

Management of Tizanidine Withdrawal Syndrome: A Case Report

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ABSTRACT: Most drugs that act on the central nervous system (CNS) require dose titration to avoid withdrawal syndrome. Tizanidine withdrawal syndrome is caused by adrenergic discharge due to its α_2 -agonist mechanism and is characterized by hypertension, reflex tachycardia, hypertonicity, and anxiety. Although tizanidine withdrawal syndrome is mentioned as a potential side effect of cessation, it is not common and there have been few reports. We present the case of a 31-year-old woman with tizanidine withdrawal syndrome after discontinuing medication prescribed for a muscle contracture (tizanidine). She showed high adrenergic activity with nausea, vomiting, generalized tremor, dysthermia, hypertension, and tachycardia. Symptoms were reversed and successful reweaning was achieved by restarting tizanidine followed by slow downward titration. Withdrawal syndrome should be considered when drugs targeting the CNS are suddenly stopped. Weaning regimens should be closely monitored for acute withdrawal reactions.

KEYWORDS: Tizanidine, withdrawal syndrome, adrenergic, hypertension, neurotransmitters, imidazole

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Introduction

Tizanidine is an imidazole derivative with central analgesic action used as a muscle relaxant to treat muscle spasms and chronic spasticity. It is structurally similar to clonidine and has a high affinity for α_2 -agonist receptors. Its presynaptic inhibition reduces the nervous reflex, thus also acting as an analgesic, so its imidazolic action allows tizanidine to decrease spasticity and movement resistance.¹

In clinical practice, we are frequently faced with situations where chronic medication is interrupted, such as during hospitalization in which the patient's acute situation does not allow its continuation. However, some drugs require a gradual dose titration to avoid abrupt discontinuation and withdrawal syndrome. Withdrawal syndromes are mostly related to drugs with action on the central nervous system (CNS), as neurotransmitter regulation is also involved in regulating cardiovascular, respiratory, or digestive system functions. There is ongoing debate as to the mechanism underlying these syndromes. Although tizanidine withdrawal is mentioned as a potential side effect of cessation, it is not common and there have been few reports to date.

We present a case of tizanidine withdrawal syndrome after discontinuing medication prescribed for a muscle contracture.

Case Report

A 31-year-old white woman with no history of drug abuse, including tobacco, and a medical history of untreated episodes of migraine, mixed anxiety, and depressive disorder diagnosed by her psychiatrist and treated with sertraline 100 mg every 24 hours and diazepam 2.5 mg every 8 hours. She also had acute episodes of hypochondria. There was no other co-diagnosis related to

cardiovascular disorders. In May 2016, she presented with neck pain due to a muscle contracture and her general practitioner prescribed tizanidine 2 mg every 8 hours (6 mg daily) for a month followed by a tapering down regimen (2 mg every 24 hours). However, by her own decision, the patient increased the dose to 2 mg every 3 hours (16 mg daily) and stopped it abruptly instead of tapering down. She did not stop the other prescribed medication and reported that she had not consumed alcohol or over-the-counter drugs the day she was hospitalized.

The patient presented in the emergency center of her primary care center with nausea, vomiting, generalized tremor, and dysthermia that started 12 hours after the last dose of tizanidine administration (after cessation). She also showed high blood pressure (systolic blood pressure of 190 mmHg and diastolic blood pressure of 130 mmHg) and was administered 25 mg of sublingual captopril to control it. The patient remained hemodynamically unstable, with noncontrolled hypertension and high pulse rate, so she was transferred to our hospital. On transfer, she had a systolic pressure of 160 mmHg and diastolic pressure of 110 mmHg, tachycardia (140 bpm) without murmurs, tachypnea (26 breaths/min) with no added noise, and febricula of 37.2°C.

