Torsades de Pointes After Administration of Low-Dose Aripiprazole

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OBJECTIVE: To describe a case of torsades de pointes (TdP) in a patient treated with aripiprazole.

CASE SUMMARY: A 42-year-old white male with schizophrenia, diabetes, hypertension, and a history of stroke was admitted to the intensive care unit following 2 days of fever, diarrhea, and altered mental status. Following the resolution of his acute illness, previous therapy with quetiapine 400 mg orally at bedtime was resumed for schizophrenia and presumed delirium. Quetiapine was discontinued after 1 dose because of QTc interval prolongation. Twenty-three days later, with a baseline QTc interval of 414 milliseconds, aripiprazole 2.5 mg orally once daily was initiated. Following 5 days of aripiprazole therapy, the patient had a cardiac arrest due to TdP. Normal sinus rhythm was restored after 30 seconds of cardiopulmonary resuscitation, 1 shock of 200 Joules, and 4 g of intravenous magnesium sulfate. Serial electrocardiographs obtained after aripiprazole discontinuation revealed resolution of QTc interval prolongation.

DISCUSSION: Aripiprazole is a second-generation antipsychotic that may be selected for patients with prolonged QTc intervals and at risk for TdP. Data from trials indicate that aripiprazole has minimal effects on the QTc interval. However, in this case, aripiprazole was associated with TdP in a patient with minimal risk factors. The Naranjo probability scale was used to determine a probable association between aripiprazole and the development of TdP. To our knowledge, this is the first reported case of TdP associated with the use of aripiprazole.

CONCLUSIONS: Five days of low-dose aripiprazole therapy was associated with the development of TdP in a man with minimal risk factors. Clinicians should be aware of this potential adverse drug event with aripiprazole.

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Haloperidol, a first-generation antipsychotic, has been considered the gold standard for the treatment of intensive care unit (ICU) delirium.[1] In an attempt to use effective, and potentially safer agents, clinicians have increasingly ordered second-generation antipsychotics (SGAs) for managing ICU delirium. However, only olanzapine, quetiapine, and ziprasidone have been studied for ICU delirium in a prospective, randomized controlled manner.[2-4] Other SGAs with literature supporting their use for delirium include aripiprazole and risperidone. However, these data involve only non-ICU populations.[5-17]

Antipsychotics primarily exert their action through dopamine antagonism. Examples of adverse effects related to this mechanism include drug-induced movement disorders and neuroleptic malignant syndrome. These types of adverse events are less likely to be caused by SGAs than by haloperidol.[18] Properties of SGAs that may account for a lower adverse effect burden include serotonin 5-HT_{2A} antagonism, faster dissociation from the dopamine D_2 receptor, and/or lower D_2 receptor occupancy.[19,20]

An additional adverse effect of many antipsychotics is prolongation of the corrected QT (QTc) interval. A medication's ability to cause QTc interval prolongation is likely related to the degree to which it blocks the delayed rectifier potassium channel, which is responsible for ventricular repolarization.[21] Delays in ventricular repolarization manifest as longer QTc intervals, a surrogate marker for torsades de pointes (TdP).[22] TdP is a polymorphic ventricular arrhythmia that may present as lightheadedness and syncope, and in rare cases, can be fatal.[23] A QTc interval greater than 450 milliseconds for men and 470 milliseconds for women indicates prolongation, with QTc intervals greater than 500 milliseconds or a change from baseline that exceeds 60 milliseconds being considered clinically significant.[24]

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Careful consideration must be given to the potential for an antipsychotic to prolong the QTc interval, since critically ill patients may have prolongation prior to antipsychotic initiation from factors such as other medications, electrolyte abnormalities, and concurrent disease states.[24] In 2007, the Food and Drug Administration (FDA) strengthened warnings regarding QTc interval prolongation and TdP with use of intravenous haloperidol, recommending continuous electrocardiograph (ECG) monitoring with its use.[25] This warning did not apply to oral haloperidol, as it has similar potential for prolonging the QTc interval compared with risperidone and olanzapine.[26,27] Among the SGAs, ziprasidone has demonstrated the greatest potential to prolong the QTc interval.[27] The FDA also recently strengthened the warning of QTc interval prolongation associated with quetiapine use.[28] Conversely, aripiprazole has been shown to have minimal effect on the QTc interval, with no reported cases of TdP.[29-38] However, we report a case of nonfatal TdP associated with the administration of aripiprazole in a patient with minimal risk factors.

Case Report

A 42-year-old white male with schizophrenia, diabetes mellitus, hypertension, and previous stroke presented to the emergency department following 2 days of fever, chills, diarrhea, and altered mental status. He was admitted to the medical ICU for the treatment of sepsis. His ICU course was complicated by the development of severe sepsis, renal failure, adrenal insufficiency, and acute respiratory distress syndrome.

One week into the hospital course, the patient was exhibiting symptoms thought to be related to hypoactive delirium, schizophrenia, or both. The dose of quetiapine used before admission (400 mg by mouth at bedtime) was restarted but discontinued after 1 dose when the QTc interval was discovered to be 644 milliseconds. The only prior ECG obtained was upon arrival at the emergency department 7 days earlier, which revealed an interval of 528 milliseconds. Twenty-three days after quetiapine administration and at resolution of the patient's acute illness, a new baseline QTc interval of 414 milliseconds was obtained. Given the significant changes with quetiapine, aripiprazole was initiated because of data supporting its minimal effect on the QTc interval. Following 5 days of aripiprazole 2.5 mg orally once daily, the patient had a cardiac arrest due to TdP, identified by an ECG. Minutes prior to the event, an ECG recorded a QTc interval of 624 milliseconds. The patient received cardiopulmonary resuscitation for 30 seconds, 1 shock of 200 Joules, and magnesium sulfate 4 g given intravenous push. Normal sinus rhythm was restored and aripiprazole was discontinued.

