Ağrı Tıp Fakültesi Dergisi 2025 3(3):134-138
e-ISSN: 2980-0978

Case Report/Olgu Sunumu
DOI:10.61845/agrimedical.1716160

Severe serotonin syndrome due to high-dose venlafaxine: A rare case successfully managed with chlorpromazine

Yüksek doz venlafaksine bağlı şiddetli serotonin sendromu: Klorpromazin ile başarıyla yönetilen nadir bir olgu

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Gönderilme Tarihi: 14/06/2025
Kabul Tarihi: 13/10/2025
Yayınlanma Tarihi: 29/10/2025

Cite this article:
Duman MB, Kızıltunç HS. Severe serotonin syndrome due to high-dose venlafaxine: A rare case successfully managed with chlorpromazine. Ağrı Med J. 2025; 3(3): 134-138.

ABSTRACT

Serotonin syndrome is a potentially life-threatening clinical condition caused by excessive serotonergic activity within the central nervous system. In this report, we present the case of a 40-year-old woman with a diagnosis of major depressive disorder who developed serotonin syndrome following a suicidal ingestion of 3000 mg extended-release venlafaxine. The patient manifested agitation, clonus, generalized tonic–clonic seizures, and altered mental status. Despite intensive supportive care and administration of oral cyproheptadine, no clinical improvement was achieved. However, following intramuscular administration of 25 mg chlorpromazine, the patient demonstrated rapid neurological and hemodynamic recovery. This case highlights that severe serotonin syndrome may occur after ingestion of a single serotonergic agent at high doses, and that chlorpromazine may provide therapeutic benefit in cases where conventional treatments fail.

Keywords: *Serotonin syndrome, Venlafaxine hydrochloride, Chlorpromazine*

ÖZ

Serotonin sendromu, merkezi sinir sistemindeki aşırı serotonerjik aktiviteye bağlı olarak gelişen, potansiyel olarak yaşamı tehdit edebilen klinik bir tablodur. Bu yazıda, majör depresif bozukluk tanısıyla takip edilen ve suisidal amaçlı 3000 mg uzatılmış salınımlı venlafaksin alan 40 yaş kadın hastada gelişen serotonin sendromu olgusu sunulmaktadır. Hastada ajitasyon, klonus, jeneralize tonik-klonik nöbet ve bilinç değişikliği gelişmiştir. Yoğun destek tedavisi ve oral siproheptadin uygulanmasına rağmen klinik düzelme sağlanamamıştır. Ancak intramüsküler yoldan 25 mg klorpromazin uygulanmasının ardından hastada hızlı nörolojik ve hemodinamik iyileşme gözlenmiştir. Bu olgu, tek bir serotonerjik ajanın yüksek doz alımı sonrasında ciddi serotonin sendromu gelişebileceğini ve konvansiyonel tedavilerin yetersiz kaldığı durumlarda klorpromazinin terapötik fayda sağlayabileceğini desteklemektedir.

Anahtar Kelimeler: *Serotonin sendromu, Venlafaksin hidroklorür, Klorpromazin*

INTRODUCTION

Serotonin syndrome, also referred to as serotonin toxicity, is a potentially life-threatening condition caused by increased serotonergic activity in the central nervous system. It may arise following therapeutic use, drug interactions, or intentional overdose. Etiologically, the most common agents implicated are selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants, triptans, opioids (e.g., tramadol, meperidine), linezolid, and dextromethorphan. Although classically defined by the triad of mental status changes, autonomic instability, and neuromuscular abnormalities, clinical presentation can range from mild symptoms to fatal outcomes (1-4). The severity of findings is generally correlated with the degree of serotonergic excess (5). Mental status changes may include anxiety, agitation, disorientation, or delirium; autonomic findings may involve hyperthermia, tachycardia, hypertension, vomiting, and diarrhea. Neuromuscular manifestations typically include hyperreflexia, clonus (often in the lower extremities), muscle rigidity, and bilateral Babinski sign (3). Life-threatening complications such as seizures and hyperthermia have been reported in severe cases (6). Although serotonin syndrome is usually associated with polypharmacy and drug interactions, it can also result from an overdose of a single serotonergic agent. In this report, we present a rare case of serotonin syndrome following the ingestion of a high dose of extended-release venlafaxine in a suicide attempt. The primary approach to the management of serotonin syndrome is discontinuation of the offending agent and provision of intensive supportive care. In mild to moderate cases, benzodiazepines are commonly employed for sedation. Among the antiserotonergic agents, cyproheptadine is the most frequently used; it is available in oral form and has been shown to be effective, particularly in controlling refractory agitation, hyperthermia, and neuromuscular manifestations. Despite standard treatment, the patient's symptoms remained refractory. Remarkably, they resolved rapidly after intramuscular administration of chlorpromazine, a serotonin antagonist that is not routinely used for serotonin syndrome.

