Case Report

Isolated sinus tachycardia following reinitiation of risperidone in a patient with suspected autonomic hypersensitivity

Melanie J Grubisha, Jessica L Brennan, Antoine Douaihy

Department of Psychiatry, Western Psychiatric Institute and Clinic, Pittsburgh, Pennsylvania, United States

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ABSTRACT

The second generation antipsychotic risperidone is generally considered to have low cardiac adverse events, with an increased risk of ventricular arrhythmias being reported only rarely in literature. We report here the case of a patient with a significant history of alcohol dependence, yet with no previous cardiac history, who had previously tolerated risperidone well, but had experienced isolated sinus tachycardia in the post detox period, following the reinitiation of risperidone therapy. The Naranjo Adverse Drug Reaction (ADR) probability scale rating for this being a medication adverse event (AE) was 4, thus indicating that this patient's AE was associated with risperidone therapy. This case report will contribute to the limited evidence of adverse cardiac events associated with risperidone therapy, with particular emphasis on the susceptibility of patients in a state of autonomic hypersensitivity.

Key words: Autonomic hypersensitivity, autonomic instability, cardiotoxicity, dual diagnosis, risperidone, sinus tachycardia

INTRODUCTION

In patients withdrawing from alcohol or benzodiazepine abuse, autonomic instability is common. It usually begins within the first six to thirty-six hours, and typically peaks in severity 72 to 120 hours after cessation of drinking, and thus, protocols exist to limit this dangerous dysautonomia over the detox period.[1] However, we suggest that continued autonomic hypersensitivity may exist, which can influence a response to medications in dually diagnosed patients.

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The atypical antipsychotic risperidone (Risperdal®) is generally considered to have a low cardiotoxic profile.[2] We report here a case of sinus tachycardia without QT-interval (QTc) prolongation in a recently detoxed, dually diagnosed patient, treated with risperidone, who had previously tolerated risperidone during a period of sobriety.

CASE REPORT

A 25-year-old Caucasian male, with a past psychiatric history of bipolar disorder, not otherwise specified (NOS), opioid dependence, and alcohol dependence began inpatient treatment at a psychiatric hospital on day zero. He was admitted on the basis of inability to care for self, secondary to depressive symptoms from his bipolar disorder, and he required concomitant detoxification from alcohol and opiates. His past medical history was not significant for any history of cardiac disease and his thyroid (Thyroid

Address for correspondence:
Melanie J Grubisha, 3501 O'Hara Street, Pittsburgh, Pennsylvania - 15213, United States. E-mail: grubisham@upmc.edu

Stimulating Hormone (TSH) 0.51), liver function (Aspartate Transaminase (AST) 13, Alanine Transaminase (ALT) 23, Alkaline phosphatase 95), and kidney (Blood Urea Nitrogen (BUN) 19, Creatinine (Cr) 0.84) testing were normal within the last two months. On admission, his substance-use history was positive for benzodiazepines (last use three days before admission), alcohol (last use one day before admission), and IV heroin (last use two days before admission). He was placed on a Withdrawal-from-Alcohol Scale (referred to as a WAS at our institution) with as-needed oxazepam (Serax) based on the scoring of the WAS,[1] in addition to a five day oxazepam taper. A Clinical Opiate Withdrawal Scale (COWS) was also initiated.[1] These were continued for the first week of his inpatient treatment and then discontinued. Records indicate that he was scoring mostly zeros on both scales, except during the 24 hours surrounding the incident described below. Vital signs at the time of admission were: A pulse of 99 and blood pressure (BP) of 128/87, both recorded in standard units of beats per minute and mm/Hg, respectively.

Initially, the patient refused medications prescribed for his depressive symptoms. On day five of admission, following completion of his oxazepam taper, he was amenable to starting risperidone 2 mg p.o. BID, to help with mood stabilization. He had been treated with risperidone in the past at this same dosage and reportedly tolerated it well. He was non-adherent with his medications over the long term, as he preferred illicit drug use and alcohol to treat his symptoms. He received his first dose on the evening of day five and his second dose on the morning of day six. Within two hours of his second dose, he reported feeling dizzy, a racing heart, and chest tightness. At that time he was found to be tachycardic at 126 bpm and hypertensive at 163/86. Although nine days had passed since his last substance use, 15 mg of oxazepam was administered out of concern for the possibility of ongoing withdrawal based on his WAS score of 17. His BP decreased to 138/88; however, the patient's heart rate did not respond to the oxazepam and continued to increase, fluctuating between 130 and 154 bpm with the BP remaining normotensive. He was given scheduled doses of both diazepam (Valium) and lorazepam (Ativan) throughout the remainder of day six, totaling to 60 mg and 2 mg, respectively. Even as he remained normotensive, his heart rate did not decrease and remained elevated above 130 bpm throughout day six.

