Prolonged QRS Widening After Aripiprazole Overdose

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Background: Aripiprazole is an atypical antipsychotic with a long half-life. Overdose can result in protracted somnolence and cardiac disturbances, particularly QT interval prolongation.

Methods: This is a single case report of a 14-year-old boy who took an overdose of aripiprazole and developed QRS widening.

Case: A 14-year-old boy intentionally ingested 20 tablets of aripiprazole (5 mg). He was brought to the emergency department when his ingestion was discovered. The patient's vital signs were as follows: temperature, 37.7°C; heart rate, 108 beats/min; blood pressure, 138/98 mm Hg; and respirations, 16 breaths/min. Activated charcoal was administered within 90 minutes of ingestion. Initial electrocardiogram (EKG) showed sinus tachycardia, with a QRS of 138 ms and QT interval of 444 ms. QRS duration was 90 ms on an EKG performed 3 months earlier. A bolus of sodium bicarbonate was administered, and the patient was transferred to the pediatric intensive care unit. Repeat EKG demonstrated a QRS of 156 ms, and a sodium bicarbonate infusion was initiated. The patient continued to have QRS prolongation for the next 8 days, reaching a peak of 172 ms 3 days postingestion. Despite aggressive treatment with sodium bicarbonate, there was persistent QRS prolongation; however, the patient did not have any dysrhythmias and remained hemodynamically stable. The patient was discharged 9 days postingestion when the QRS duration normalized to 82 ms. Genetic testing revealed that the patient was a CYP2D6 poor metabolizer.

Conclusions: This case suggests that aripiprazole toxicity may possibly be associated with QRS prolongation without associated dysrhythmias or cardiovascular compromise. In addition, toxicity may be prolonged in patients who are CYP2D6 poor metabolizers.

Key Words: aripiprazole overdose, EKG abnormality, QRS prolongation

(*Pediatr Emer Care* 2018;00: 00–00)

Aripiprazole (Abilify) is a second-generation (atypical) antipsychotic that is used to treat a variety of conditions, such as schizophrenia and bipolar disorder, and as an adjunct for major depressive disorder.[1] Aripiprazole acts as a partial agonist at both the dopamine D_2 and serotonin 5-HT_{1A} receptors and as an antagonist at 5-HT_{2A} receptors; however, its mechanism of action remains to be fully elucidated.[1,2] Aripiprazole undergoes hepatic metabolism primarily by 2 cytochrome P450 isozymes, CYP2D6 and CYP3A4, to an active metabolite. Aripiprazole has a relatively long elimination half-life, ranging from a mean of 75 hours in normal patients to 146 hours in slow or poor metabolizers.[1–3]

Because of its long half-life, aripiprazole overdose can result in prolonged toxicity, lasting for several days. Clinical manifestations commonly associated with aripiprazole toxicity include gastrointestinal disturbance, somnolence, orthostatic hypotension, and extrapyramidal symptoms, as well as cardiac disturbances, most commonly tachycardia and QT interval (QTc) prolongation. QRS prolongation is generally not observed after therapeutic administration or overdose of aripiprazole.[4–6] We report a case of significant and prolonged QRS widening after an acute isolated aripiprazole overdose in a 14-year-old boy who was found to be a poor metabolizer of CYP2D6 substrates.

CASE

A 14-year-old boy with a history of depression and anxiety reported taking approximately 20 of his own aripiprazole (5 mg) tablets to "calm his nerves." He was brought to a community emergency department (ED) when he disclosed the ingestion to his parents. His prescribed dose was 5 mg once daily, and a pill count and refill history was performed, which supported his claim that he ingested 20 5 mg tablets. The only other medication the patient was taking was citalopram, but no tablets were missing based on pill count and refill history and the patient denied ingesting additional citalopram. No other medications in the home were missing. The patient denied ingestion of alcohol or illicit substances and had no history of substance abuse. When he presented to the ED, he was drowsy but arousable. On arrival, the patient's vital signs were as follows: temperature, 37.7°C; heart rate, 108 beats/min; blood pressure, 138/98 mm Hg; respirations, 16 breaths/min; and oxygen saturation, 95% on room air. Activated charcoal was administered within 90 minutes of ingestion. Laboratory studies for aspirin, acetaminophen, and ethanol were negative. Urine drug screen was also negative. Initial electrocardiogram (EKG) showed sinus tachycardia, with a QRS duration of 138 ms and QTc of 444 ms. The QRS duration was 90 ms on a baseline EKG performed 3 months earlier (before starting medication), and there was no personal or family history of syncope or sudden cardiac arrest. A bolus of sodium bicarbonate (1 mEq/kg) was administered, and the patient was transferred to a tertiary care facility with a pediatric intensive care unit.