The only additional risk factor present at the time of TdP was concomitant intravenous famotidine 20 mg daily. Relevant laboratory findings included potassium 3.8 mEq/L, magnesium 1.5 mg/dL, and calcium 8.8 mg/dL. Additionally, a cardiac catheterization conducted the following day did not reveal any significant disease. Follow-up QTc measurements 1, 5, and 14 days after aripiprazole discontinuation were 537, 472, and 450 milliseconds, respectively. There were no ECG data prior to this hospitalization for analysis and no documentation of a congenital long QT syndrome. After evaluation of the case using the Naranjo probability scale,[39] it was determined that there was a probable relationship between the onset of TdP and aripiprazole therapy in this patient.

Discussion

Aripiprazole is an antipsychotic with partial dopamine agonist properties that may have positive effects on attention, concentration, and sleep-wake cycle reversal in delirium.[7] It has been proposed that these properties may make aripiprazole an ideal agent in hypoactive delirium, a commonly underdiagnosed form of ICU delirium.[7,40] Other properties of aripiprazole include minimal antagonism on muscarinic, histaminic, and α_1 adrenergic receptors. Aripiprazole also has lower incidences of drug-induced movement disorders and neuroleptic malignant syndrome as compared with haloperidol.[41] Additionally, aripiprazole is available as an intramuscular injection, an orally disintegrating tablet, a tablet, and a liquid, allowing for administration when barriers to drug delivery may be present.[42] Despite these properties, there is a lack of data supporting efficacy and safety of aripiprazole for the treatment of delirium.

No data regarding the effect of aripiprazole on the QTc interval in ICU populations exist. Available cardiac safety data may be extrapolated from psychiatric clinical trials, non-ICU delirium trials, and overdose reports, which have shown aripiprazole to have a minimal effect on the QTc interval, with no reported cases of TdP. In fact, some data suggest that QTc interval shortening may occur. In a recent letter, Muzyk et al. retrospectively evaluated the effects of intramuscular aripiprazole administration on the QTc interval in medically ill patients.[43] Intramuscular aripiprazole (mean dose 9.64 ± 1.96 mg) was administered to 14 men and 7 women (mean age 61.1 ± 14.5 years), 86% of whom were on concomitant medications known to cause QTc prolongation. The reported change of the QTc interval was 2.1 ± 7.3 milliseconds from a mean baseline of 479.8 ± 46.2 milliseconds ($p = 0.39$). Ten of the 21 patients had a decrease in QTc interval (range 10-32 milliseconds). However, 6 patients had an increase of greater than 30 milliseconds from baseline (range 30-82 milliseconds). Discussion regarding patients with large increases in QTc interval was not provided, making it difficult to estimate the probability that aripiprazole was responsible. Limitations of this study consist of the small number of patients, and while the au-

thors concluded that there was no statistically significant change in QTc intervals from baseline, approximately 30% of the patients had noteworthy prolongation.

In a prospective, open-label study, Straker et al. evaluated the effects of aripiprazole in the treatment of delirium in 14 general medicine patients.[7] The mean age of the 6 men and 8 women was 70.9 ± 11.3 years. Oral aripiprazole was used, with a mean dose of 8.9 ± 3.5 mg per day. Changes in delirium rating scales were the primary outcome measures; QTc interval data were also assessed. Mean QTc interval length at baseline was 442 ± 44 msec. Follow-up ECGs were obtained in 10 of the 14 patients and revealed a mean decrease of the QTc interval from 451 ± 50 to 434 ± 22 milliseconds. The authors mentioned that the QTc interval increased in 3 patients; however, the degree of change was not noted. While it was not the study's primary objective to evaluate the cardiac safety of aripiprazole in delirious patients, there were no reports of TdP and aripiprazole demonstrated minimal effects on the QTc interval.

Given the lack of data associating aripiprazole with QTc interval prolongation and the patient's response to quetiapine, aripiprazole was initiated for treatment of delirium in our patient with schizophrenia. At the time of TdP, the only other risk factor identified was concomitant famotidine. The prescribing information for famotidine states that, in patients with renal impairment, QTc interval prolongation occurs very rarely. Cases identified also indicate that significant renal impairment is an important factor in famotidine-induced QTc interval prolongation.[44,45] Finally, in vitro and in vivo tests have concluded that famotidine does not affect potassium channels responsible for cardiac repolarization.[46] Given that the patient had an estimated creatinine clearance greater than 60 mL/min, the literature would suggest that famotidine was less of a risk, if at all, contributory in our case. Furthermore, our patient was receiving famotidine both before and after aripiprazole use, with documented QTc intervals within normal limits.

One additional consideration when evaluating the association between aripiprazole administration and TdP is the normalization of QTc interval upon withdrawal of the drug. After the occurrence of TdP and discontinuation of aripiprazole, the patient's QTc interval returned to normal over 14 days, which is possibly related to the 75-hour half-life of the agent.[42] This would further suggest that aripiprazole was the precipitating factor for QTc interval prolongation and TdP in this case.

To our knowledge, this is the first reported case of TdP associated with aripiprazole therapy. Clinicians should be aware that low-dose aripiprazole may produce significant QTc interval prolongation and TdP in patients with minimal risk factors. Since aripiprazole may be selected for patients with a history of QTc interval prolongation or a high baseline interval, more cardiac data are needed to assess the safety of the drug in this population.

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