CASE

A 40-year-old female with a known diagnosis of major depressive disorder was on 75 mg/day of extended-release venlafaxine. She presented to the emergency department one hour after ingesting 40 tablets (3000 mg total) of venlafaxine in a suicide attempt. On arrival, she exhibited with generalized muscle rigidity and agitation. Initial vital signs were blood pressure 116/86 mmHg, heart rate 117 bpm, respiratory rate 14 breaths/min, SpO_2 96% on room air, and body temperature 37.4°C. Gastric lavage and activated charcoal administration were promptly performed. The patient was subsequently transferred to the intensive care unit for close monitoring. Laboratory results on admission were BUN 11 mg/dL, creatinine 0.84 mg/dL, AST 19 U/L, ALT 22 U/L, glucose 104 mg/dL, sodium 139 mEq/L, potassium 3.7 mmol/L, and creatine kinase (CK) 108 U/L. During follow-up, her Glasgow Coma Scale score dropped to E3V4M5, and her pupils were noted to be bilaterally mydriatic. Arterial blood gas showed: pH 7.16; pCO_2 42 mmHg; HCO_3 15.1 mmol/L; SpO_2 80%; and lactate 8.4 mmol/L. She experienced a 15-second generalized tonic-clonic seizure and was treated with intravenous midazolam, followed by endotracheal intubation. Her blood pressure dropped to 84/63 mmHg and heart rate increased to 140 bpm. Intravenous isotonic saline and magnesium sulfate were administered. ECG revealed sinus tachycardia at 136 bpm and a prolonged QTc interval of 545 ms, which improved to 403 ms after treatment. After the ingestion of a high dose of serotonergic agent, the patient manifested spontaneous clonus. A comprehensive review of medical history revealed no concomitant use of additional serotonergic agents or other pharmacological substances. There was no evidence of intravenous drug or stimulant use, nor clinical features suggestive of a withdrawal syndrome related to such agents. Physical examination and laboratory investigations demonstrated no findings consistent with an infectious process. Furthermore, cranial computed tomography did not reveal any additional pathological abnormalities. Taken together, the patient's clinical history, physical examination, laboratory data, and imaging studies supported the diagnosis of serotonin syndrome, established in accordance with the Hunter Serotonin Toxicity Criteria in the context of high-dose serotonergic exposure (Table 1). According to these criteria, in a patient with a history of serotonergic agent use, the presence of any one of the specified clinical findings is sufficient to establish the diagnosis of serotonin syndrome. Despite supportive measures, her vital signs and neurological status did not improve. Oral cyproheptadine 12 mg was administered via a nasogastric tube without clinical improvement over the following two hours. Subsequently, 25 mg intramuscular chlorpromazine was administered. Two hours after chlorpromazine administration, the patient's heart rate normalized to 81 bpm and blood pressure stabilized at 119/65 mmHg. Repeat blood gas analysis showed pH 7.31, pCO_2 28 mmHg, HCO_3 19 mmol/L, and lactate 1.7 mmol/L. She remained hemodynamically stable, and her neurological symptoms progressively improved. She was successfully extubated within 24 hours and transferred to the inpatient ward. All serotonergic agents were discontinued. The patient made a full recovery and was discharged in good condition.

Table 1. Hunter serotonin toxicity criteria

➢ Spontaneous clonus
➢ Inducible clonus+ [agitation or diaphoresis]
➢ Ocular clonus + [agitation or diaphoresis]
➢ Tremor + hyperreflexia
➢ Hypertonia + temperature > 38°C + [ocular clonus or inducible clonus]