On arrival to the pediatric intensive care unit, a repeat EKG demonstrated a QRS of 156 ms and a sodium bicarbonate infusion (150 mEq in 1 L of D5W run at 1.5–2 times maintenance) was initiated. The patient continued to have QRS prolongation with intermittent QTc abnormalities for the next 8 days, with the QRS duration reaching a peak of 172 ms 3 days postingestion (Fig. 1). The QTc prolongation was intermittent, peaking at 546 ms on the first day of the hospitalization (Table 1). He was also noted periodically to have a left bundle branch block. He was treated with a combination of sodium bicarbonate boluses (1 mEq/kg) and infusions (150 mEq in 1 L of D5W run at 1.5–2 times maintenance). Despite aggressive treatment, there was persistent QRS prolongation; however, the patient did not have any ectopy or dysrhythmias and remained hemodynamically stable during his hospitalization. The patient also had mild hypokalemia, hypocalcemia, and hypomagnesemia during the admission, which was aggressively treated; however, QRS widening persisted despite electrolyte correction (Table 2). Blood gas measurements were not obtained. Cardiology was consulted to investigate other etiologies of increased QRS duration, but none were identified. The sodium bicarbonate infusion was discontinued on hospital day 4. The patient was discharged 9 days postingestion when the QRS duration normalized to 82 ms. In addition to the EKG abnormalities,

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Disclosure: The authors declare no conflict of interest.

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ISSN: 0749-5161

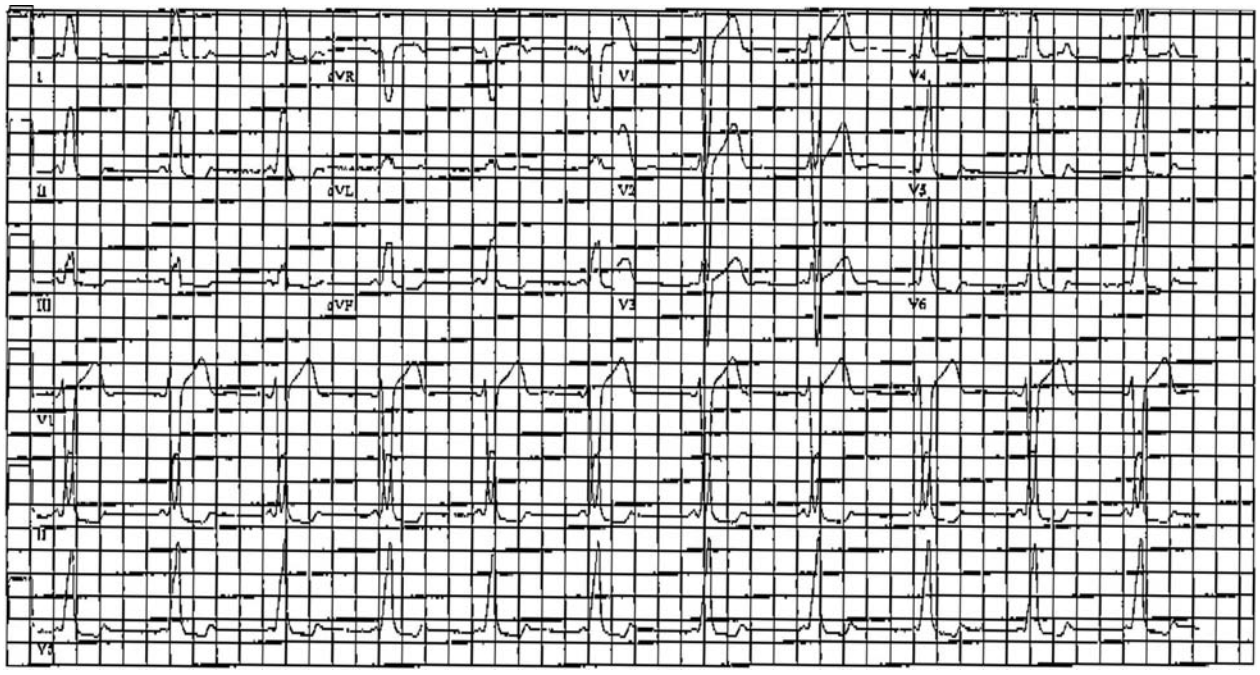

FIGURE 1. EKG obtained during admission demonstrating QRS prolongation.