Additional diagnostic tests showed normal laboratory parameters; C-reactive protein, thyrotropin, and electrolytes; increased creatine kinase (CK) values; and positive urine benzodiazepine screening. Neurologically, she showed a Glasgow Coma Scale 15/15 with tremors not attributable to any focus. An electrocardiogram revealed sinus tachycardia (150–160 bpm), so she was administered 2 intravenous bolus of 25 mg esmolol and heart rate decreased to 130 bpm. Then, she was prescribed 1 dose of



intravenous propranolol 10 mg, which lowered her heart rate to 100 to 110 bpm. Due to her hyperadrenergic state, oral β -blocker with propranolol 10 mg every 4 hours was maintained, keeping her heart rate at 100 to 110 mm Hg and her blood pressure values around 150/110 mm Hg (systolic and diastolic, respectively). Hyperthermia was treated with intravenous paracetamol 1 g every 8 hours, and her anxiety was managed with sublingual diazepam 10 mg.

This episode of sudden adrenergic discharge suggested tizanidine withdrawal syndrome. We searched for other cases of tizanidine withdrawal in the literature (PUBMED and MEDLINE databases) and found only 2 reports^{2,3} in which withdrawal was managed by restarting medication at low dose to reduce symptoms and then reduced progressively until it was fully stopped. Based on this literature, we restarted medication with tizanidine 2 mg every 8 hours (her previous regimen was 2 mg 8 times a day) and tapered down for 12 days (2 mg every 8 hours for 4 days, 2 mg every 12 hours for the next 4 days and 2 mg per day for the last 4 days).

When tizanidine was reintroduced, clinical improvement was observed immediately after the first dose was given. The patient's heart rate decreased to 80 to 85 bpm, although her blood pressure remained high (approximately 150/110 mm Hg systolic and diastolic, respectively); her tremors disappeared, and her agitation was controlled. In the following 24 hours, the patient was hemodynamically stable and was discharged with the new treatment regimen. There were no changes to her other usual medication and she was followed up by her primary care center.

Discussion

Tizanidine is an imidazole derivative with central analgesic action used as a muscle relaxant to treat muscle spasms and chronic spasticity. Its main adverse events are also derived from its mechanism of action (similar to other α_2 -agonists such as clonidine), resulting in hypotension and bradycardia.⁴ These inhibitory receptors (α_2) inhibit noradrenaline release. Withdrawal syndrome is a well-described phenomenon due to cessation of adrenal catecholamine secretion blockade and a subsequent surge in their circulating levels causing vasoconstriction with high cardiac work and tachycardia.

Tizanidine shows linear pharmacokinetics with a half-life ($t_{1/2}$) of 2.5 hours and a peak plasma concentration (t_{max}) at 1.5 hours⁵⁻⁷. Bioavailability is 40% to 95% of the administered dose due to its extensive hepatic metabolism by CYP1A2. Tizanidine metabolites have a $t_{1/2}$ of 20 to 40 hours and are not known to be active. It is recommended to start with 4 mg per day and, to prevent hypotension peaks, gradually increase the dose (by 2-4 mg) to a maximum of 36 mg per day divided into 3 administrations.^{4,7} However, due to its narrow therapeutic window and high interindividual variability, dose should be adjusted to each patient. Pharmacodynamic studies show that response and adverse events are related to tizanidine concentrations, and that these are linearly related to dose.⁵⁻⁷

The incidence of tizanidine withdrawal is difficult to ascertain as there are only 2 published case reports of its management.^{2,3} Mörkl et al² described a 53-year-old patient who developed serious withdrawal syndrome after long-term high-dose treatment in the context of stress cardiomyopathy (with reflex tachycardia, hypertension, tremor, hypertonicity, and anxiety). They concluded that tizanidine dose should be gradually reduced under the supervision of a psychiatrist. Karol et al³ reported a case of delirium, extrapyramidal symptoms, and autonomic dysfunction in a 59-year-old man following abrupt cessation of baclofen and tizanidine. It was resolved within 24 hours after reintroduction of baclofen. The authors concluded that withdrawal syndrome of muscle relaxants must be suspected, especially in patients with symptoms of stiffness and dysfunction.

