Case Reports of Aripiprazole Causing False-Positive Urine Amphetamine Drug Screens in Children

Justin Kaplan, PharmD[a,b], Pooja Shah, PharmD[a,b], Brian Faley, PharmD[a,b], Mark E. Siegel, MD[c]

Urine drug screens (UDSs) are used to identify the presence of certain medications. One limitation of UDSs is the potential for false-positive results caused by cross-reactivity with other substances. Amphetamines have an extensive list of cross-reacting medications. The literature contains reports of false-positive amphetamine UDSs with multiple antidepressants and antipsychotics. We present 2 cases of presumed false-positive UDSs for amphetamines after ingestion of aripiprazole. Case 1 was a 16-month-old girl who accidently ingested 15 to 45 mg of aripiprazole. She was lethargic and ataxic at home with 1 episode of vomiting containing no identifiable tablets. She remained sluggish with periods of irritability and was admitted for observation. UDS on 2 consecutive days came back positive for amphetamines. Case 2 was of a 20-month-old girl who was brought into the hospital after accidental ingestion of an unknown quantity of her father's medications which included aripiprazole. UDS on the first day of admission came back positive only for amphetamines. Confirmatory testing with gas chromatography–mass spectrometry (GC-MS) on the blood and urine samples were also performed for both patients on presentation to detect amphetamines and were subsequently negative. Both patients returned to baseline and were discharged from the hospital. To our knowledge, these cases represent the first reports of false-positive amphetamine urine drug tests with aripiprazole. In both cases, aripiprazole was the drug with the highest likelihood of causing the positive amphetamine screen. The implications of these false-positives include the possibility of unnecessary treatment and monitoring of patients.

Urine drug screens (UDSs) are commonly ordered in the emergency department (ED) in evaluation of patients with suspected or confirmed drug ingestion. They are useful in detection of parent compounds or their metabolites after intentional or accidental ingestion of a substance. The most common types of UDSs use qualitative immunoassay techniques to detect substances at concentrations above a certain threshold.[1] UDSs are widely used because they are inexpensive, sensitive, easy to perform, and provide results quickly.[2] The major drawback of UDSs, compared with the quantitative gold-standard gas chromatography–mass spectrometry (GC-MS), is that they lack specificity, which results in a high rate of false-positive results.[1,2] In particular, amphetamine testing is most commonly implicated in false-positives with >30 substances identified to have cross-reactivity.[1,3] A majority of these false-positive results stem from compounds that are structurally similar. More reliable testing methods such as GC-MS are used to rule out false-positive UDS results.[2]

Aripiprazole is an atypical antipsychotic indicated for multiple

[a]Department of Pharmacy, Hackensack University Medical Center, Hackensack, New Jersey, and [b]Ernest Mario School of Pharmacy, Rutgers University, New Brunswick, New Jersey; [c]Department of Pediatrics, Hackensack University Medical Center, Hackensack, New Jersey

Dr Kaplan interviewed the patient and families, performed data collection, performed a literature search, and drafted the initial manuscript; Dr Shah acquired the patient information, carried out initial analysis, and reviewed and revised the manuscript for intellectual content; Drs Faley and Siegel coordinated and supervised obtaining of the data, interpretation of the results, and management of the patients and critically reviewed and revised the manuscript for intellectual content; and all authors approved the final manuscript as submitted.

www.pediatrics.org/cgi/doi/10.1542/peds.2014-3333

DOI: 10.1542/peds.2014-3333

Accepted for publication Aug 24, 2015

Address correspondence to Pooja Shah, PharmD, Department of Pharmacy, Hackensack University Medical Center, 30 Prospect Ave, Hackensack, NJ, 07601. E-mail: poojashah@hackensackumc.org

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2015 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

Downloaded from www.aappublications.org/news by guest on October 14, 2019

psychiatric disorders.[4,5] In addition to 5-HT_{2A} antagonism, it has unique activity as a partial dopamine agonist that may represent a therapeutic advantage compared with other second-generation antipsychotics.[5] Aripiprazole's tolerability and favorable side effect profile make it a popular therapeutic option.[5,7]

To our knowledge, there are no published reports about aripiprazole causing false-positive amphetamine toxicology screens. However, other psychotropic drugs have been implicated, including tricyclic antidepressants,[1,2] trazodone,[1–3,8,9] and bupropion.[1–3,10,11] We report 2 pediatric patients who had false-positive UDSs after accidental ingestion of aripiprazole.

