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Neuroleptic Malignant Syndrome From Aripiprazole in an Agitated Pediatric Patient

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Abstract

Objective:
Neuroleptic malignant syndrome was induced by aripiprazole in a 12 1/2-year-old boy. The patient had a history of reactive airway disease, pervasive developmental disorder, and learning disability.

Method:
The patient was interviewed and examined, and additional history was taken from the medical records. The Naranjo adverse drug reaction rating scale was applied.

Results:
The patient developed neuroleptic malignant syndrome 2 days after starting aripiprazole 10 mg/d. This patient had no history of exposure to dopamine-blocking drugs or selective serotonin reuptake inhibitors or of neurological disorder, movement disorder, or substance use. Aripiprazole discontinuation and supportive treatment led to resolution. The Naranjo scale indicates high probability of neuroleptic malignant syndrome from aripiprazole.

Conclusions:
Aripiprazole can rapidly induce neuroleptic malignant syndrome in adolescents.

Key Words: neuroleptic malignant syndrome, movement disorder, abilify, aripiprazole, antipsychotic, neuroleptic

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Neuroleptic malignant syndrome is a serious complication of neuroleptic medications, first reported by Delay in 1960.[1] Neuroleptic malignant syndrome typically evolves over several days and becomes problematic in the first few weeks after initial exposure, but it can develop anytime. Principal manifestations are muscle rigidity with myonecrosis, a delirium resembling catatonia, and autonomic dysfunction with hyperthermia, tachycardia, and a labile blood pressure.

We observed neuroleptic malignant syndrome in a 12-year-old boy who was recently started on aripiprazole. This is the first known case of neuroleptic malignant syndrome from aripiprazole occurring in an antipsychotic naive adolescent patient. The Food and Drug Administration approved aripiprazole in 2004 for treating schizophrenia and bipolar disorder in adults.

METHODS

We interviewed and examined the patient, and additional history was taken from the medical records. The Naranjo adverse drug reaction rating scale indicated a "high probability" of neuroleptic malignant syndrome from aripiprazole.[2]

CASE REPORT

This is a 12-year-old white boy with a history of reactive airway disease and pervasive developmental disorder not otherwise specified. He showed difficulties with attention and hyperactivity and is under treatment with methylphenidate 36 mg daily. He was independent with activities of daily living and spoke in complete sentences. He was in fifth grade special classes for developmentally delayed children.

He presented to his primary care physician after developing an upper respiratory tract infection. Later, he became increasingly irritable and hyperactive. This physician started aripiprazole 10 mg daily for agitation control. This was the patient's first exposure to an antipsychotic drug. Two days later, his respiratory symptoms worsened and he was brought to the emergency department. He received nebulizer treatments. He showed tremors and an acute confusional state. Computed tomographic scan, lumbar puncture, and toxicology screen results were negative, but creatinine phosphokinase was increased at 401 U/L.

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On admission, his temperature was 37°C, pulse rate was 77 beats per minute, and blood pressure was 115/76 mm Hg. Neurological examination revealed muscle rigidity, and reflexes could not be elicited. Initially, the patient was able to respond to commands although he was disoriented. He deteriorated into unresponsiveness during the next day, with no response to pain and sustained clonus in lower extremities bilaterally. An electroencephalogram revealed diffuse slowing with no seizure activity. A chest radiograph was suspicious for aspiration pneumonia and a 10-day course of clindamycin was started, aripiprazole and methylphenidate were discontinued, and he was transferred to the intensive care unit.