the patient had transient drowsiness, which did not require intervention and an acute dystonic reaction (tongue and jaw fasciculation) that was successfully treated with one dose of diphenhydramine on hospital day 2. The patient underwent concomitant psychiatric evaluation and was discharged on hospital day 9. He was not restarted on any psychiatric medications at that time, as the results of genetic testing were pending. The results of genetic testing sent during the hospitalization revealed that the patient was a CYP2D6 poor metabolizer. He tested positive for 2 copies of CYP2D6*4ABDJK, which is a poor metabolizer allele.

TABLE 1. QRS and QTc Interval After Aripiprazole Overdose

Day Postingestion/ Time of EKG	QRS Duration, ms	QT/QTc Interval, ms
Day 0/9:00 PM	138	*/444
Day 1/11:00 AM	156	400/435
Day 1/5:00 PM	152	400/537
Day 2/9:00 AM	162	400/447
Day 2/11:00 PM	172	430/447
Day 3/10:00 AM	164	400/473
Day 3/9:00 PM	162	432/482
Day 4/9:00 AM	146	418/463
Day 4/10:00 PM	134	396/456
Day 5/11:00 AM	164	422/541
Day 5/9:00 PM	160	430/495
Day 6/7:00 AM	170	442/459
Day 6/10:00 PM	164	418/482
Day 7/8:00 AM	164	410/523
Day 7/7:00 PM	164	414/509
Day 8/8:00 AM	168	424/457
Day 8/10:00 PM	154	406/450
Day 9/8:00 AM	82	372/463

*Unavailable in records.

DISCUSSION

This case is unique in that we report significant and prolonged QRS widening associated with a presumed aripiprazole overdose. A Naranjo score, used to assess the likelihood of causation, was 5 (probable). The toxicity of aripiprazole is an exaggeration of its effects on dopaminergic and serotonergic receptors as well as actions on other receptors including histamine H_1 receptors and α_1-adrenergic receptors. Aripiprazole does not bind muscarinic receptors.[1,5,6] Previous experience with aripiprazole overdose suggests that this medication is generally well tolerated in overdose; however, a dose of more than 5 times the regular daily dose is considered potentially toxic.[4–6] The target dose for adolescents is 10 mg daily, although doses up to 20 mg a day can be used. It is

TABLE 2. Electrolyte Concentrations After Aripiprazole Ingestion

Day Postingestion	Potassium, mEq/L	Calcium, mg/dL	Magnesium, mg/dL
1	3.6	8.7	N/A
2 (AM)	3.4	8.2	1.6
2 (PM)	3.7	9.2	N/A
3	3.7	8.7	2.3
4	3.5	8.9	1.8
5	N/A	N/A	N/A
6	4.3	9.4	2.0
7	4.3	9.5	N/A
8	3.8	8.5	1.6

N/A indicates not available.

recommended that the dose be reduced by 50% for known CYP2D6 poor metabolizers.[1] The patient presented in this case reported taking 100 mg. The most common adverse effects are drowsiness, likely related to effects at H_1 receptors, hypotension with reflex tachycardia due to α_1-adrenergic receptor antagonism, and extrapyramidal effects.[4–6] One case series that examined pediatric aripiprazole exposures noted prolonged lethargy and extrapyramidal effects but no seizures or dysrhythmias.[6]