Treatment decision making was also based on clonidine withdrawal management because it has the same chemical structure and mechanism of action but different pharmacokinetics and pharmacodynamics. It has a higher potency than tizanidine due to its major affinity to adrenergic receptors, especially central α_2 receptors, whereas tizanidine acts on peripheral α receptors and has a greater effect on the cardiovascular system. It is also an imidazole that reduces sympathetic efferences, and its therapeutic uses are treatment of abstinence syndrome and as a central antihypertensive drug. Adverse events are also attributable to its mechanism of action, but clonidine has a major and longer hypotension effect, around 10 to 50 times higher compared with tizanidine, due to its longer $t_{1/2}$ and its action on central α receptors. The effects of withdrawal are similar to those of tizanidine withdrawal, but with a major impact on the vascular balance: hypertensive outbreak, severe tachycardia, tachypnea, and hypothermia sensation.⁸

Management of tizanidine and clonidine withdrawal syndrome includes^{3,8} the following. (1) Hemodynamic control with adrenergic blocker drugs. During treatment of clonidine withdrawal syndrome, hypertension may be aggravated using β -blocker monotherapy, so it is recommended to associate α -blockers to β -blockers (eg, propranolol or labetalol). (2) Reintroduction of the drug in a lower dose followed by a gradual dose titration.

Considering the potential pharmacodynamic drug interactions, the sedative effect of tizanidine may be potentiated by concomitant use of other CNS depressants (eg, diazepam in our patient). In addition, tizanidine and diazepam can also exhibit additive hypotensive effects and could aggravate rebound after abrupt cessation. In these situations, a more gradual dose titration might be appropriate to minimize the risk of withdrawal. We detected another interaction between tizanidine and sertraline: both drugs can cause QT interval prolongation, which may result in additive effects and increased risk of ventricular arrhythmias. In our case, the sinus tachycardia observed in the patient's electrocardiogram may be due to tizanidine and sertraline treatment.

Other drugs also present withdrawal syndrome, such as antidepressants (eg, trazodone and venlafaxine),⁹ antipsychotics,¹⁰

GABAergic drugs¹¹ (eg, baclofen), and benzodiazepines.^{12,13} Our patient was under diazepam treatment, which could have contributed to her symptoms. However, her urine drug test was positive for benzodiazepines and she confirmed that she was taking benzodiazepine without discontinuation.

The syndrome associated with discontinuing selective serotonine reuptake inhibitors has been widely reported and is distinctly different from the classic withdrawal syndrome, which is mainly observed with alcohol and barbiturates, and is not associated with dependence, tolerance or drug-seeking behavior.¹⁴ Serotonergic syndrome could have been misdiagnosed as it is presented with similar symptoms, including neuromuscular hyperreactivity (tremor, hyperreflexia, myoclonus), hyperthermia, altered mental status, muscle rigidity, leukocytosis, elevated CK, elevated hepatic transaminases, and metabolic acidosis. However, we could differentiate between this and tizanidine withdrawal syndrome because of the time-related effects. Symptoms appeared after abruptly discontinuing tizanidine and were reversed when treatment was restarted.

Conclusions

We report the case of a 31-year-old patient having tizanidine withdrawal syndrome. Management included treatment of acute symptoms and the reintroduction of tizanidine at a lower dose and tapering down until stopping treatment.

When drugs are suddenly stopped, especially those involved in the CNS, the possibility of withdrawal syndrome should be considered. Patients should be closely monitored for acute withdrawal reactions during the weaning regimes. However, more studies are needed to explore the risk, mechanisms of discontinuation, withdrawal syndromes, and how they can be avoided and treated.

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Author Contribution

AS-L and AP made an equal contribution to this article, in the bibliographic search and in the pharmaceutical intervention at the moment of the event. Both dedicated the same time to

writing and reviewing the case report. TL, SC-S, and MC were involved in the bibliographic search and in reviewing the case report. RJ was involved in the writing process.

Disclosures and Ethics

The authors have read and confirmed their agreement with the ICMJE criteria on authorship and conflict of interest. The authors also confirm that this article is unique and has not been published or is currently under consideration in any other publication.

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