# Prolonged toxicity in a 2-year-old after accidental ingestion of aripiprazole.

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# Prolonged Toxicity in a 2-Year-Old After Accidental Ingestion of Aripiprazole

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**Abstract:** Aripiprazole (Abilify), or 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butyloxy}-3,4-dihydro-2(1H)-quinolone, is a novel atypical antipsychotic possessing a long half-life. Although not a Food and Drug Administration–approved indication, low-dose aripiprazole is used to treat pediatric psychiatric conditions. Data regarding toxicity of low-dose aripiprazole ingestions in children are limited. We report the case of an accidental ingestion of two 5-mg aripiprazole tablets by a 2-year-old girl with a measured drug level of 160 ng/mL approximately 34 hours after ingestion. She exhibited marked lethargy, tremor, and tachycardia persisting over 72 hours. Emergency physicians, pediatricians, and psychiatrists should be aware of the potential for significant and prolonged toxicity in children even with relatively small-dose aripiprazole exposures.

**Key Words:** aripiprazole, toxicity

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Aripiprazole is a relatively new psychotropic agent approved by the Food and Drug Administration (FDA) for the treatment of schizophrenia in adults and, most recently, in adolescents ages 13 to 17 years with a recommended daily dose of 10 to 30 mg.[1] Recognized advantages of this atypical antipsychotic include a lower propensity for extrapyramidal symptoms, weight gain, cardiovascular abnormalities, hyperprolactinemia, hypercholesterolemia, and glucose dysregulation.[2] The most common adverse effects reported include headache, insomnia, nausea, vomiting, somnolence, and dizziness.[1] Aripiprazole has been used off-label to treat pediatric attention-deficit/hyperactivity disorder, as well as both oppositional defiant and conduct disorder.

There is a paucity of data regarding aripiprazole toxicity in children, with most case reports describing large-quantity ingestions. The most commonly described signs and symptoms of toxicity include somnolence, nausea, vomiting, ataxia, and tremulousness. There is a single report of facial muscle weakness.[3]

We describe the case of a 2-year-old girl who accidentally ingested 10 mg of aripiprazole resulting in prolonged lethargy and tremor.

## CASE

A 2-year-old previously healthy, 10.9-kg girl prescribed no medications presented to a pediatric tertiary care emergency department (ED) approximately 36 hours after ingesting two 5-mg tablets (0.92 mg/kg) of a sibling's aripiprazole as confirmed by pill count. The parents reported that the patient had been lethargic and difficult to arouse the day of ingestion, prompting them to visit a local ED. After unremarkable basic diagnostic examination, including urine emit toxicology screen, she was discharged home. Her lethargy persisted, however, and the parents reported she slept most of the day and was tremulous with irritability and persistent crying. She also exhibited an ataxic gait and difficulty maintaining head posture.

The parents brought the patient to a tertiary care pediatric ED 36 hours after ingestion, where she was sleepy with intermittent crying. Vital signs included temperature of 37.5°F; heart rate, 160 beats/min; respirations, 36 rpm; blood pressure, 102/68 mmHg; and room air $Sa_{O_2}$ 98%. Physical examination revealed: a blank stare, generalized lethargy and an intention tremor. Diagnostic testing including complete blood count, electrolytes panel, electrocardiogram (ECG), noncontrast brain computed tomogram, and lumbar puncture were unremarkable. A comprehensive urine drug screen (gas chromatography/mass spectroscopy) revealed only small amounts of nicotine, lidocaine, and caffeine. The patient was admitted to a monitored setting. Lethargy, tachycardia, and irritability persisted until the third hospital day. She was discharged on hospital day 4 after returning to a normal level of activity. Telephone follow-up with the patient's mother on the day after discharge revealed that the patient was still experiencing some intermittent tremor and irritability.

An aripiprazole level obtained at an estimated 34 hours after ingestion measured160 ng/mL (adult reference: 70–126 ng/mL for 5 mg daily, 109–216 for 10 mg daily, 206–278 for 15 mg daily, 212–574 for 20 mg daily, and 320–585 for 30 mg daily). The laboratory was unable to perform concentration measurement of the active metabolite, dehydroaripiprazole.