Table 2. Clinical timeline of the patient

Time (Hour)	Clinical Status	Interventions	Key Findings
0 (Arrival)	Agitation, clonus, altered consciousness	Gastric lavage, activated charcoal	GCS E3V4M5, stable vitals
+1 h	Generalized seizure	IV midazolam, intubation	Lactate ↑, pH ↓, SpO_2 ↓
+2 h	Supportive care + cyproheptadine	Cyproheptadine via NG tube	No improvement
+4 h	IM chlorpromazine administration	IM chlorpromazine 25 mg	HR ↓, BP stabilized
+6 h	Stabilization of vitals and consciousness	Continued monitoring	Improved neurological status
+24 h	Extubation, ICU discharge	Transferred to inpatient ward	Full recovery trajectory

DISCUSSION

Serotonin syndrome is a clinical diagnosis and can be easily overlooked, especially in patients with psychiatric disorders who are undergoing pharmacologic treatment. Serotonin syndrome, a diagnosis of exclusion, is established using the Hunter Toxicity Criteria. In patients with a history of serotonergic agent exposure, the presence of any single Hunter criterion is considered sufficient to confirm the diagnosis (Table 1). The absence of specific diagnostic laboratory or imaging findings further complicates recognition. Although most cases follow a benign course and resolve upon discontinuation of the offending agent, high-dose exposure can result in severe neurological and cardiovascular complications with fatal outcomes.

The majority of reported cases in the literature involve drug interactions, especially combinations of antidepressants, antipsychotics, and serotonergic antimicrobials such as linezolid (7). However, serotonin syndrome due to monotherapy overdose with venlafaxine is rarely reported (8,9). Beyond venlafaxine, cases have demonstrated that serotonin toxicity can also develop with isolated bupropion use (10). Our case highlights that even in the absence of polypharmacy, high-dose venlafaxine alone can lead to life-threatening toxicity.

The rapid clinical deterioration observed in our patient was likely due to the cardiotoxic effects of venlafaxine. Although the drug typically causes only mild tachycardia and QT prolongation at therapeutic doses, toxic doses can result in significant arrhythmias and hemodynamic instability (11). Prolongation of the QT interval reflects delayed ventricular repolarization and predisposes affected individuals to potentially life-threatening arrhythmias and torsades de pointes (TdP). The normal range for the rate-corrected QT interval (QTc) is similar in males and females from birth until the start of adolescence, while after puberty and in adults, females have slightly longer QT intervals than males. Before puberty, a QTc <450 ms is considered normal, between 450 and 459 borderline, and ≥460 prolonged. After puberty in males, a QTc between 460 and 469 is borderline and ≥470 is considered prolonged. In post-pubertal females, 460 to 479 is borderline and ≥480 ms is considered prolonged. In our case, the patient developed sinus tachycardia and a markedly prolonged QTc interval (545 ms), which resolved following magnesium sulfate administration. In relation to QT prolongation, the principal role of magnesium sulfate is its use in the treatment of TdP. It stabilizes intracellular ion currents and, by inhibiting L-type calcium channels, reduces the risk of arrhythmia development. For all patients with TdP, IV magnesium sulfate is first-line therapy since it is highly effective for both the treatment and prevention of recurrence of long QT-related ventricular ectopic beats or TdP (12). This underscores the importance of continuous ECG monitoring and prompt correction of QT prolongation in such cases.

Although cranial CT plays no direct role in the diagnosis of serotonin syndrome, it is essential to exclude differential diagnoses such as intracranial hemorrhage or mass lesions. Similarly, while EEG is not a definitive diagnostic tool, it may support the diagnosis or assist in differentiating from other neuropsychiatric conditions. EEG findings in serotonin syndrome may include delta activity, generalized slowing, and triphasic waves (13). Our patient exhibited generalized slowing, which correlated with her clinical presentation. As the diagnosis of serotonin syndrome is primarily one of exclusion, a detailed history, physical examination, and emergency laboratory and imaging studies were conducted. This evaluation effectively ruled out infectious diseases, concomitant drug use, withdrawal syndromes, toxic exposures, and acute central nervous system pathologies such as hemorrhage or ischemia as alternative explanations for the clinical presentation. Following these exclusions, the patient's high-dose venlafaxine exposure and compatibility with the Hunter Toxicity Criteria led to the clinical diagnosis of acute serotonin syndrome.

Laboratory findings in serotonin syndrome are typically nonspecific. In our patient, transient lactic acidosis was observed, likely secondary to hypoxia and impaired perfusion rather than primary serotonergic toxicity. Notably, CK levels remained within normal limits, possibly due to early seizure control and lack of sustained neuromuscular hyperactivity.

