

Received: 2017.12.06
Accepted: 2018.01.26
Published: 2018.04.07

e-ISSN 1941-5923
© Am J Case Rep, 2018; 19: 410-412
DOI: 10.12659/AJCR.908412

Tachyphylaxis to the Sedative Action of Mirtazapine

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABDE 1 **Georgios Papazisis**
BDF 1 **Spyridon Siafis**
EG 1,2 **Dimitrios Tzachanis**

1 Department of Clinical Pharmacology, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece
2 Department of Medicine, University of California San Diego, La Jolla, CA, U.S.A.

Corresponding Author: Georgios Papazisis, e-mail: papazisg@auth.gr
Conflict of interest: None declared

Patient: Female, 30
Final Diagnosis: Depression
Symptoms: —
Medication: Mirtazapine
Clinical Procedure: —
Specialty: Psychiatry

Objective: Unusual or unexpected effect of treatment

Background: The pharmacological term tachyphylaxis is used to describe rapidly occurring response desensitization, a situation where the biological response to a given drug dose diminishes when it is given continuously. This pharmacological phenomenon is well observed in some drug categories such as ephedrine, nitrates, beta blockers and H₂ antagonists. Mirtazapine is a widely-used antidepressant with a multimodal mechanism of action.

Case Report: In the present case, we report rapid onset and consistent tachyphylaxis regarding the sedative action of mirtazapine in a 30-year-old female.

Conclusions: To our knowledge this is the first reported case of rapid onset and consistent tachyphylaxis to the sedative effect of mirtazapine confirming the complexity of the pharmacological profile of the drug.

MeSH Keywords: Conscious Sedation • Histamine Antagonists • Tachyphylaxis

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/908412>



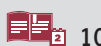
1043



—



—



10



Background

The pharmacological term tachyphylaxis is used to describe rapidly occurring response desensitization, a situation where the biological response to a given drug dose diminishes when it is given continuously or repeatedly. It is observed in some drug categories such as ephedrine [1], nitrates [2], beta-blockers [3], and H₂ receptor antagonists [4]. Concerning antidepressants, in most studies tachyphylaxis (or “poop-out”) is usually used to describe a relapse of an episode of major depression after full recovery despite continued treatment with a previously effective antidepressant dose, but pharmacologically, this is rather confusing and the term tolerance is much more comprehensive [5,6].

Mirtazapine is a widely-used antidepressant with a multimodal mechanism of action (a noradrenergic and specific serotonergic antidepressant) having no effect as monoamine reuptake inhibitor. It is a potent 5-HT_{2A}, 5-HT₃, H₁, and central presynaptic α₂-adrenergic autoreceptor antagonist, a moderate peripheral α₁-adrenergic and muscarinic receptor antagonist, but also exhibits inverse agonistic properties at 5-HT_{2C} receptors. Mirtazapine, especially in low doses (7.5 or 15 mg/day), produces sedative effects due to potent histamine H₁ receptor antagonism, and is widely used off-label for sleep disturbances. However, H₁-antagonism is a target not thought to contribute to its therapeutic antidepressant efficacy [7,8]. We report a case of a 30-year-old female rapidly developing tachyphylaxis to the sedative action of mirtazapine. Considering the off-label use of the drug for insomnia, awareness of the possibility of tachyphylaxis is important for the management of the patient.

Case Report

A 30-year-old female presented 2.5 years ago with depressed mood, anhedonia, psychomotor retardation, fatigue, and insomnia receiving a DSM-IV-TR diagnosis of Major Depression. The patient had no history of drug, tobacco, or alcohol misuse and was free of medical comorbidities. She was put on venlafaxine, gradually increased up to 150 mg daily and 15 mg of mirtazapine at bedtime, aiming to improve her sleep. The core depressive symptoms (depressed mood and anhedonia) gradually improved after 2 weeks and full remission of depression occurred 2 months after treatment initiation. Nine months later venlafaxine was tapered off. However, during this period her sleep was not successfully managed. It improved initially but after a few days of treatment the patient complained of insomnia. Mirtazapine was increased to 30 mg but couldn't restore the original response and a benzodiazepine (triazolam) was suggested to improve her sleep. However, the patient refused to receive a benzodiazepine because she was afraid of its addictive properties and continued to use 15 mg of mirtazapine.

Notably, she reported a rapidly decreasing sedative effect after 7 days of use. The recommendations of her physician after the 9-month period was to stop using mirtazapine (and venlafaxine); a follow-up appointment was set up after 3 months. The patient didn't show up for the first follow-up appointment but presented a year later after a reminder call for her second follow-up. No symptoms of depression or other mental disorders were diagnosed, and she stated no use of any other licit or illicit substance. However, the patient reported that she was still taking mirtazapine at bedtime, but in her own way: after she had noticed that the medication had no effect taking it for 7 days consecutively, she changed to taking a 3-day break for its sedative effect to return. So, during this year, she had been taking it 7 days on, 3 days off.