## DISCUSSION

Aripiprazole was approved by the FDA for use in adults for the treatment of both acute and chronic schizophrenia in 2002 and, in 2007, for the treatment of adolescent schizophrenia.[4] The drug has an affinity for brain dopaminergic, serotonergic, histaminergic, and α-adrenergic receptors.[5] In basal dopamine excess, aripiprazole acts as an agonist at the presynaptic $D_2$ autoreceptor to decrease dopamine synthesis and release. In addition, it acts as a competitive antagonist at the postsynaptic $D_2$ receptor to blunt the effects of excess dopamine in the synapse. However, aripiprazole also possesses agonist activity and maintains $D_2$ receptor activation, avoiding the movement disorders associated with nonspecific dopamine blockade.[6,7]

Aripiprazole is well absorbed orally, with peak plasma concentrations achieved in 3 to 5 hours. Liver metabolism via CYP3A4 and CYP2D6 generates an active metabolite, dehydroaripiprazole. The mean half-life of the parent compound and the active metabolite are 74 and 94 hours, respectively. In patients with slow CYP2D6 metabolism, the drug's half-life can increase to as long as 146 hours.[1]

Aripiprazole has been prescribed to children, although guidelines for dosages have not been established. In a 2-week

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study of 12 children (aged 6–12 years) and 11 adolescents (aged 13–17 years) diagnosed with conduct disorder or oppositional defiant disorder, a dosing schedule of 2 mg for body weight of less than 25 kg, 5 mg for 25 to 50 kg, 10 mg for 50 to 70 kg, and 15 mg for body weight of more than 70 kg was well tolerated. No serious adverse events, ECG changes, laboratory value, or vital sign abnormalities were evident. The most common adverse events were vomiting and somnolence.[8] A case series of 5 pediatric patients reported a 2-year-old girl who ingested 40 mg of aripiprazole and was brought to the ED 12 hours after ingestion, with vomiting and lethargy but normal vital signs and ECG. Her symptoms resolved 30 hours after ingestion. The remaining 4 patients were aged between 6 and 16 years. Two ingested large amounts of aripiprazole (120 and 300 mg), one ingested an unknown number of 20-mg tablets, and one ingested the first dose of his prescribed 10-mg dose. All were monitored in an ED for mild symptoms and then discharged without sequelae.[3] A 9-year-old girl was lethargic with tremor approximately 3.5 hours after her first prescribed 15-mg aripiprazole dose. She was somnolent but discharged without residual symptoms 48 hours after ingestion.[9] A10-year-old bipolar patient developed torticollis after the third day of treatment with 10 mg of aripiprazole daily, which resolved with discontinuation of the drug and benztropine therapy.[10]

There are reports of aripiprazole toxicity in children in which serum levels have been obtained. A 2.5-year-old girl ingested thirteen 15-mg tablets (17.1 mg/kg) and became lethargic with normal vital signs and ECG. She awoke over the next 24 hours but remained somnolent and ataxic for another 48 hours. She was discharged with a resolving hand tremor on day 4 after ingestion. Her serum aripiprazole concentration was measured at 1420 ng/mL 10 hours after ingestion and 342 ng/mL at 57.25 hours after ingestion.[11] A 3-year-old boy demonstrated extreme lethargy, flat affect, intention tremor, truncal ataxia, and a parkinsonian gait 48 hours after a suspected ingestion of one half of a 15-mg aripiprazole tablet. A serum aripiprazole concentration collected 87 hours after ingestion was 63 ng/mL, and the patient improved over 7 days.[12]

Our case report is unique in the marked and prolonged lethargy and tremor found in a child after ingestion of a small dose of aripiprazole confirmed with a serum level. Interestingly, her level of 160 ng/mL falls within the range of normal steady-state plasma level for a 10-mg daily dose of aripiprazole. Although aripiprazole may be detected via urine comprehensive drug screening (gas chromatography/mass spectroscopy), testing is not routinely performed because of the complexity of the assay.[13] Serum levels are therefore usually required to confirm and quantify ingestion.

The reason for the profound effects of aripiprazole in these cases is not understood. Aripiprazole's pharmacokinetics in children is poorly defined, making it possible that the drug has amplified effects in young children, although the reports on children of similar age and larger ingestions with symptoms of much shorter duration would argue against this. Differences in CYP2D6 metabolism could lend a suitable explanation, especially given the known differences in drug half-life between slow and fast CYP2D6 metabolizers. Our patient's CYP2D6 metabolism status is unknown. Determination of CYP2D6 metabolism status before therapeutic aripiprazole administration may aid in predicting response and is now possible using FDA-approved genotype testing.[14]

## CONCLUSIONS

Literature describing aripiprazole toxicity in children with level confirmation is scant. Prolonged neurological manifestations may result from relatively small ingestions necessitating continued monitoring despite previous reports of benign courses in a case series of pediatric exposures. Emergency physicians, pediatricians, and psychiatrists should be aware of the drug's potential toxicity. More literature regarding aripiprazole complete with serum drug levels, and possibly CYP2D6 metabolism status via pharmacogenetic testing, would be greatly beneficial in elucidating the nature of the drug's toxicity.

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