Dusunen Adam The Journal of Psychiatry and Neurological Sciences 2018;31:304-307
DOI: 10.5350/DAJPN2018310309

Case Report / Olgu Sunumu

Therapeutic Single-Dose Mirtazapine-Induced Symptomatic Bradycardia: a Case Report

Pinar Demir Gundogmus[1], Ibrahim Gundogmus[2], Emrah Burak Olcu[1], Abdulkadir Karagoz[2], Ayhan Algul[2]

[1]Sultan Abdulhamid Han Training and Research Hospital, Department of Cardiology, Istanbul - Turkey
[2]Sultan Abdulhamid Han Training and Research Hospital, Department of Psychiatry, Istanbul - Turkey

ABSTRACT

Therapeutic single-dose mirtazapine-induced symptomatic bradycardia: a case report

Cardiotoxicity is an important adverse effect of some psychotropic drugs. However, cardiac side effects with mirtazapine, which is used for an effective treatment of depression and anxiety, are rare. In this article, a forty-eight-year-old woman referred to psychiatric clinics with depressive symptoms. According to Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) criteria, major depressive disorder was diagnosed and mirtazapine 30mg/day was started. 30 minutes after the first dose of mirtazapine was brought to the emergency room with syncope, nausea, vomiting. She was examined in emergency service. Routine blood tests and ECG was studied. During the examination, the patient was followed up with a heart rate of 33 beats per minute, blood pressure arterial 80/50mmHg and a temperature of 36.1°C. 0.5mg atropine IV and theophylline inhaler were administered and cardiology consultation was requested. After atropine and theophylline administration, the heart rate was 48 beats/min in the second ECG. To the best of our knowledge, it is the first bradycardia developed after mirtazapine use in the literature. Bradycardia has been resolved after the half-life of mirtazapine has passed (37 hours for women). The initial heart rate of our patient was within normal limits prior to mirtazapine administration. There was no reason to explain bradycardia, we think that symptomatic bradycardine is caused by mirtazapine. In conclusion, this case report suggests that mirtazapine may cause bradycardia in patients. Risk factors for bradycardia caused by mirtazapine are unknown. Although in many patients this bradycardine does not cause a clinical outcome, clinicians should be aware of this and should perform ECG monitoring in patients with underlying cardiac disease, especially when prescribing mirtazapine.

Keywords: Bradycardia, mirtazapine, side effect

ÖZ

Terapötik tek doz mirtazapine bağlı gelişen semptomatik bradikardi: Bir olgu sunumu

Kardiyotoksisite bazı psikotrop ilaçların önemli bir yan etkisidir. Bununla birlikte, depresyon ve anksiyetenin etkili tedavisi için kullanılan mirtazapin ile kardiyak yan etkiler nadirdir. Bu yazıda, kırk sekiz yaşında bir kadın, depresif belirtileri olan psikiyatri kliniğine başvurdu. DSM-5 kriterlerine göre majör depresif bozukluk tanısı konmuş ve mirtazapin 30mg/gün başlanmıştır. Mirtazapinin ilk dozundan 30 dakika sonra senkop, mide bulantısı, kusma ile acil servise getirildi. Acil serviste muayene edildi. Rutin kan testleri ve EKG çalışıldı. Muayene sırasında hasta kalp atım hızı dakikada 33 atım, kan basıncı arteriyel 80/50mmHg ve 36.1°C sıcaklık ile takip edildi. 0.5mg atropin IV ve teofilin inhaler uygulandı ve kardiyoloji konsültasyonu istendi. Atropin ve teofilin uygulamasından sonra, ikinci EKG'de kalp atım hızı 48 atım/dk idi. Bildiğimiz kadarıyla, literatürde mirtazapin kullanımından sonra geliştirilen ilk bradikardidir. Bradikardi, mirtazapinin yarı ömrü sona erdikten sonra geriledi (kadınlar için 37 saat). Olgumuzun ilk kalp hızı, mirtazapin uygulamasından önce normal sınırlardaydı. Bradikardi açıklamak için hiçbir neden yoktu, biz semptomatik bradikardine mirtazapin neden olduğunu düşünüyoruz. Sonuç olarak, bu olgu sunumu mirtazapinin hastalarda bradikardiye neden olabileceğini düşündürmektedir. Mirtazapinin neden olduğu bradikardi için risk faktörleri bilinmemektedir. Birçok hastada bu bradikardinin klinik bir sonuca neden olmamasına rağmen, klinisyenler bunun farkında olmalı ve özellikle mirtazapin reçete ederken altta yatan kalp hastalığı olan hastalarda EKG izlemi yapmalıdır.