Neuroleptic malignant syndrome was diagnosed consistent with diagnostic and statistical manual of mental disorders, fourth edition, text revision criteria.[3] The patient presented with fluctuating consciousness, fever, generalized muscle rigidity, labile vital signs, increased creatinine phosphokinase, increased white cell count, and respiratory distress. These occurred only after aripiprazole was initiated. The Naranjo adverse drug reaction rating of 9 points indicates high probability of neuroleptic malignant syndrome from aripiprazole.[2] This patient had the following 5 risk factors for neuroleptic malignant syndrome: neuroleptic exposure, confusion, male gender, young age, and agitation.[4–6]

Dantrolene was started at 36 mg every 6 hours and bromocriptine at 2.5 mg every 8 hours. He initially experienced delirium; frequent crying spells, increased irritability, and agitation. He became aggressive, attempting to kick and bite the staff. He was switched to oral medications after a swallowing study observed no aspiration. His clinical status improved after 3 days, evidenced by decreased rigidity, improved alertness, and disappearance of clonus. He continued to be incontinent and needed assistance with ambulation for 5 days. He was discharged after 6 days in the hospital when all physical and laboratory findings return to baseline. He received physical and occupational therapy at home.

DISCUSSION

Second-generation antipsychotic use in children and adolescents is guided by case reports and small open-label studies.[7] Such off-label use has been described in mood disorder with and without psychotic features, tic disorder, disruptive behavior disorder, and pervasive developmental disorder.

Antipsychotic medications can cause serious adverse effects, including extrapyramidal signs (dystonia, akathisia, parkinsonian tremor, and tardive dyskinesia), cardiovascular problems (hypotension, tachycardia, and arrhythmias), anticholinergic effects (dry mouth, blurred vision, constipation, urinary retention, and cognitive blunting), elevation of serum prolactin levels (galactorrhea, amenorrhea, and gynecomastia), diabetes, diabetic ketoacidosis, lipid abnormalities, neutropenia, seizures, and neuroleptic malignant syndrome.[8]

Second-generation antipsychotics usually have a lower incidence of tardive dyskinesia and extrapyramidal adverse effects than older drugs. A double-blind random-assignment study of 1,714 adult patients showed a 0.52% long-term risk for tardive dyskinesia with olanzapine compared to 7.45% with haloperidol.[9] Another well-controlled study of 26- to 48-year-old patients showed a 1% risk of tardive dyskinesia with olanzapine (2.5–20 mg/d) and 4.6% risk with haloperidol (5–20 mg/d).[10]

Weight gain from second-generation antipsychotics may contribute to noncompliance and increase the risk of having metabolic syndrome. A recent meta-analysis estimated weight change after 10 weeks as 4.45 kg from clozapine, 4.15 kg from olanzapine, 2.10 kg from risperidone, and 0.04 kg from ziprasidone.[11] Metabolic disturbances associated with second-generation antipsychotics include hyperglycemia, hyperlipidemia, exacerbation of existing type 1 and 2 diabetes mellitus, new onset type 2 diabetes, and diabetic ketoacidosis, which is a life-threatening condition that requires immediate medical attention. Mortality rates for diabetic ketoacidosis and hyperosmolar nonketotic coma are approximately 9% to 14% and 10% to 50%, respectively.[12–14]

Diagnostic and statistical manual of mental disorders, fourth edition, text revision criteria for neuroleptic malignant syndrome include severe muscle rigidity and increased temperature. At least 2 of diaphoresis, dysphagia, tremor, incontinence, decreased level of consciousness, mutism, tachycardia, increased or labile blood pressure, leukocytosis, and laboratory evidence of muscle injury (eg, increased creatinine phosphokinase).

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Four cases of neuroleptic malignant syndrome from aripiprazole have been published, 3 in adults and 1 in a 17-year-old. The latter had 3 different antipsychotic medication trials in a 4- to 8-week period before 15 mg/d of aripiprazole medication and showing neuroleptic malignant syndrome.[15] Antipsychotic naive neuroleptic malignant syndrome occurred in a 23-year-old adult. However, this patient had methamphetamine dependence with possible methamphetamine-induced psychosis, being treated with 30 mg of aripiprazole. [16] A 43-year-old man with severe depression and psychosis was treated with 30 mg/d of aripiprazole and 20 mg/d of fluoxetine. This patient developed symptoms similar to neuroleptic malignant syndrome.[17] Another case report indicated a 42-year-old man with childhood onset schizophrenia who developed neuroleptic malignant syndrome 9 days after starting aripiprazole.[18]

