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TITLE

A case of tizanidine withdrawal showing hallucination, decorticate posture and tremor, with hyper-sympathetic vital signs

AUTHORS

Jun Tanimura, MD, MSc [1], Takao Hashimoto, MD, PhD [1]

[1] Department of Neurology, Aizawa Hospital, 2-5-1 Honjo, Matsumoto, Nagano 390-8510, Japan.

SUMMARY

Tizanidine, an α2-adrenergic receptor agonist commonly prescribed as a muscle relaxant, has been associated with limited cases of acute intoxication or withdrawal. Here we present a case of tizanidine withdrawal in a woman in her 40s who presented with an unusual combination of systemic and neurological symptoms. These included hallucinations, decorticate posture, limb and eyelid tremors, along with hypertension, tachycardia and tachypnoea. The diagnosis of tizanidine withdrawal was established by a comprehensive assessment of the patient's medical history and the systematic exclusion

of other potential diseases. Our approach to managing the withdrawal symptoms was to initiate symptomatic treatment with a combination of a beta-blocker and a calcium channel blocker. Remarkably, this intervention successfully resolved both vital signs and neurological manifestations by the following day. In conclusion, tizanidine withdrawal is associated with a distinct and diagnostically significant neurological syndrome characterised by hallucinations, decorticate posture, tremors, and hyper-sympathetic vital signs.

BACKGROUND

Tizanidine is a centrally acting α2-adrenergic receptor agonist used as a muscle relaxant for the treatment of chronic spasticity, myofascial pain, neck and/or lower back pain, rebound headache resulting from analgesic withdrawal, or chronic migraine [1]. When discontinuing tizanidine, it is imperative to implement a tapering process due to concerns regarding withdrawal. Based on evidence from previous clinical experience, tapering typically takes place over a week and involves a gradual reduction in dose to approximately 2 mg per day [2-4]. To date, three cases of tizanidine withdrawal have been documented [3,5,6], showing hyper-sympathetic vital signs such as tachycardia and hypertension, along with tremors and psychiatric manifestations such as confusion or visual hallucinations.

This report presents a unique case of tizanidine withdrawal characterised by an unusual combination of symptoms, including visual hallucinations, decorticate posture, and tremors affecting the eyelids and extremities. Our aim is to provide valuable information for early diagnosis by highlighting these novel manifestations of tizanidine withdrawal.

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CASE PRESENTATION

A woman in her 40s presented to the emergency department with a chief complaint of abnormal behaviour and monologue. Three days before admission, she experienced auditory hallucinations, including hearing conversations and doorbell ringing. Two days before admission, visual hallucinations were reported, involving a gorilla driving a car. The day before admission, she suffered from insomnia, went out late at night due to delusions, and expressed a surreal belief that she had been shot and was expecting help from a gorilla. The decision to admit her to the emergency department was prompted by her immobility and persistent engagement in unintelligible monologue. The patient had a history of receiving treatment for insomnia and chronic neck pain with etizolam (0.5 mg/day) and tizanidine (3 mg/day). She denied illicit substance abuse or alcohol abuse.

On arrival, she presented as afebrile (37.3°C) with marked hypertension (215/133 mmHg), tachycardia (132 bpm in sinus rhythm), and tachypnoea (32 breaths/min). Neurological examination revealed delirium characterised by intermittent utterances of meaningless phrases. Her upper and lower limbs exhibited a decorticate posture, with flexor posture with internal rotation of the upper limbs and extensor posture of the lower limbs, accompanied by plantar flexion of the feet (Figure 1, Video 1). This posture was sustained even in the absence of noxious stimuli. Additionally, fine postural tremors with a frequency of 7–9 Hz were observed in the eyelids, fingers, and toes (Movie 1A-C). Increased muscle tone was noted in all extremities, while tendon reflexes were not hyperactive, and no pathological reflexes were elicited.

INVESTIGATIONS

Urinalysis was positive results for occult blood, protein, and ketones. Routine blood tests showed indicated elevated white blood cell count (12,000/μL [3,500–9,100/μL]), lactate dehydrogenase (272 U/L [124–222 U/L]), creatine phosphokinase (300 U/L [45–163 U/L]), blood urea nitrogen (34.0 mg/dL [8.0–22.0 mg/dL]), creatinine (1.68 mg/dL [0.47–0.79 mg/dL]), and blood glucose (292 mg/dL [70–109 mg/dL]). Serum sodium level was decreased (132 mEq/L [136–147 mEq/L]). Metabolic and endocrine tests, including calcium, magnesium, ammonia, thyroid function, and cortisol, were within normal limits. HIV antigen-antibody tests were negative. Cerebrospinal fluid findings were unremarkable. Magnetic resonance imaging of the brain showed no abnormalities.