Anahtar kelimeler: Bradikardi, mirtazapin, yan etki

How to cite this article: Demir-Gundogmus P, Gundogmus I, Olcu EB, Karagoz A, Algul A. Therapeutic single-dose mirtazapine-induced symptomatic bradycardia: a case report. Dusunen Adam The Journal of Psychiatry and Neurological Sciences 2018;31:304-307.
https://doi.org/10.5350/DAJPN2018310309

Address reprint requests to / Yazışma adresi:
Ibrahim Gundogmus,
Sultan Abdulhamid Han Training and Research Hospital, Department of Psychiatry,
Selimiye Mh. Tibbiye Cd. 34668,
Uskudar/Istanbul, Turkey

Phone / Telefon: +90-216-542-2020/3760

E-mail address / Elektronik posta adresi:
dribrahim06@gmail.com

Date of receipt / Geliş tarihi:
October 31, 2017 / 31 Ekim 2017

Date of the first revision letter / İlk düzeltme öneri tarihi:
December 21, 2017 / 21 Aralık 2017

Date of acceptance / Kabul tarihi:
December 28, 2017 / 28 Aralık 2017

INTRODUCTION

Over the past years, there has been a large increase in the number of patients prescribed antidepressants and the occurrence of side effects due to antidepressant use. Side effects of antidepressants can increase after discontinuation and be treatment resistant; for that reason, it is crucial to take into account possible side effects when choosing an antidepressant (1,2). Mild and transient side effects are more frequent than lethal or irreversible ones (1). Antidepressants may involve a wide range of serious cardiovascular side effects such as brady- or tachycardia and hypo- or hypertension (3,4). Among these side effects, bradycardia, which can be defined by a heart rate of 60 beats per minute or less, is thought to be uncommon but dangerous (5). As bradycardia can lead to cardiac arrest, it is important to know that bradycardia may present as a medical emergency and hospitalization might be needed for follow up (5).

As an antidepressant with a unique psychopharmacological mechanism, mirtazapine is used effectively in the treatment of depression and anxiety (6,7). As is the case for any antidepressant, there is a potential for side effects with each use. Most frequently reported side effects of mirtazapine are sedation and weight gain (6). Other side effects are the occurrence of increased appetite, headache, and postural hypotension (8). In clinical practice, mirtazapine seems to offer real advantages over other antidepressants used, with fewer adverse drug reactions and important side effects, a lack of cardiotoxicity, and overall safety (7,8). Cardiovascular side effects can be an important adverse effect of antidepressant drugs, but mirtazapine has no cardiotoxic potential, and no study found in the literature has shown any mirtazapine-associated cardiovascular side effects.

As far as we know, there are no published reports of bradycardia as a result of using only mirtazapine. We describe a unique case of symptomatic bradycardia in a middle-aged female patient who had been taking a single dose of 30mg of mirtazapine.

CASE

A 48-year-old woman, single, university graduate, presented at the psychiatry clinic showing depressive symptoms. Her recurrent complaints were insomnia, hopelessness, crying attacks, reluctance, restlessness, and difficulty to concentrate over the last few months. There was no psychiatric disease in her personal background and she had no psychiatric or non-psychiatric medication. Her own and her family history were also negative for substance use, alcohol, and smoking. The scores for the Hamilton Anxiety Rating Scale and the Hamilton Depression Rating Scale were 26 and 34, respectively. According to Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) criteria, she was diagnosed with major depressive disorder and prescribed mirtazapine 30mg/day. Thirty minutes after she had used a single dose of 30mg of mirtazapine, she was brought by ambulance to our emergency department with syncope, nausea, and vomiting. In the emergency room, she was examined. Routine blood tests and electrocardiogram (ECG) were performed and she was monitored. On examination, the patient was alert, with a heart rate of 33 beats/min, arterial tension 80/50mmHg, 12 breaths/min, and a temperature of 36.1°C. Her neurologic, chest, and abdominal examinations and blood tests were normal. There was no symptom of any allergic reaction. As stated, her medical history included no prior diagnosis of bradycardia or any other cardiovascular disease. Half a mg of intravenous atropine and theophylline inhaler were administered and the cardiology department was consulted. On cardiovascular examination, the patient had normal heart sounds, normal peripheral pulses, normal jugular venous pressure, and no additional sounds or murmurs. In the examination by 12-lead first ECG, sinus bradycardia (33 beats/min), QT 440msec, and QTc 364msec were recorded. The heart rate was 48 beats/min in the second ECG after being administered atropine and theophylline. During six hours of follow-up, her heart rate varied from 48 to 53 beats/min on cardiac monitoring. It was decided that the patient be hospitalized and followed up in the