CASE SERIES

Case 1

A 2-year-old girl with no significant medical history was brought to the pediatric ED by her parents after suspected ingestion of her father's aripiprazole. She was found holding an open bottle of aripiprazole 15-mg tablets. According to the parents, there were initially 5 tablets in the container, and only 2 tablets were found after the patient was discovered holding it. The patient was lethargic and ataxic at home and experienced 1 episode of vomiting. No tablets were identified in the patient's emesis.

On admission to the ED, the patient was hypothermic with a temperature of 95.6°F. All other vital signs and laboratories were within normal limits at this time. As part of our hospital's policy for treatment of all potential ingestions, blood acetaminophen and salicylate levels were obtained and were undetectable. A urine sample for a UDS was unable to be obtained until the early morning because the patient arrived at midnight and slept throughout the night. On physical examination, the patient was noted to be sleepy but arousable with intermittent periods of agitation. The local Poison Control Center was contacted and recommended supportive care for potential aripiprazole ingestion, and the patient was admitted to the PICU for further monitoring. She received only normal saline and Lactated Ringer's infusions while in the hospital.

A urine drug screen was performed on the morning after admission and revealed an amphetamine concentration of 1048 ng/mL. The assay used at our hospital has a threshold for detection of 300 ng/mL. After the first positive UDS, Child Social Services was contacted to investigate family dynamics and child safety. Repeat urine testing the following day again tested positive for amphetamines with a slightly lower concentration of 949 ng/mL. Blood samples from the time of admission and urine samples from the day after admission were sent to an outside laboratory for quantitative amphetamine confirmatory testing. Both confirmatory tests were negative for amphetamine, suggesting that the in-house UDS represented false-positive results. The child's lethargy resolved with time, and there were no further medical issues. She was discharged from the hospital with her parents 2 days after admission.

Case 2

A 20-month-old girl with no significant medical history presented to the pediatric ED for possible accidental ingestion after being found in her crib holding her father's weekly pill organizer. The pill box was open with medications scattered throughout the crib. According to the father, a 1-week supply of his medications included the following cumulative drugs and dosages: alprazolam 2.5 mg, fluvoxamine 2100 mg, clonazepam 17.5 mg, buspirone 420 mg, and aripiprazole 35 mg. The father reported noncompliance with his medications and therefore could not definitively state how much of each medication was in the pill organizer at the time.

On presentation to the ED, the parents reported that their daughter was more sluggish than usual. She was unable to stand or ambulate without falling. All vital signs were within normal limits. Acetaminophen and salicylate assays were negative. The initial UDS from admission tested positive only for amphetamines at 311 ng/mL. A repeat UDS 5 hours after admission was negative. The local poison control center was contacted, and the patient was admitted to the PICU for close monitoring. In response to the positive urine amphetamine findings, local police questioned the father and detained him overnight.

Similar to the previous case, the initial urine specimen and blood samples, drawn 6 hours after arrival to the ED, were sent to an outside laboratory for confirmatory amphetamine testing. All confirmatory laboratory work was negative suggesting a false-positive amphetamine toxicology screen.

The patient was monitored in the PICU for 1 day and returned to her baseline mental status and functionality the day after admission. However, the patient remained in the hospital for a total of 4 days pending the clearance of a social hold imposed by Child Social Services.

DISCUSSION

To our knowledge, this case series is the first to document potential false-positive UDSs after accidental ingestion of aripiprazole. Case 1 represents a more compelling argument because aripiprazole was the only known drug ingested before the urine toxicology screen. In both cases, the presentation of drowsiness, lethargy, and ataxia were more consistent with ingestion of an atypical antipsychotic than with amphetamines. Neither patient

Downloaded from www.aappublications.org/news by guest on October 14, 2019

experienced any of the classic sympathomimetic symptoms of amphetamine toxicity (eg, hyperthermia, hypertension, tachypnea, hyperreflexia, tremor, or mydriasis).[12] A study by Matteucci et al reviewed 47 cases reported to the California Poison Control System of children <6 years of age with accidental methamphetamine poisoning.[13] On the basis of their results, 82% of children with methamphetamine exposure presented with agitation, making it even less likely that the 2 children in our case series ingested amphetamines.[13]