Discussion

In this case of tachyphylaxis to the sedative action of mirtazapine was evident even in the first period of use, while the physiological effects of tachyphylaxis resolved when dosing was re-initiated after the 3-day hiatus. According to the WHO-UMC system for standardized case causality assessment this clinical event is defined as “certain” [9]. Tachyphylaxis occurred in a plausible time related to drug administration and cannot be explained by disease or other drugs, since mirtazapine was the only drug used. Drug discontinuation resulted in insomnia and re-exposure produced sedative effects, so the de-challenge and re-challenge criteria are fulfilled.

The term tachyphylaxis describes a decreasing response to a drug that occurs very rapidly, sometimes with its initial administration. Tachyphylaxis and tolerance differ in time to onset, tolerance is defined as a slow decrease in responsiveness to a drug (days/week) [10]. Tachyphylaxis can be the consequence of different types of molecular changes in the target tissue (i.e., a decrease or increase in receptor number, known as receptor desensitization or hypersensitization, respectively). Thus, tachyphylaxis correctly refers to a desensitization of response, not necessarily a desensitization of receptors [3].

The mechanism of mirtazapine tachyphylaxis is speculative. The present case suggests tachyphylaxis to the sedative action of mirtazapine likely resulting from H₁ antagonism. Histamine tachyphylaxis has been described for over 50 years; however, this effect is attributed to H₂ antagonists. Tachyphylaxis to H₂ antagonists develops rapidly, is evident by the second day of use and does not appear to be progressive. Once tachyphylaxis to an H₂ antagonist has developed, increasing the dose does not appear to be effective in overcoming the loss of its effect [4]. Tachyphylaxis may be also exemplified by the rapid tolerance that develops to the effects of indirect acting drugs, meaning drugs that produce their effects by stimulating the

release of a normal neurotransmitter. Ephedrine, a drug which stimulates the sympathetic nervous system, effects as a model of tachyphylaxis [1]. Mirtazapine indirectly augments monoamine transmission presumably through antagonist activity at multiple receptors including the adrenergic α_2 and serotonin 5-HT_{2A/C} receptors [7]. In the case of tachyphylaxis to beta blockers (e.g., timolol for glaucoma treatment), it has been shown that treatment can lead to a rapid increase in the density of beta-adrenergic receptors, an effect that can occur within a day of the initial dosage [3]. However, similar findings with mirtazapine are not reported in the literature.

It is necessary to notice the difference that, regarding antidepressants, the condition in which a depressed patient loses a previously effective antidepressant treatment response despite staying on the same drug and dosage for maintenance

References:

1. Timmons R, Hamilton L: Drugs, brains and behavior. 1990. Available from: <http://www.rci.rutgers.edu/~lwh/drugs/chap09.htm#Tachyphylaxis>
2. Munzel T, Daiber A, Mulsch A: Explaining the phenomenon of nitrate tolerance. *Circ Res*, 2005; 97: 618–28
3. Abelson M, Vashishan A: The truth about tachyphylaxis. *Review of Ophthalmology*, 2006 Mar 16. Available from: www.reviewofophthalmology.com/article/the-truth-about-tachyphylaxis
4. McRorie JW, Kirby JA, Miner PB: Histamine2-receptor antagonists: Rapid development of tachyphylaxis with repeat dosing. *World J Gastrointest Pharmacol Ther*, 2014; 5: 57–62
5. Solomon DA, Leon AC, Mueller TI et al: Tachyphylaxis in unipolar major depressive disorder. *J Clin Psychiatry*, 2005; 66: 283–90
6. Targum SD: Identification and treatment of antidepressant tachyphylaxis. *Innov Clin Neurosci*, 2014; 11: 24–28
7. Labasque M, Meffre J, Carrat G et al: Constitutive activity of serotonin 2C receptors at G protein-independent signaling: Modulation by RNA editing and antidepressants. *Mol Pharmacol*, 2010; 78: 818–26
8. Croom KF, Perry CM, Plosker GL: Mirtazapine: A review of its use in major depression and other psychiatric disorders. *CNS Drugs*, 2009; 23: 427–52
9. World Health Organization. The use of the WHO-UMC system for standardised case causality assessment. 2010. Available from: http://www.who.int/medicines/areas/quality_safety/safety_efficiency/WHOcausality_assessment.pdf
10. Katzung BG: *Basics of clinical pharmacology*. 8th ed. London: McGraw/Hill, 2001

treatment should be described as tolerance rather as tachyphylaxis [5].

Conclusions

To our knowledge this is the first reported case of rapid onset and consistent tachyphylaxis to the sedative effect of mirtazapine confirming the complexity of the pharmacological profile of the drug. Since mirtazapine is commonly used off-label for insomnia, clinicians should be aware of the potential for rapid development of tachyphylaxis.

Conflicts of interest

None.