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Arrhythmias in Severe Trazodone Overdose

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

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Patient: Female, 55-year-old
Final Diagnosis: Trazodone overdose
Symptoms: Altered mental status • seizure • shock • arrhythmia
Medication: —
Clinical Procedure: —
Specialty: Toxicology

Objective: Rare disease
Background: Trazodone is widely used in the treatment of depression, anxiety, and insomnia. It is thought to have a safe cardiac profile due to the relative lack of anticholinergic effects. Publications about cardiac toxicities of trazodone are scant.

Case Report: A 55-year-old woman presented with acute disorder of consciousness secondary to an intentional trazodone overdose. She was found to have seizure activity without cerebral edema. The initial electrocardiogram was unremarkable, with a normal QTc interval. She eventually developed QTc prolongation that evolved into ventricular tachycardia, and then into a transient right bundle-branch block, left anterior fascicular block, and variable degrees of atrioventricular nodal blocks at 12–24 h after ingestion. She then developed generalized tonic-clonic seizures, cardiogenic shock, and respiratory arrest. She was intubated and treated with antiepileptics, norepinephrine, and dopamine infusion. QTc interval prolongation gradually resolved and the various forms of heart block did not recur after at 24–36 h. She did not require transcutaneous pacing, and was successfully extubated with intact neurological function.

Conclusions: Fatal arrhythmias can occur in trazodone overdose. Close monitoring and supportive care are crucial for patient survival.

MeSH Keywords: Arrhythmias, Cardiac • Atrioventricular Block • Bundle-Branch Block • Drug Overdose • Long QT Syndrome • Trazodone

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Background

Depression is a major public health problem and is the leading cause of disability in the United States and worldwide [1]. Depression has significant potential morbidity and mortality, contributing to suicide, with nearly 800 000 people committing suicide every year [2]. Trazodone is a serotonin antagonist and reuptake inhibitor that is widely used for the treatment of depression, anxiety, and insomnia. Trazodone was the second most prescribed medication for sleep and the sixth most prescribed psychiatric medication in 2016 [3]. Trazodone possesses minimal anticholinergic properties, and thus is generally regarded as having less cardiotoxic potential than other antidepressants. Although trazodone was initially thought to have a safe cardiac profile, there has been increasing concern about its cardiotoxicity, as cardiac arrhythmias in trazodone overdose cases became known [4]. Here, we report the case of a patient who intentionally overdosed on trazodone who developed QTc prolongation, wide-complex tachycardia, and variable heart blocks arrhythmias as a result of trazodone cardiotoxicity.

Case Report

The patient was a 55-year-old woman with no known chronic illness who was brought in by ambulance for altered mentation. She was last seen conversing normally on the day before hospital admission. At about midnight, the patient reportedly told her son that she had ingested a large amount of trazodone, apparently in an attempt to commit suicide. The exact

dosage was unknown, but she said she took all that remained of a bottle of trazodone (50 milligrams, 90 tablets when full). The bottle was not full when she took it and the possible ingested dose could have been 2000–4500 milligrams. According to the son, the patient was initially well but acutely decompensated, with what he described as staggering movement, loss of balance, and complete unresponsiveness, with purposeless shaking and twitching. Paramedics were called, and upon arrival the patient was found minimally responsive and notably hypertensive and tachycardic. No seizures were observed and she was brought to the Emergency Department of our center. She arrived approximately 3–4 h after ingestion, and her initial vitals were: blood pressure 228/120 mmHg, heart rate beats 105 per minute, axillary temperature 37.1°C, respiratory rate 14 breaths per minute, and oxygen saturation 95% on room air. On examination, she had spontaneous eye opening but was without any response to verbal stimuli. Nonspecific eye twitching was noted and she did not blink to threat. She grimaced to painful stimuli but did not localize pain. There was rigidity in the proximal muscle groups but flaccidity in the distal muscle groups. Periods of purposeful-seeming movements, grabbing at the blanket and attempting to cover herself were noted. Gag and cough reflexes were intact, without any concern for airway compromise at that time. A computed tomography of the brain was negative for acute pathology, ruling out head injury, acute intracranial bleed, or any other space-occupying lesions. Due to high suspicion of subclinical seizure activity, the patient was loaded with intravenous levetiracetam 1 gram twice daily. There was minimal improvement after administration of the antiepileptics. She was given intravenous

Figure 1. Initial electrocardiogram on presentation. Sinus rhythm without QT prolongation.

Figure 2. Sinus tachycardia with QTc interval widening.

hydralazine 10 mg twice to reduce the systolic blood pressure to below 180 mmHg. Her status did not change noticeably for the next few hours, as she remained nonverbal, with occasionally purposeful-appearing movements punctuated by minimal responsiveness and staring into space. Initial electrocardiogram showed sinus rhythm, U waves, QTc interval of 390 ms, without evidence of heart block (Figure 1). Initial laboratory results were significant for hypokalemia, with potassium of 2.7, which was treated with slow intravenous infusion of potassium chloride; however, her serum magnesium and phosphorous levels were normal. Serum alcohol level, salicylate, and acetaminophen levels were undetectable and a urine toxicology screen was also negative.