DIFFERENTIAL DIAGNOSIS

The patient exhibited a combination of psychiatric symptoms (hallucinations and insomnia) and motor symptoms (decorticate rigidity and tremor), indicative of encephalopathy. Alongside these neurological manifestations, her vital signs were suggestive of a hypersympathetic state, raising the suspicion of either sympathomimetic syndrome or serotonin syndrome [7,8]. Therefore, a comprehensive differential diagnosis should include hyperthyroidism, pheochromocytoma crisis, drug intoxication, or withdrawal.

In cases of drug intoxication or withdrawal, verifying the use of regular medications, illicit drugs, and alcohol is crucial. Sympathomimetic syndrome may be induced by substances such as amphetamines, cocaine, theophylline, and caffeine [9]. Withdrawal symptoms, on the other hand, may be associated with designer stimulants such as amphetamines and 3,4-methylenedioxymethamphetamine (MDMA or ecstasy), α2-

receptor agonists including tizanidine, clonidine, and xylazine, as well as the GABA-B receptor agonist baclofen [10,11]. Serotonin syndrome, with its diverse causes, can be triggered by tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), opiates such as tramadol, over-the-counter cough suppressants such as dextromethorphan, and certain antibacterial agents like linezolid, all of which may play a role in both intoxication and withdrawal scenarios [8].

In this case, the patient had no history of illicit substance or alcohol abuse but was using etizolam, a benzodiazepine. Benzodiazepine withdrawal typically manifests as tachycardia, hypertension, psychosis, and insomnia [12]. Therefore, it is important to establish the temporal relationship between drug exposure and symptom onset.

Despite abnormalities in routine blood tests indicating inflammation and liver and kidney dysfunction, the exact cause of the psychiatric and motor symptoms remained unclear. Additional tests, including cerebrospinal fluid analysis and brain imaging, yielded unremarkable results.

Subsequent interviews with the patient's family unveiled that she had independently increased her tizanidine dosage (from 3 to 8 mg/day) 20 days prior in response to neck pain. Following this dose escalation, she experienced nausea that prevented her from eating or drinking. Despite the discomfort, she continued to take both tizanidine and etizolam. However, when her tizanidine prescription ran out four days before admission, she abruptly discontinued it. Auditory hallucinations occurred the next day, followed by visual hallucinations, delusions, and insomnia. With the onset of delusions, the patient

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could no longer take etizolam (0.5 mg/day). On the following day, she became immobile and began to speak in an unintelligible monologue, leading to her eventual visit to the emergency department. Although tremors and a decorticate posture were observed during the presentation, the precise timing of the onset of these motor symptoms remained unclear. Based on the historical data obtained and the exclusion of other potential causes, tizanidine withdrawal was strongly suspected.

TREATMENT

Symptomatic treatment was initiated with continuous intravenous nicardipine and landiolol to control hypertension and tachycardia. Notably, replacement and tapering therapies, such as reintroduction of tizanidine or introduction of dexmedetomidine, another α2-receptor agonist, were not pursued.

OUTCOME AND FOLLOW-UP

The following day, approximately 12 hours after initiating symptomatic treatment, the patient's vital signs normalized, and tremors and abnormal posture completely resolved. She demonstrated alertness and coherent speech, with no recurrence of abnormal posture. Considering the trajectory of self-remission, we conclusively diagnosed her with tizanidine withdrawal. On the fourth hospitalization day, the patient was discharged home, and tizanidine prescriptions were discontinued.

DISCUSSION

This case experienced tizanidine intoxication followed by subsequent tizanidine withdrawal. In comparison with three previous cases of tizanidine withdrawal (Table 1),

the current case stands out for its distinctive clinical manifestation of decorticate posture.

Decorticate posture typically indicates severe brain dysfunction involving the brainstem and more rostral regions, commonly resulting from causes such as trauma, stroke, metabolic abnormalities, infection, or intoxication [13]. The rubrospinal tract is involved in the abnormal posture of upper limbs, while the vestibulospinal tract is responsible for the extended posture of lower limbs in decorticate postures [14,15]. Tizanidine, an α2-adrenergic receptor agonist, induces withdrawal syndrome on cessation, characterised by an increase in catecholamine secretion [3]. Given that adrenergic stimulation through α2-adrenergic receptors can modulate the vestibulospinal and rubrospinal projections [16,17], a catecholamine surge following tizanidine withdrawal may contribute to the development of decorticate posture.

Our patient exhibited postural tremors with a relatively high frequency in the eyelids and extremities, suggesting an increased physiological tremor [18] associated with the sympathomimetic state in tizanidine withdrawal.

Visual hallucinations have been reported as both a withdrawal symptom and an adverse effect of tizanidine (Table 1) [19]. Although the underlying mechanism remains unclear [20], a catecholamine surge during tizanidine withdrawal may trigger visual hallucinations because noradrenergic projections from the locus coeruleus modulate neuronal activity in the visual cortex [21].

