A Fatal Case of Venlafaxine Overdose

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ABSTRACT

Introduction: Based on its primary action of serotonin reuptake inhibition, venlafaxine overdose would be expected to result in serotonergic effects.

Case Report: A 40 year old male ingested venlafaxine without co-ingestants in a suicide attempt. The patient developed refractory ventricular fibrillation and expired approximately 9 hours post-ingestion. ECG monitoring revealed significant QRS and QT_C interval prolongation prior to his demise.

Discussion: A literature review of venlafaxine overdose cases and investigation into its mechanism of action was conducted. The potential for sodium channel blockade and implications for therapy are discussed.

INTRODUCTION

Venlafaxine, a bicyclic hydroxycycloalkylphenylethylamine-derivative antidepressant, has serotonin, norepinephrine, and dopaminergic reuptake inhibition properties. It is structurally more closely related to tramadol, a non-opioid analgesic, than it is to tricyclic antidepressants (TCA), monoamine oxidase inhibitors (MAOI), or selective serotonin reuptake inhibitors (SSRI) [1,2]. It reportedly does not have the sodium channel blocking properties of TCA, thereby resulting in fewer cardiac side effects [3]. Due to its primary action of serotonin reuptake inhibition, toxic effects after overdose are likely to be similar to those seen with SSRI. It is considered a first-line agent for the treatment of depression [4]. We report a fatal venlafaxine acute overdose without coingestants that produced significant cardiac toxicity.

CASE REPORT

A 40-year-old male with a history of non–insulin-dependent diabetes mellitus and depression presented to a community emergency department (ED) approximately 45 minutes after intentionally ingesting ninety 150-mg venlafaxine extended release (Effexor XR) and seventy-five 75-mg venlafaxine extended release (Effexor XR) tablets in a suicide attempt. The total amount ingested was 19 g. The medication was prescribed to him for treatment of depression. He had no other medical problems and took no other medications, prescription or over the counter. He denied alcohol, illicit drug, or tobacco abuse.

On initial presentation, the patient was asymptomatic except for nausea. Initial vital signs were heart rate 136 bpm, blood pressure 133/90 mmHg, respiratory rate 16/min, pulse oximetry 99% on room air, and weight 106.8 kg. No temperature was recorded. Physical examination revealed an alert male in no distress with clear lungs, a soft abdomen, and a non-focal neurologic examination. Cardiac exam revealed tachycardia with a regular rhythm. The patient received a 500 mL bolus of normal saline. Fifty grams of activated charcoal with sorbitol was administered orally. Acting on recommendations from the regional poison control center, whole-bowel irrigation was initiated with polyethylene glycol solution at 1–2 L/hr. The initial electrocardiogram (ECG) revealed

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Table 1: ECG characteristics from time of ingestion

Time from ingestion	PR interval (msec)	QRS interval (msec)	QTc (msec)
1hr, 35 min	143	90	422
4 hr, 20 min	144	112	425
8 hr, 40 min	400	158	564

ECG = electrocardiogram, hr = hours, min = minutes, msec = milliseconds.

sinus tachycardia with no ischemic changes (Table 1). The comprehensive metabolic profile and complete blood count were normal. Acetaminophen, salicylate, and ethanol levels were undetectable. The patient had two episodes of emesis. He was noted to be sleepy but arousable approximately two hours post-ingestion, at which time he was transferred to a tertiary care facility. During transport the patient had a tonic-clonic seizure lasting 2–3 minutes.

The patient arrived at the tertiary ED 3.5 hours post-ingestion. His presenting vital signs at the referral ED were heart rate 140 bpm, blood pressure 116/65 mmHg, respiratory rate 38/min, temperature 37.5° C, and pulse oximetry 96% on room air. He was described as alert, oriented, in no acute distress, and diaphoretic. No other abnormalities were identified on physical exam. He subsequently had a third episode of emesis. He was given 25 mg intravenous (IV) promethazine for continued nausea. A second tonic-clonic seizure was observed by the ED staff 4.5 hours post-ingestion, for which he was given 2 mg IV lorazepam.

Urine drug screen was positive for phencyclidine, and negative for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates. Confirmational testing of the phencyclidine was negative. A repeat ECG showed sinus tachycardia (see Table 1), and his chest radiograph was normal. He was admitted to the intensive care unit for further monitoring and supportive treatment. He became progressively more lethargic, and approximately 9 hours post-ingestion developed refractory ventricular fibrillation (VF) and subsequently expired. An ECG, showing no ventricular ectopy, was obtained just prior to his demise (see Table 1).