Cardiovascular effects have been rarely reported with aripiprazole. When present, the most common clinical manifestation is tachycardia.[7,8] QTc prolongation has occurred infrequently after aripiprazole exposure, but ventricular dysrhythmias and torsades de pointes are rare in healthy patients after an acute ingestion.[1,7,9] Patients with baseline QTc prolongation may be at higher risk of torsades de pointes after ingestion of an agent that prolongs the QTc.[9] QRS prolongation may occur owing to sodium channel antagonism and has been reported with overdoses of other atypical antipsychotics including quetiapine, risperidone, and ziprasidone.[7] QRS prolongation has not been demonstrated with aripiprazole.[10] Because second generation antipsychotics have a relatively lower affinity for cardiac sodium channels, it is believed that isolated overdose is better tolerated and does not lead to significant dysrhythmia or cardiovascular collapse.[11] This lower affinity for the cardiac sodium channels may also be the reason why there was a limited response to sodium bicarbonate administration.[11] Another potential mechanism for these findings could be related to gap junction dysfunction, rather than sodium channel blockade, as in the case of bupropion overdose.[12] Although there are limited data pertaining to aripiprazole, the clinical course of our patient was very similar to patients with overdoses of other second generation antipsychotics in that he had QRS prolongation, but did not develop significant dysrhythmias or cardiovascular collapse. Interestingly, the patient's EKG abnormalities did not correct with sodium bicarbonate therapy.

The duration of our patient's EKG abnormalities was possibly related to both the long half-life of aripiprazole and its active metabolite as well as the patient's CYP2D6 poor metabolizer status. Aripiprazole undergoes hepatic metabolism via the CYP3A4 and CYP2D6 enzymes. The elimination half-life of aripiprazole is approximately 75 hours, and the half-life of its major active metabolite dehydroaripiprazole is 94 hours.[1] In patients who are CYP2D6 poor metabolizers, the half-life of aripiprazole can be up to 146 hours.[3] CYP2D6 polymorphisms are common and approximately 8% of Caucasians, and 3% to 8% of African Americans are CYP2D6 poor metabolizers.[1–3] A dose reduction is recommended for patients who are CYP2D6 poor metabolizers and patients who are concomitantly taking CYP3A4 inhibitors to avoid adverse effects.[1] Patients who are CYP2D6 poor metabolizers can experience even more prolonged toxicity in the setting of overdose. Our patient had 2 copies of CYP2D6*4ABDJK, which is a poor metabolizer allele, but this was not known before initiating therapy with aripiprazole. In addition, the patient was taking citalopram, which is also metabolized by CYP2D6. This may have impacted aripiprazole metabolism, although in vivo data are lacking. Studies have shown that citalopram steady state-concentrations are not significantly different in CYP2D6 poor metabolizers.[13]

The recommended management of aripiprazole overdose is largely supportive in nature, with attention to airway protection in the setting of lethargy. Activated charcoal should be considered for early-presenting patients with potentially toxic ingestions and an intact airway. There is currently no evidence for delayed or erratic absorption or enterohepatic recirculation; therefore, multidose activated charcoal is not typically recommended at this time.[1] Fluids are first line therapy for hypotension. Patients should have an EKG performed and be placed on a cardiac monitor. QTc prolongation can be treated with magnesium sulfate if there is evidence of dysrhythmia such as torsades de pointes.[14] Prophylactic administration of magnesium sulfate in the setting of a normal QTc interval is unlikely to be of benefit, although there is a great deal of practice variation among medical toxicologists.[14,15] QRS prolongation can be treated with sodium bicarbonate; however, there is no experience with the use of bicarbonate to treat QRS prolongation that results from aripiprazole exposure.[16] In addition, use of sodium bicarbonate may worsen QTc prolongation by causing hypokalemia.[12] Aripiprazole has a large volume of distribution, and the use of hemodialysis is not recommended. Most patients can be observed in the ED until their symptoms resolve and then be discharged or cleared for psychiatric evaluation; however, patients with prolonged alterations in mental status and vitals signs, EKG abnormalities, or dysrhythmias should be admitted.[5–7]

The data we present are limited in that this is a single-case report and there was no true confirmation of exposure with serum aripiprazole concentrations. pH determinations were not obtained, and therefore, therapeutic dosing of bicarbonate could not be confirmed. We also did not have access to records from outpatient follow-up to determine if subsequent EKGs remained normal and what outpatient medications, if any, were used for the ultimate stabilization of the patient's depression and anxiety.

CONCLUSIONS

This case suggests that aripiprazole toxicity may possibly be associated with QRS prolongation without associated dysrhythmias or cardiovascular compromise. In addition, toxicity may be prolonged in patients who are CYP2D6 poor metabolizers.

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