Initially, with only isolated tachycardia, recent substance abuse, and no cardiac history, there was low concern for an acute cardiac etiology. However, when the tachycardia did not resolve, electrocardiography (EKG) was performed two hours after symptom onset. This showed sinus tachycardia (145 bpm) without ST-segment changes and without QTc prolongation (QTc 412 ms). The chart review revealed that the recent TSH screening level was within normal limits. Stat laboratories for electrolytes, blood urea nitrogen (BUN)/Creatinine, and Complete Blood Count (CBC) with differential were drawn, to rule out electrolyte abnormalities, depleted volume status, and infection, as being the precipitators of his isolated tachycardia. All the laboratory values were within normal limits, and were unchanged from his admission laboratories seven days prior. Risperidone was discontinued and the patient was monitored. On day seven of admission, 23 hours after his last risperidone dose, his heart rate was 86, BP was 106/74, and he had no subjective symptoms. A repeat EKG showed normal sinus rhythm, without any other abnormalities.

DISCUSSION

Risperidone has an oral bioavailability of 70% and reaches maximum plasma concentration within one hour of ingestion.[3] Within two hours of ingesting his second dose, our patient began feeling tachycardic. This time coincided with what was likely to be his peak plasma concentration window. His tachycardia worsened, was unresponsive to benzodiazepines, and persisted for 24 hours after his risperidone dose. Failure of the benzodiazepines to lower his heart rate made it unlikely that his tachycardia was the result of anyongoing withdrawal. Furthermore, the patient was not taking any other medications concomitantly, thus ruling out other potential pharmacological causes of his tachycardia.

Risperidone is hepatically metabolized, exclusively through CYP2D6, with an elimination half-life of two to twenty hours for oral administration.[3] The resolution of his tachycardia within 24 hours of his last risperidone dose temporally correlates with the elimination half-life of the drug. Even as a genetic polymorphism impairing the metabolic functioning of CYP2D6 could explain an adverse effect at a therapeutic dosage,[4] our patient reportedly tolerated therapeutic dosages of risperidone in the past, without consequence. Thus, it is unlikely that he had genetically impaired CYP2D6 function, and his lack of concomitant medication use that could potentially alter the CYP2D6 function further argues against a deficit in metabolism underlying this adverse event. Furthermore, while chronic alcohol intake has been shown to induce hepatic metabolism, it has primarily been shown to affect the CYP2E1 isoform.[5] As risperidone is exclusively CYP2D6 metabolized, it is unlikely that this patient's ongoing alcohol consumption, prior to this reinitiation of risperidone, was contributing to this adverse effect. Rather, we postulate that the nature of this AE was due in a large part to a state of autonomic hypersensitivity in a susceptible patient.

Autonomic instability is a hallmark of alcohol withdrawal, with the initial onset at six to thirty-six hours. It can become life-threatening (delirium tremens or DTs) when hallucinations, disorientation, and severe dysautonomia are present. This

generally occurs 72-120 hours after cessation of alcohol ingestion.[6] Benzodiazepines will both prevent and treat the autonomic instability caused by alcohol withdrawal, and thus, their use during the first 48-72 hours can prevent the escalation to DTs.[1] Our patient was managed appropriately with an oxazepam taper for five days to treat his high risk for dysautonomia from his alcohol withdrawal, and his vital signs throughout those first five days were all within normal limits. The timing of his tachycardia seven days after his last drink was not consistent with acute alcohol withdrawal.

Even as the antipsychotic activity of risperidone is thought to be related primarily to its 5HT-2 and D2 receptor antagonism, it is also known to exert some α1 and α2 receptor affinity.[7] Antagonism of the α1 receptor causes a decrease in blood pressure and reflex tachycardia. In cases with underlying autonomic hypersensitivity, such as is seen in patients who have recently undergone alcohol detoxification, this small amount of α receptor activity may lead to an exaggerated response.

According to the package insert, results from a double-blind placebo-controlled trial demonstrated tachycardia in 0.01% of patients treated with risperidone, compared to none in the controls.[8] However, our patient had previously tolerated risperidone without experiencing sinus tachycardia. His current state of recent alcohol detoxification, however, placed him in a state of autonomic hypersensitivity, which may have led to isolated sinus tachycardia related to the reinitiation of a therapeutic dose of risperidone.

We have presented here, the case of isolated sinus tachycardia in response to initiation of risperidone therapy in a young patient with a recent history of alcohol detoxification, but otherwise no cardiac history. The Naranjo ADR probability rating scale assesses the likelihood of an event being associated with a medication, and in this case it has indicated a possible association, with a score of 4.[9] This case will add to the limited body of evidence for possible cardiac adverse events of risperidone treatment, particularly in autonomically sensitive patients. Substance abuse is commonly comorbid with other psychiatric disorders, thus, providers must be aware of the increased risk for autonomic side effects of medications, when initiating therapy in this patient population.

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