlands between 1985 and 1999, analyzing 24,263 drug side effect reports, found that SSRIs cause EPS more frequently

than other antidepressants (4). Based on the number of case reports and the antidopaminergic effect of serotonin on the striatum, we can say that SSRIs constitute EPS more frequently than other antidepressants (5). It has been reported that the incidence of EPS in SSRI use is 1/1,000 or less (6).

Leo (7) reported 71 cases developing SSRI-related EPS; the most commonly observed side effects in these cases were akathisia (45%), dystonia (28%), parkinsonism (14%), and tardive dyskinesia-like states (11%).

Venlafaxine and its active O-desmethyl metabolite inhibit the reuptake of serotonin, norepinephrine, and dopamine. A daily dose of 75-150mg venlafaxine selectively inhibits serotonin reuptake. For this reason, venlafaxine causes SSRI-like effects. At a dose above 150mg/day, venlafaxine acts as a non-selective serotonin reuptake inhibitor (8). It has been reported that SSRI-induced EPS may occur due to the inhibitory effect of serotonin on the dopamine neurotransmission in the striatum. The antidopaminergic effect in the striatum may disturb normal coordination and

Table 1: Venlafaxine-induced extrapyramidal symptoms reported in the literature

Patient, age, sex	Daily dosis	Extrapyramidal symptoms	Concomitant therapy	Diagnosis	Study
A- 83, M	150mg	Parkinsonism	Enalapril	Depressive disorder	Garcia-Parajua et al., 2003
B- 40, M	150mg	Akathisia	None	Depressive disorder	Lai, 2013
C- 69, M	150mg	Akathisia	Metoprolol, Glipizide, Metformin, Aspirin, Valproic acid	Dementia	George and Campbell, 2012
D- 53, F	150mg	Akathisia and movement disorder in the upper limbs	Methimazole, Amlodipine, Bisoprolol, Clopidogrel, Glipizide, Prednisone, Lansoprazole	Depressive disorder	Ng et al., 2009
E- 46, F	112.5mg	Tremor	Lithium	Depressive disorder	Geber et al., 2013
F- 50, M	150mg	Bruxism	Clonazepam, omeprazole	Bipolar disorder Type I	Brown and Hong, 1999
G- 33, F	225mg	Akathisia	Mesolamine	Depressive disorder	Grover and Valaparla, 2014
H- 29, F	75mg	Dystonia	None	Depressive disorder	Fonseca et al., 2010

M: Male, F: Female

movement and cause EPS (4,9). As venlafaxine also inhibits serotonin reuptake, it may provoke side effects similar to those of SSRIs.

It has been reported that EPS related to the use of antidepressants are seen more frequently in women than in men (10). This may be related to the fact that women have a greater predisposition for antidepressant-induced EPS and that the incidence of depression and utilization of treatment are higher in women (7). Advancing age, female sex, and CYP2D6 inhibition of concurrently used drugs have been defined as risk factors for the development of EPS (1). Venlafaxine-related EPS cases reported until today are summarized in Table 1.

We are here presenting what to our knowledge is the second case in the literature developing venlafaxine-induced dystonia, with the aim to emphasize that EPS, a clinically highly important side effect requiring intervention, may also develop related to serotonin noradrenalin reuptake inhibitors (SNRIs) such as venlafaxine.

CASE

A 22-year-old woman, university student, unmarried, living in a student dormitory. Presenting to the psychiatric policlinic with complaints of unhappiness, pessimism, lack of energy, not wanting to leave her room, and drop in academic success. The complaints had existed for 6 months; 4 months earlier, the patient had consulted a doctor and been treated with fluoxetine 20mg/day initially, with a dose increase to 60mg/day. The patient had been using the medication

for 2 months, but the complaints did not subside.

In her medical history, there was no previous mental disorder nor physical disease history. In the mental state examination, her psychomotor activity was slowed down. A depressive affect was observed and a diagnosis of depressive mood made. She spoke with a low tone of voice. Associations were straight and expedient. Her thoughts contained ideas of failure, worthlessness, and hopelessness. No deficit in perception was found. Assessment of reality was complete. The patient scored 45 points on the Beck Depression Inventory (BDI) (11). In her family history, it was believed that that her aunt had been diagnosed with recurrent depressive disorder.