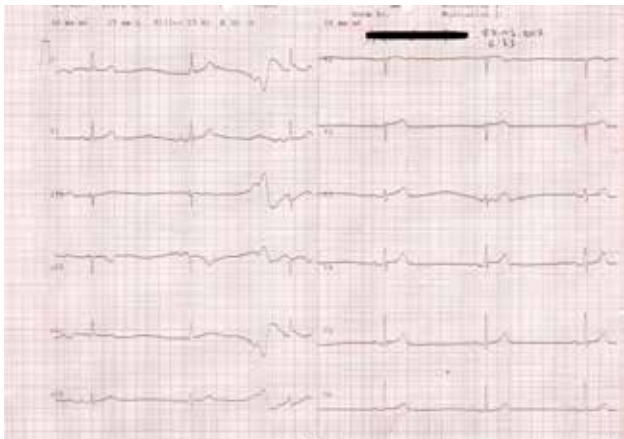

Figure 1: The first ECG of patient at the time of admission to the emergency department.

cardiology clinic. Bradycardia resolved within 36 hours after mirtazapine administration. Cardiovascular examinations including ECG, treadmill exercise electrocardiography, and echocardiogram showed no abnormalities. According to the Naranjo algorithm for the evaluation of adverse effects, it was found to be probable that the adverse reaction causing bradycardia was induced by mirtazapine: 5-8=probable drug advers effects were identified. The patient was discharged with a heart rate of 70 beats/min two days after hospitalization. Mirtazapine was stopped and venlafaxine 75mg/day started. The patient's complaints did not return in control examinations.

The patient gave us a full written consent to publish this case report that was signed and dated in front of witnesses.

DISCUSSION

As far as we know, the present case is the first one in the literature reporting bradycardia in a female after taking a single dose of mirtazapine. The bradycardia resolved after a period corresponding to the half-life of mirtazapine, which is 37 hours for females on average. Our patient's baseline heart rate had been within normal limits before the administration of mirtazapine. She had no medical conditions to explain bradycardia; therefore, we think that mirtazapine was the cause of her symptomatic bradycardia. It has been reported previously that antidepressants can induce bradycardia in susceptible patients. The reports have described episodes of bradycardia associated with the use of antidepressants such as escitalopram (9), citalopram (10,11), fluoxetine (12,13), paroxetine (14), and mianserin (15,16).

Mirtazapine, which is a noradrenergic and specific serotonergic antidepressant (NaSSA), increases noradrenaline and serotonin release by blocking presynaptic α-2 autoreceptors and heteroreceptors (6,17). It is also a potent antagonist of postsynaptic 5-HT2 and 5-HT3 receptors and has only a weak affinity for 5-HT1 receptors and very weak muscarinic, anticholinergic, and histamine-antagonist properties (6,18). For that reason, mirtazapine directly increases norepinephrine release and indirectly serotonin release in the central and peripheral nervous system (6,17). The mechanism of mirtazapine-related bradycardia is still not fully understood. There are several hypotheses that endeavor to clarify the mechanism of this relationship. In our case, the most likely mechanism for this condition is that the central effects of 5-HT can cause vagal-mediated bradycardia or tachycardia by activation of 5-HT1A and 5-HT2 receptors (19). Since mirtazapine possesses 5-HT affinity, this can induce bradycardia (19). Another hypothesis is that this side effect could occur as a result of mirtazapine's antagonist action on the presynaptic α-2 autoreceptors and heteroreceptors (18). On the other hand, one needs to keep in mind a certain predisposition to mirtazapine or nontherapeutic component hypersensitivity.

The limitations of this report include the absence of measurement of mirtazapine in plasma, electrophysiological studies, and not repeating the administration of mirtazapine for observation; however, these examinations were not practicable in the clinical setting.