Case 2 presents a muddier picture because of the possibility of a mixed ingestion. Alprazolam and clonazepam have never been documented to cause false-positive amphetamine UDSs. Furthermore, the urine benzodiazepine assay was negative. The remaining potential cross-reacting agents were fluvoxamine, buspirone, and aripiprazole, none of which have been implicated in false-positive amphetamine results in the literature. It is not possible to determine definitively which drug was responsible for the false-positive result in this case, but we suspect aripiprazole given our experience with the patient from Case 1 from just a few weeks earlier.

There are several limitations to UDS immunoassays. Most important, poor specificity is associated with a risk of false-positive testing.[2] A negative result does not exclude the possibility that the substance is present if it is below the lower threshold of detection. Additionally, there is no way to quantitatively correlate a positive result with the extent of exposure. Therefore, immunoassays are the first step in a 2-step system, in which all positive results must be confirmed by more reliable methods such as GC-MS.[2] In our case series, the confirmatory samples sent to outside laboratories were negative, indicating that these were most likely false-positive amphetamine screens.

Confirmatory testing should take into account other substances that are known to cause false- positive tests. For example, in our cases, we not only tested for amphetamines but also pseudoephedrine, ephedrine, and ecstasy. All of these drugs have structures or metabolites similar to that of methamphetamine. Although this is not an inclusive list, testing for all known substances would not be practical in the clinical setting. Because both patients reported here are children, the likelihood that they ingested other medications than what was reported is unlikely. In addition, on review of the list of medications that each child had access to, none have been known to cross-react with amphetamine assays. Because the only common substance ingested was aripiprazole, it heightened our suspicion that aripiprazole may be responsible for the false- positive results.

Aripiprazole levels were not drawn to confirm our suspicion that the false-positive amphetamine results were secondary to aripiprazole ingestion. This was mainly due to the results not affecting the clinical care of the patient and the lack of immediate availability of the results. This may be an area of future interest so that the threshold for a false-positive amphetamine test can be defined.

Another confounder in our cases is that we use enzyme multiplied immunoassay technique as our initial immunoassay for UDS. Because these are the first 2 cases of false-positive amphetamine testing due to aripiprazole that we are aware of, the cross-reaction may be specific to our reagents and testing method and not ubiquitous throughout all assay methods.

As with other reports of pediatric accidental ingestions, our information is limited to the history provided by the patients' families. It is not possible to know what drugs were truly in the pill bottle or pill organizer. There is always a possibility that the families provided us with misinformation. However, we have no reason to suspect that in either case. In both cases, the pediatricians educated the families on keeping curious children safe from dangerous medications. Furthermore, despite initial involvement of social services and law enforcement, both families were ultimately cleared of any offenses.

Positive UDSs can have serious social and legal implications. In particular, screens that are falsely positive for drugs of abuse can lead to consequences with social services and law enforcement. In the worst-case scenario, parents may serve jail time or lose custody of their children for child endangerment. Despite the outcome of the investigations, false-positive assays may lead to prolonged hospital stays and increased costs pending the release of social holds.

The manufacturer of aripiprazole was notified of the potential false-positive urine screens. They were unaware of any other cases of false-positive urine amphetamine assays after ingestion of aripiprazole. In addition, it is unclear whether aripiprazole could cause false-positive UDS in adults. Aripiprazole pharmacokinetics may behave differently in adult patients with respect to absorption, distribution, metabolism, and excretion.[6] It is possible that our case series represents a toxicokinetic phenomenon only experienced by pediatric patients. Nevertheless, UDSs are commonly used by employers, and employment is contingent on passing a toxicology screen. False-positive screens for amphetamines could create a barrier to new employment or a risk to continued employment or threaten professional licensure for individuals on aripiprazole; furthermore, in the case of accidental ingestion by toddlers,

Downloaded from www.aappublications.org/news by guest on October 14, 2019

these consequences could affect adult caregivers.