The patient received a diagnosis of depressive episode according to ICD-10 (12). She was started on venlafaxine XR 75mg/day and the dose was increased after 1 week to 150mg/day; a control visit to the policlinic was recommended to be made two weeks later. On the fifth day of treatment, the patient reported to the emergency department with complaint of spasm in her neck. Assessment in emergency found dystonia in the cervical region. After injecting an ampule of biperiden intramuscularly, the patient's dystonia state resolved within thirty minutes. From the patient history and her records, it was found that she had already presented to emergency the previous night with acute dystonia, where she had received an ampule biperiden and been discharged after the problem subsided, with a recommendation to attend the psychiatric policlinic. The patient used venlafaxine regularly and did not experience any other side effects. In order to exclude

organic causes, the neurological consultation requested a brain computer tomography, full blood count, biochemistry, thyroid function tests, and a vitamin B12 level test; results were all normal. As it appeared that the patient was suffering a venlafaxine-induced extrapyramidal side effect, she was started on an antidepressant from a different group, citalopram 20mg/day, and was requested to attend the polyclinic for a control one week later. In the control examination, no EPS was found. The depressive complaints continued. At a control one month later, again no EPS was found and the BDI score was 30. Citalopram was increased to 40mg/day. At a consultation in the second month, the patient's BDI score was 16 and she was recommended to continue treatment with cognitive behavioral therapy.

DISCUSSION

Our patient's dystonia developed after use of venlafaxine and did not recur after stopping the drug. She was young, had no history of physical disease and did not use any other medication; laboratory tests were all in the normal range. Therefore, we made a diagnosis of venlafaxine-induced dystonia.

Side effects of drugs can be assessed with Naranjo's Adverse Drug Reaction (ADR) probability scale (13). A score of 9 and above is considered certain, 5-8 points highly likely, 1-4 points probable, and a score of 0 doubtful. Applying the instrument to our case, we reached a total score of 7 points: There have been previous publications in the literature reporting dystonia triggered by venlafaxine (1 point), dystonia occurred after administering the suspected drug (2 points), the side effect improved after giving a specific antagonist (1 point), besides the drug no other possible cause for the dystonia was found (2 points), and the side effect was confirmed with objective evidence (1 point) (the side effect in our patient was confirmed with a neurological examination). We can thus assume that with high probability the side effect was induced by venlafaxine.

Until today, one case of venlafaxine-induced dystonia has been reported (14). In a 29-year-old female patient receiving venlafaxine for a diagnosis of depression, two hours after taking the drug, movement disorder in the

tongue and cervical torsion were observed; the situation resolved after administering biperiden. It was reported that the patient's complaints subsequently recurred frequently; at first presentation, the patient suffered from venlafaxine-induced movement disorder; during the subsequent ones, she displayed psychogenic movement disorders of conversive nature she had learned about at her first attendance. Until now, 4 cases developing venlafaxine-induced akathisia have been reported (15-18). Those cases were patients aged 53, 69, 40, and 33 years, respectively, three of whom had a concurrent physical disease and used polypharmacy. Our case and the venlafaxine-induced dystonia case presented above (4) were both characterized by the patients' young age, absence of physical disease, and no use of other medicines. This difference between the venlafaxine-induced akathisia and dystonia cases is remarkable, as it makes us think that in the light of these observations, the reasons for venlafaxine-induced akathisia and dystonia may be different. In the drug-related akathisia, as Lane (19) reported, the inhibitory effects of serotonergic and noradrenergic neurons stimulating the ventral tegmental area on the dopamine transmission may be important. This could explain the SSRI- and venlafaxine-induced akathisia.

Venlafaxine is metabolized by CYP2D6. As Preskorn et al. (20) reported, after the use of slow-release venlafaxine, they found a high plasma concentration of the drug in persons who due to a CYP2D6 polymorphism were slow metabolizers. Another study demonstrated that the enzyme cytochrome P450 and polymorphisms in serotonin-dopamine transporter and receptor were significant in the development of EPS in SSRI users (21). The P450 enzyme system and polymorphisms in the serotonin-dopamine transporter and receptor, which have been studied in the last years, might also be factors playing a role in the development of dystonia in our case.

Finally, as venlafaxine and other antidepressants that are often used in depression and anxiety disorder can evoke EPS side effects, we want to point out that in patients presenting clinically with EPS, this group of medicines needs to be particularly investigated, and we recommend informing the patients about these issues. Studies on EPS side effects using a large sample are needed.