A venlafaxine blood level obtained 5 hours post-ingestion was 9000 ng/mL, and the 0-desmethylvenlafaxine blood level, the first metabolite of venlafaxine, was 3000 ng/mL. A post-mortem venlafaxine blood level drawn from a peripheral site was 5500 ng/mL. No other substances were found in the post-mortem analysis.

DISCUSSION

The patient we present had a clear progression of his QRS and QTc prolongation with subsequent refractory ventricular fibrillation, suggesting that sodium channel poisoning may have been responsible for his dysrhythmia and subsequent death. This patient had no signs of serotonin syndrome such as rigidity, clonus, tremor, or hyperthermia.

This patient had a positive urine immunoassay for phencyclidine with negative confirmational testing. Although this patient denied taking any other medication, a potential coingestant such as tramadol or diphenhydramine could potentially explain the positive test. However, studies have shown that venlafaxine alone can cause false-positive urine immunoassay results for phencyclidine [5,6].

This patient also received one 25-mg dose of promethazine. Promethazine has been shown in guinea pig myocytes to have similar sodium channel blocking effects as class I antidysrythmics [7]. Despite this action, it is unlikely with one 25-mg dose to have contributed significantly to the patient's clinical course.

This case is illustrative due to the clear documentation and observation of the patient's symptoms, cardiac manifestations, and clinical decline from very early on in his ingestion through the terminal event. There was a relatively rapid progression of his cardiac dysrhythmia and atrioventricular block.

Venlafaxine is an atypical antidepressant whose actions primarily involve inhibition of serotonin reuptake in presynaptic neurons. At therapeutic doses, it has minor effects on the reuptake of norepinephrine and dopamine, which is probably not clinically relevant [1]. Venlafaxine overdose has been reported to cause seizures, dysrythmias, central nervous system (CNS) depression, and hypotension [3,8].

In a case series of SSRI, venlafaxine, and TCA overdoses, venlafaxine-induced QRS prolongation occurred more frequently than TCA-induced QRS prolongation [1]. The study also compared the rates of seizures, serotonin toxicity, and ICU admissions between SSRI, venlafaxine, and TCA. Seizures, as well as serotonin syndrome, occurred more frequently with venlafaxine overdose [1]. The incidence of ICU admission is greater for venlafaxine than SSRI, though less than that of TCA [1].

Previous reports suggest that venlafaxine does not have the sodium channel toxicity manifested by the TCA [3]. However, one potential mechanism for the cardiac toxicity observed with venlafaxine may relate to sodium channel poisoning. In a guinea pig myocyte model, venlafaxine significantly reduced the sodium channel conduction rate, specifically by acting on the fast inward sodium current, the primary regulator of cardiac depolarization [9]. This effect was dose dependent and conduction returned to normal with removal of the venlafaxine. These experiments were done with a venlafaxine concentration of 10^{-6} M. Steady-state therapeutic concentrations in humans have been reported to range from $2 \times 10^{-7} - 10^{-6}$ M, with overdose concentrations in

humans easily exceeding 3×10^{-5} M (10–12). The sodium channel poisoning effect of venlafaxine may occur with binding to the resting state of the channel, which differs from the effects of TCA and traditional class I antiarrhythmic drugs [9].

Other pharmacokinetic processes may also contribute to venlafaxine's toxicity, including significant differences in the metabolism of venlafaxine between individuals with extensive vs. poor metabolizer CYP2D6 phenotypes [4]. Patients who may be poor CYP2D6 metabolizers, or patients receiving medications known to inhibit CYP2D6 may be at greater risk for toxicity from venlafaxine [4]. In addition, venlafaxine overdose resulting in serotonin syndrome, a potentially fatal reaction, has been reported [13].

Therapy for venlafaxine overdose has not been well established. The impact of early supportive treatments—including intubation and fluid resuscitation—are unknown in this setting, but should be utilized in any unstable patient. This patient's initial tachycardia may represent effects from beta receptor stimulation from excess dopamine and norepinephrine from toxic levels of venlafaxine; the significance and prognostic value of this is one area for future research. Given the possibility of sodium channel poisoning, sodium bicarbonate therapy in venlafaxine overdose associated with widened QRS on ECG or ventricular dysrhythmias may be beneficial, and further investigation of its use may prove valuable. Sodium bicarbonate is used in similar settings of cardiac toxicity secondary to TCA and related agents.

Until further research clarifies these questions, it may be prudent to recommend prolonged observation in patients presenting with initial tachycardia, and to suggest administration of sodium bicarbonate at the first signs of QRS widening.

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