Symptomatic treatment often involves benzodiazepines or propranolol (Table 1) [3,5],

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referencing the approach used for baclofen withdrawal, another α2-receptor agonist [6,22,23]. In previous cases, reintroduction of tizanidine and subsequent tapering led to rapid symptom resolution (Table 1). Notably, our case deviates from this pattern as the patient improved without restarting tizanidine, responding well to symptomatic therapy for autonomic symptoms within half a day. When considering alternatives, switching to another α2-receptor agonist, such as dexmedetomidine, may be a viable option [10,11,23].

In our case, withdrawal occurred despite a relatively low dose of tizanidine. This may have been due to the important nausea and anorexia, frequent adverse events with tizanidine, leading to dehydration and functional renal impairment. This renal impairment decreased the clearance of the drug, likely causing hepatotoxicity. Given the hepatic metabolism and renal excretion of tizanidine, dose reduction is recommended in cases of hepatic or renal dysfunction. Routine monitoring of aminotransferase levels is essential, especially at higher doses that may induce hepatic dysfunction.

In conclusion, our case highlights that tizanidine can cause withdrawal syndrome even in a relatively small dosage, especially in cases of chronic or acute renal or hepatic dysfunction. Close monitoring of transaminase levels is essential to detect potential overdosage. The unique combination of visual hallucinations, decorticate posture, and limb and eyelid tremors observed in our patient may be indicative of tizanidine withdrawal. Although our case demonstrated rapid resolution with autonomic symptom management alone, restarting therapy with low-dose tizanidine or considering intravenous dexmedetomidine replacement should be important options if symptoms are inadequately controlled.

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LEARNING POINTS/TAKE HOME MESSAGES

- Tizanidine can cause withdrawal syndrome even at relatively low doses, particularly in patients with hepatic and renal dysfunction.
- To avoid the risk of tizanidine overdose, it is recommended to closely monitor transaminase levels and reassess tizanidine dosage, especially in patients with liver and kidney dysfunction.
- A characteristic combination of visual hallucinations, decorticate posture, and tremor accompanied by hyper-sympathetic vital signs suggests tizanidine withdrawal.
- In addition to symptomatic therapy for autonomic symptoms, reintroduction or replacement of tizanidine should be considered as a feasible alternative.

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FIGURE/VIDEO CAPTIONS

Figure 1:

Photographs of decorticate posture caused by tizanidine withdrawal. A) Upper limb posture; B) lower limb posture.

Video 1:

Tremors of extremities and eyelid, and decorticate posture caused by tizanidine

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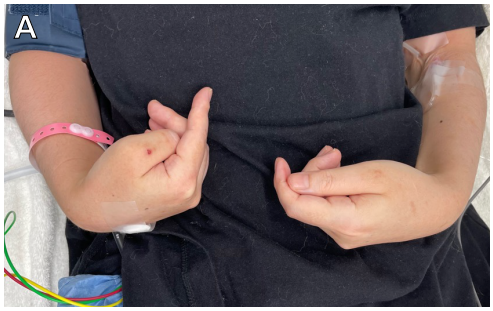
withdrawal. A) Upper limb tremor and posture; B) lower limb tremor and posture; C) eyelid tremor.

Table 1. Summary of tizanidine withdrawal patients in literature review and present case.

Reference	Dose (per day)	Symptoms	Symptomatic Treatment	Tizanidine restart and tapering treatment
5	60 mg	tremor, confusion, hypertension, tachycardia	lorazepam, oxazepam, propranolol	80 mg → tapering (Schedule not mentioned)
3	16 mg	tremor, hypertension, tachycardia	esmolol, propranolol, paracetamol, diazepam	6 → 4 → 2 mg (4 days each)
6	6 mg (+ Baclofen 240 mg)	delirium, visual hallucination, rigidity, hypertension, tachycardia	labetalol, haloperidol,	none (Baclofen 40 mg)
Present case	8 mg	tremor, decorticated posture, confusion, hallucination, hypertension, tachycardia	nicardipine, nifedipine, landiolol, bisoprolol	none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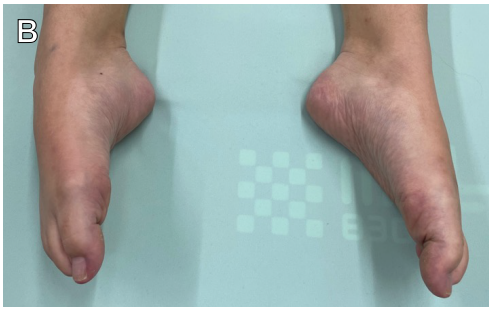
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