REFERENCES

1. Madhusoodanan S, Alexeenko L, Sanders R, Brenner R. Extrapyramidal symptoms associated with antidepressants: a review of the literature and an analysis of spontaneous reports. *Ann Clin Psychiatry* 2010; 22:148-156.
2. Foster AR, Lancaster NP. Disturbance of motor function during treatment with imipramine. *Br Med J* 1959; 2:1452-1453. **[CrossRef]**
3. Gill HS, DeVane CL, Risch SC. Extrapyramidal symptoms associated with cyclic antidepressant treatment: a review of the literature and consolidating hypotheses. *J Clin Psychopharmacol* 1997; 17:377-389. **[CrossRef]**
4. Schillevoort I, Van Puijenbroek EP, de Boer A, Roos RA, Jansen PA, Leufkens HG. Extrapyramidal syndromes associated with selective serotonin reuptake inhibitors: a case-control study using spontaneous reports. *Int Clin Psychopharmacol* 2002; 17:75-79. **[CrossRef]**
5. Kapur S, Remington G. Serotonin-dopamine interaction and its relevance to schizophrenia. *Am J Psychiatry* 1996; 153:466-476. **[CrossRef]**
6. Coulter DM, Pillans PI. Fluoxetine and extrapyramidal side effects. *Am J Psychiatry* 1995; 152:122-125. **[CrossRef]**
7. Leo RJ. Movement disorders associated with the serotonin selective reuptake inhibitors. *J Clin Psychiatry* 1996; 57:449-454. **[CrossRef]**
8. Venlafaxine and extrapyramidal effects. http://www.lareb.nl/LarebCorporateWebsite/media/publicaties/kwb_2004_2_venla.pdf. Accessed February 20, 2015.
9. Caley CF. Extrapyramidal reactions and the selective serotonin-reuptake inhibitors. *Ann Pharmacother* 1997; 31:1481-1489.
10. Gerber PE, Lynd LD. Selective serotonin-reuptake inhibitor-induced movement disorders. *Ann Pharmacother* 1998; 32:692-698. **[CrossRef]**
11. Hisli N. Validity and reliability of Beck Depression Inventory for university students. *Journal of Psychology* 1989; 7:3-13. (Turkish)
12. World Health Organization. ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. Ozturk MO, Ulug B (Translation Editors) First ed, Ankara: Turkiye Sinir ve Ruh Sagligi Dernegi, 1993. (Turkish)
13. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; 30:239-245. **[CrossRef]**
14. Fonseca L, Rodrigues M, Machado A. Psychogenic movement disorder after a venlafaxine-induced dystonia. *Mov Disord* 2010; 25:506-507. **[CrossRef]**
15. Ng J, Sansone RA, McDonald S. Akathisia and abnormal movements of the upper extremities with venlafaxine and methimazole. *Gen Hosp Psychiatry* 2009; 31:388-390. **[CrossRef]**
16. George M, Campbell JJ 3rd. Venlafaxine causing akathisia: a case report. *J Neuropsychiatry Clin Neurosci* 2012; 24:E3-4. **[CrossRef]**
17. Lai CH. Venlafaxine-related akathisia side-effects and management in a depressed patient. *Psychiatry Clin Neurosci* 2013; 67:127-128. **[CrossRef]**
18. Grover S, Valaparla VL. Venlafaxine induced akathisia: a case report. *Indian J Pharmacol* 2014; 46:660-661. **[CrossRef]**
19. Lane RM. SSRI-induced extrapyramidal side-effects and akathisia: implications for treatment. *J Psychopharmacol* 1998; 12:192-214. **[CrossRef]**
20. Preskorn S, Patroneva A, Silman H, Jiang Q, Isler JA, Burczynski ME, Ahmed S, Paul J, Nichols AI. Comparison of the pharmacokinetics of venlafaxine extended release and desvenlafaxine in extensive and poor cytochrome P450 2D6 metabolizers. *J Clin Psychopharmacol* 2009; 29:39-43. **[CrossRef]**
21. Hedenmalm K, Guzey C, Dahl ML, Yue QY, Spigset O. Risk factors for extrapyramidal symptoms during treatment with selective serotonin reuptake inhibitors, including cytochrome P-450 enzyme, and serotonin and dopamine transporter and receptor polymorphisms. *J Clin Psychopharmacol* 2006; 26:192-197. **[CrossRef]**
22. Garcia-Parajua P, Alvarez Iniesta I, Magarinos M. Reversible and dose-related parkinsonism induced by venlafaxine. *Med Clin (Barc)* 2003; 120:759. (Spanish) **[CrossRef]**
23. Geber C, Ostad Haji E, Schlicht K, Hiemke C, Tadic A. Severe tremor after cotrimoxazole-induced elevation of venlafaxine serum concentrations in a patient with major depressive disorder. *Ther Drug Monit* 2013; 35:279-282. **[CrossRef]**
24. Brown ES, Hong SC. Antidepressant-induced bruxism successfully treated with gabapentin. *J Am Dent Assoc* 1999; 130:1467-1469. **[CrossRef]**