There is also a case report of aripiprazole being used to treat agitation in neuroleptic malignant syndrome, resulting in a mild worsening of symptoms evidenced by an increase in tachycardia and brief worsening of serum creatinine kinase level.[19] The potential of any drug to induce neuroleptic malignant syndrome is related to the antidopaminergic activity of the drug in the central nervous system, mainly the striatum. Children and adolescents have more adverse effects with antipsychotics because of their sensitivity to dopamine-blocking medications.[20–22]

Neuroleptic malignant syndrome is a rare but potentially life threatening adverse effect, commonly associated with antipsychotics and characterized by rigidity, autonomic instability, altered mental status, obtundation, catatonia, tachycardia, dysphagia, mutism, tremors, and low-grade fevers.[23] Neuroleptic malignant syndrome can be distinguished from general medical conditions like infections by looking for recent neuroleptic exposure, extremely increased temperatures, and the presence of rigidity. Numerous neurological disorders (eg, heat stroke, Parkinson disease, subcortical brain lesions, systemic conditions like intermittent acute porphyria, and tetanus) and drug-induced movement disorders need to be excluded as causes. Catatonia and serotonin syndrome are important exclusionary differential diagnoses. Catatonia has a mortality rate as high as 31%.[24] Death from serotonin syndrome is rare, with only 23 deaths reported until 1999.[24–26]

Laboratory studies show increased creatinine phosphokinase and leukocytosis. Although increased creatinine phosphokinase has low specificity for neuroleptic malignant syndrome, it is present in 95% of reported cases. Other laboratory findings include metabolic acidosis, hypoxia, and electrolyte abnormalities. An electroencephalogram may show diffuse slowing.[23] Potential complications of neuroleptic malignant syndrome include aspiration pneumonia, cardiopulmonary arrest, myoglobinuric renal failure, and disseminated intravascular coagulation.

Neuroleptic malignant syndrome has been reported with the second-generation antipsychotics risperidone, olanzapine, and aripiprazole; 66% of cases occur during the first 2 weeks of therapy, and 96% occur within the first 30 days.[27] The mean recovery time is 7 to 10 days, and low estimates of mortality are 10%, and high estimates being at 20%.

Treatment of neuroleptic malignant syndrome should be initiated as soon as possible. Specific treatment includes stopping the offending medication and supportive antipyretics, for example, dantrolene and a cooling blanket. It is also important to use intravenous fluids to correct dehydration and electrolyte abnormalities. Dopamine agonists such as bromocriptine or amantadine can help. Most patients recover from neuroleptic malignant syndrome in 2 to 14 days without cognitive impairment. Persistent dysfunction is usually attributable to very high fever, hypoxia, or other complications.[28]

CONCLUSIONS

From a clinical perspective, the change of behavior in our patient was possibly related to breathing discomfort and was not

an indication for an atypical antipsychotic medication. The use of aripiprazole in the treatment of pervasive developmental disorder must be considered an off-label one. Clinical trials are necessary to evaluate its effectiveness for precisely defined target symptoms.

Although unusual, this case highlights the dangers of prescribing antipsychotic medications to pediatric patients. There is a dearth of adverse effect information related to aripiprazole use in the child and adolescent population. The lack of adolescent or child reports might correspond to deficient physician reporting using the United States of America Food and Drug Administration's Adverse Event Reporting System.[29] Such reporting is not mandatory in the United States. Only 10% of serious adverse events are reported.[30] It is noteworthy to point out that the reporting system is very difficult to maneuver through. It is the authors' opinion that more research and effort is needed to create a much more user-friendly system for physicians so they will be able to properly use this very important resource.

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