In summary, we suspect that accidental ingestion of aripiprazole was associated with false-positive amphetamine UDSs in 2 children that presented to our pediatric ED. Clinicians need to be aware of the potential for false-positive UDSs secondary to aripiprazole ingestion. Clinicians should always assess the complete clinical picture and order confirmatory quantitative testing to verify any preliminary positive urine toxicology results.

ABBREVIATIONS

ED: emergency department
UDSs: urine drug screens

REFERENCES

1. Moeller KE, Lee KC, Kissack JC. Urine drug screening: practical guide for clinicians. *Mayo Clin Proc*. 2008;83(1):66–76
2. Markway EC, Baker SN. A review of the methods, interpretation, and limitations of the urine drug screen. *Orthopedics*. 2011;34(11):877–881
3. Brahm NC, Yeager LL, Fox MD, Farmer KC, Palmer TA. Commonly prescribed medications and potential false-positive urine drug screens. *Am J Health Syst Pharm*. 2010;67(16):1344–1350
4. Yatham LN. A clinical review of aripiprazole in bipolar depression and maintenance therapy of bipolar disorder. *J Affect Disord*. 2011;128(suppl 1):S21–S28
5. Ching H, Pringsheim T. Aripiprazole for autism spectrum disorders (ASD). *Cochrane Database Syst Rev*. 2012;5:CD009043
6. DeLeon A, Patel NC, Crismon ML. Aripiprazole: a comprehensive review of its pharmacology, clinical efficacy, and tolerability. *Clin Ther*. 2004;26(5):649–666
7. Marder SR, McQuade RD, Stock E, et al. Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term, placebo-controlled trials. *Schizophr Res*. 2003;61(2–3):123–136
8. Baron JM, Griggs DA, Nixon AL, Long WH, Flood JG. The trazodone metabolite meta-chlorophenylpiperazine can cause false-positive urine amphetamine immunoassay results. *J Anal Toxicol*. 2011;35(6):364–368
9. Roberge RJ, Luellen JR, Reed S. False-positive amphetamine screen following a trazodone overdose. *J Toxicol Clin Toxicol*. 2001;39(2):181–182
10. Casey ER, Scott MG, Tang S, Mullins ME. Frequency of false positive amphetamine screens due to bupropion using the Syva EMIT II immunoassay. *J Med Toxicol*. 2011;7(2):105–108
11. Weintraub D, Linder MW. Amphetamine positive toxicology screen secondary to bupropion. *Depress Anxiety*. 2000;12(1):53–54
12. Greene SL, Kerr F, Braitberg G. Review article: amphetamines and related drugs of abuse. *Emerg Med Australas*. 2008;20(5):391–402
13. Matteucci MJ, Auten JD, Crowley B, et al. Methamphetamine exposures in young children. *Pediatr Emerg Care*. 2007;23:638–640

Downloaded from www.aappublications.org/news by guest on October 14, 2019

Case Reports of Aripiprazole Causing False-Positive Urine Amphetamine Drug Screens in Children

Justin Kaplan, Pooja Shah, Brian Faley and Mark E. Siegel

Pediatrics 2015;136;e1625
DOI: 10.1542/peds.2014-3333 originally published online November 2, 2015;

Updated Information & Services	including high resolution figures, can be found at: http://pediatrics.aappublications.org/content/136/6/e1625
References	This article cites 12 articles, 1 of which you can access for free at: http://pediatrics.aappublications.org/content/136/6/e1625#BIBL
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): **Pharmacology** http://www.aappublications.org/cgi/collection/pharmacology_sub **Toxicology** http://www.aappublications.org/cgi/collection/toxicology_sub **Public Health** http://www.aappublications.org/cgi/collection/public_health_sub
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.aappublications.org/site/misc/Permissions.xhtml
Reprints	Information about ordering reprints can be found online: http://www.aappublications.org/site/misc/reprints.xhtml

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

Downloaded from www.aappublications.org/news by guest on October 14, 2019

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Case Reports of Aripiprazole Causing False-Positive Urine Amphetamine Drug Screens in Children

Justin Kaplan, Pooja Shah, Brian Faley and Mark E. Siegel

Pediatrics 2015;136;e1625
DOI: 10.1542/peds.2014-3333 originally published online November 2, 2015;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/136/6/e1625

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2015 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

Downloaded from www.aappublications.org/news by guest on October 14, 2019