The cornerstone of treatment is discontinuation of serotonergic agents and supportive care. With proper treatment, serotonin syndrome usually resolves within 24 h without sequelae (14). Supportive care is the mainstay of therapy and includes the administration of oxygen and intravenous (IV) fluids, continuous cardiac monitoring, and correction of vital signs. Clinicians should provide sufficient oxygen to maintain the oxygen saturation ≥ 94 percent, and give IV crystalloid to treat volume depletion, and to some extent hyperthermia. In overdose cases, early gastric decontamination may help reduce systemic absorption. Vital signs should be closely monitored, and patients should be admitted to intensive care units if needed. Cyproheptadine is a histamine-1 receptor antagonist with nonspecific 5-HT1A and 5-HT2A antagonistic properties with antiserotonergic properties and is commonly used when supportive care alone is insufficient. It also has weak anticholinergic activity. It is

available in 4 mg tablets or 2 mg/5 mL syrup. When administered as an antidote for serotonin syndrome, an initial dose of 12 mg is recommended, followed by 2 mg every two hours until clinical response is seen. However, it is available only in oral form and may not be effective in all patients (15). Chlorpromazine, although not routinely recommended in treatment guidelines, acts as a serotonin receptor antagonist and has been used in rare cases. In our case, because cyproheptadine failed to produce the anticipated clinical response within an appropriate time interval and the patient's condition was critical, intramuscular chlorpromazine was administered, based on the rationale that it could exert a more rapid therapeutic effect. Subsequently, chlorpromazine led to rapid clinical improvement after failure of cyproheptadine and supportive therapy. Although the available evidence is limited, several authors have suggested that 5-HT2A serotonin antagonists may be justified even in suspected cases of serotonin toxicity as empiric therapy or employed as 'lifesaving' antidotes in cases of severe toxicity (16). A review of the literature revealed only two previously published reports from the 1990s describing the use of chlorpromazine in serotonin syndrome (17,18). One such case documented toxic serotonin syndrome triggered by the concomitant use of a monoamine oxidase inhibitors (MAOI) and a tricyclic antidepressant (TCA), in which a rapid therapeutic response to chlorpromazine was observed.

This case is unique in demonstrating life-threatening serotonin syndrome due to venlafaxine monointoxication, marked QT prolongation in the absence of elevated CK, and successful resolution of symptoms following intramuscular chlorpromazine administration. When serotonergic agents are ingested in high doses, particularly in the context of suicidal attempts, drug-induced metabolic disturbances are often the primary consideration. However, serotonin syndrome must also be carefully considered, as it may develop even with high-dose exposure in the absence of drug interactions. In most patients, serotonin syndrome generally resolves with discontinuation of the offending agents and supportive care. However, it should be remembered that in severe cases, in those unresponsive to cyproheptadine, and in life-threatening situations where a more rapid therapeutic effect is required, chlorpromazine may serve as a potential rescue agent. Further clinical investigation is needed to clarify the role of chlorpromazine in the management of serotonin syndrome.

CONCLUSION

Serotonin syndrome should always be considered in patients receiving serotonergic agents, particularly in the context of overdose. Although it is typically associated with drug interactions, this case demonstrates that a single-agent overdose of venlafaxine can lead to severe, potentially fatal manifestations. It should be considered that toxic serotonin syndrome may also occur following the administration of other serotonergic agents at high doses. Early recognition, intensive supportive care, and continuous cardiac monitoring are essential to improve outcomes. While cyproheptadine remains the first-line pharmacologic treatment, this case highlights the potential role of chlorpromazine as a therapeutic option in refractory cases. It is important to recognize that chlorpromazine therapy may be considered in patients with critical clinical presentations, given that intramuscular administration has the potential to achieve a more rapid therapeutic response. Further studies are warranted to evaluate the efficacy and safety of chlorpromazine in serotonin syndrome management

Informed Consent
An informed consent form was obtained from the patient and/or the patient's legal representative for the collection and publication of the patient's clinical information.

Conflict of Interest
The authors have no conflict of interest to declare.

Financial Disclosure
The authors declare that no financial support was received for this study.

Authors' Contributions
Data collection and processing, M.B.D.; Data analysis and interpretation, M.B.D., H.S.K.; Writing, H.S.K.; Review and editing, M.B.D., H.S.K.

Data sharing statement
No new data were created or analyzed in this study. Data sharing is not applicable to this article.

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