In conclusion, this case report suggests that mirtazapine may induce bradycardia. The risk factors for mirtazapine-induced bradycardia are unknown. Although bradycardia may not induce any clinical results in most patients, clinicians should be aware of the risk and perform clinical ECG monitoring, particularly in patients with a known underlying heart

Contribution Categories		Author Initials
Category 1	Concept/Design	P.D.G., A.A.
	Literature review	I.G., A.K.
	Data analysis/Interpretation	E.B.O., A.A.
	Case follow-up (if applicable)	E.B.O., I.G., A.K.
Category 2	Drafting manuscript	I.G., P.D.G.
	Critical revision of manuscript	A.K., I.G., E.B.O.
Category 3	Final approval and accountability	A.A., I.G., E.B.O., P.D.G., A.K.
Other	Technical or material support	E.B.O., A.K.
	Supervision	A.A., I.G., P.D.G.
	Securing funding (if applicable)	N/A

disease, when prescribing mirtazapine. It can be provided information and advice about the side effects of mirtazapine.

Informed Consent: Written consent was obtained from the participants.

Peer-review: Externally peer-reviewed.

Conflict of Interest: Authors declared no conflict of interest.

Financial Disclosure: Authors declared no financial support.

REFERENCES

1. Schmid C, Grohmann R, Engel RR, Ruther E, Kropp S. Cardiac adverse effects associated with psychotropic drugs. Pharmacopsychiatry 2004; 37(Suppl 1):S65-69. **[CrossRef]**

2. Zajecka JM. Clinical issues in long-term treatment with antidepressants. J Clin Psychiatry 2000; 61(Suppl 2):20-25.

3. Coupland N, Wilson S, Nutt D. Antidepressant drugs and the cardiovascular system: a comparison of tricylics [sic] and selective serotonin reuptake inhibitors and their relevance for the treatment of psychiatric patients with cardiovascular problems. J Psychopharmacol 1997; 11:83-92. **[CrossRef]**

4. Sarlon J, Habich O, Schneider B. Elevated rest heart rate in psychiatric patients and different effects of psychotropic medication. Pharmacopsychiatry 2016; 49:18-22.

5. Wung SF. Bradyarrhythmias: Clinical Presentation, Diagnosis, and Management. Crit Care Nurs Clin North Am 2016; 28:297-308. **[CrossRef]**

6. Nutt D. Mirtazapine: pharmacology in relation to adverse effects. Acta Psychiatr Scand Suppl 1997; 391:31-37. **[CrossRef]**

7. Stimmel GL, Dopheide JA, Stahl SM. Mirtazapine: an antidepressant with noradrenergic and specific serotonergic effects. Pharmacotherapy 1997; 17:10-21.

8. Masand PS, Gupta S. Long-term side effects of newer-generation antidepressants: SSRIS, venlafaxine, nefazodone, bupropion, and mirtazapine. Ann Clin Psychiatry 2002; 14:175-182. **[CrossRef]**

9. Beyenburg S, Schonegger K. Severe bradycardia in a stroke patient caused by a single low dose of escitalopram. Eur Neurol 2007; 57:50-51. **[CrossRef]**

10. Padala KP, Padala PR, Wengel SP. Dose-dependent bradycardia with citalopram in an elderly patient. Prim Care Companion J Clin Psychiatry 2010; 12:PCC 09100789.

11. Isbister GK, Prior FH, Foy A. Citalopram-induced bradycardia and presyncope. Ann Pharmacother 2001; 35:1552-1555. **[CrossRef]**

12. Anderson J, Compton SA. Fluoxetine induced bradycardia in presenile dementia. Ulster Med J 1997; 66:144-145.

13. Friedman EH. Fluoxetine-induced bradycardia. J Clin Psychiatry 1991; 52:477.

14. Pae CU, Kim JJ, Lee CU, Lee SJ, Chul-Lee CL, Paik IH. Provoked bradycardia after paroxetine administration. Gen Hosp Psychiatry 2003; 25:142-144. **[CrossRef]**

15. Carcone B, Vial T, Chaillet N, Descotes J. Symptomatic bradycardia caused by mianserin at therapeutic doses. Hum Exp Toxicol 1991; 10:383-384. **[CrossRef]**

16. Koseoglu Z, Kara B, Satar S. Bradycardia and hypotension in mianserin intoxication. Hum Exp Toxicol 2010; 29:887-888. **[CrossRef]**

17. de Boer T. The pharmacologic profile of mirtazapine. J Clin Psychiatry 1996; 57(Suppl 4):19-25.

18. Blier P. Pharmacology of rapid-onset antidepressant treatment strategies. J Clin Psychiatry 2001; 62(Suppl 15):12-17.

19. Villalon CM, Centurion D. Cardiovascular responses produced by 5-hydroxytriptamine:a pharmacological update on the receptors/mechanisms involved and therapeutic implications. Naunyn Schmiedebergs Arch Pharmacol 2007; 376:45-63. **[CrossRef]**