There was little neurological improvement on reassessment the following morning. Approximately 12 h after ingestion, a significant widening of the QTc interval was observed on telemetry. A repeat electrocardiogram showed the QTc interval increased to 519 ms and P pulmonale (Figure 2). A repeated electrolyte panel showed a potassium level of 3.4, for which further intravenous potassium chloride therapy was given. At about 15 h after ingestion, telemetry showed abrupt onset of a wide-complex tachycardia at a rate of 126 per min (Figure 3). The patient was found unresponsive by the registered nurse, but still with a thready pulse and without any spontaneous breathing, triggering code blue activation. The patient was emergently intubated, after which she developed generalized tonic-clonic seizure which was quickly terminated with intravenous pushes of lorazepam. The patient became hypotensive and the rhythm switched to sinus bradycardia at a rate of 40 beats per min,

with right bundle-branch block and left anterior fascicular block (Figure 4). She also developed first-degree heart block, Wenckebach phenomenon, wandering pacemaker, and a junctional rhythm (Figures 5–7). She was given intravenous pushes of atropine and epinephrine. Chest compression was not started because her pulse was palpable throughout the course. She was also not cardioverted since the wide-complex tachycardia episode was brief and the rhythm transitioned to bradyarrhythmia. With a provisional diagnosis of cardiogenic shock in the setting of bradycardia and heart blocks, intravenous infusion of norepinephrine and then dopamine were started. She was also loaded with intravenous phenytoin and transferred to the Intensive Care Unit (ICU).

The right bundle-branch block and the left anterior fascicular block quickly resolved after a few hours (Figure 8). The norepinephrine and dopamine infusion were eventually titrated off within 12 h after the event. Creatinine kinase levels were elevated, peaking at 5590, with a CKMB index of 0.4. Troponin levels were elevated, peaking at 4, which was interpreted as a type II myocardial infarct in the setting of arrhythmia with cardiogenic shock secondary to substance overdose. Transthoracic echocardiogram was done while she was intubated, and her left ventricular ejection fraction was 65–70%, without any wall-motion abnormalities. No further ischemic work-up was warranted at this time. The patient was eventually extubated on the next day. The ICU course was pertinent for aspiration pneumonia in the right lower lobe, which likely happened during her seizures. Her mental status eventually improved and she was responding appropriately to questions over the next few

Figure 3. Wide-complex tachycardia, followed by seizure activity.

Figure 4. Sinus bradycardia with intermittent ventricular escape with right bundle-branch morphology and left anterior fascicular block.

Figure 5. Wandering pacemaker with different P wave morphologies.

Figure 6. Junctional rhythm with occasional P wave.

Figure 7. Gradual PR interval prolongation with a drop beat. Wenckebach phenomenon.

days. She became hypertensive afterwards, with her systolic blood pressure hovering around 150, but she refused treatment. She confirmed not taking any additional medications in this suicide attempt and did not know the exact number of trazodone pills she took. She was subsequently transferred to an inpatient psychiatric facility to continue treatment of her major depression with suicide attempt.

Discussion

Trazodone was developed in Italy in 1966. The U.S. Food and Drug Administration (FDA) approved its use for major depression treatment in 1981 [5]. Trazodone is both a selective serotonin reuptake inhibitor (SSRI) and a 5HT₂ receptor antagonist, and the net result of this action on serotonergic transmission and its role in the antidepressant effect of trazodone is unknown [5].

QT prolongation was described in several case reports of trazodone overdose [4,6]. Atrioventricular nodal blockage was also described previously [4]. The cellular mechanisms of trazodone cardiotoxicity were explained in a study in which trazodone dose-dependently decreased the maximum upstroke velocity (V_{max}), inhibited all of the major ion channels, (IKr, IKs, INa, and ICa), and prolonged the action potential (AP) duration, triggering ventricular arrhythmias in human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) [7]. Trazodone has also been implicated in Torsades de pointes in patients with deliberate trazodone overdose [8,9]. Our patient presented with wide-complex tachycardia, transient right bundle-branch block, left anterior fascicular block, and variable degrees of atrioventricular nodal block, which eventually resolved. The rhythm was not consistent with Torsades in our case, and our patient did not require pacer placement for her bradyarrhythmia.

Figure 8. Resolution of right bundle-branch block and left anterior fascicular block.

In our patient, hypotension was likely due to cardiogenic shock in the setting of severe arrhythmia burden, and vasopressors were eventually titrated off as her rhythm improved. It is also noted that severe hypotension can persist without significant arrhythmias and might need intensive care admission and pressor administration [10].

Serotonin syndrome was reported in trazodone overdose with concomitant intake of other serotonergic agents [11–13]. Serotonin syndrome is classically described as hyperthermia, tachycardia, hypertension, altered mental status, agitation, diaphoresis, tremor, myoclonus, and hyperreflexia. Our patient confirmed that she did not take any drugs other than trazodone in her suicide attempt. She did not exhibit agitation, tremor, or myoclonus, and there was also no hyperthermia on presentation until she developed aspiration pneumonia and became febrile. She was only briefly hypotensive during her arrhythmias due to the cardiogenic shock and she did have elevated blood pressure afterwards, which could have been pre-existing prior to drug overdose. Nevertheless, we could not rule out the likelihood of serotonergic activity from acute trazodone overdose, which could possibly explain the development of seizures [14].

There have been case reports of trazodone overdose in which patients developed hyponatremia because of a syndrome of inappropriate antidiuretic hormone secretion, seizure, and cerebral edema [15]. Our patient's sodium level had been normal throughout, and repeated CT head scans were negative

for cerebral edema. As stated above, her seizures could have been due to serotonin syndrome, but also possibly could have resulted from acute cerebral ischemic insult from the cardiogenic shock caused by trazodone cardiotoxicity.

In our case, there was evidence of an empty bottle of trazodone, and the patient also said she took the medication, which confirmed the diagnosis. The serum trazodone level could not be determined, which is a limitation of this case report.

Conclusions

Trazodone overdose can induce life-threatening electrophysiological abnormalities of the heart, even in those without previous cardiac comorbidity. There is no antidote for trazodone overdose, and supportive care is the mainstay of therapy. It is important to closely monitor for rhythm disturbances and manage these accordingly.

Department and Institution where work was done

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Conflict of interest

None.

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