



## A case series involving young children presenting with accidental ingestion of amphetamine based stimulants

Kelly E. Wood<sup>a,\*</sup>, Patrick J. McCarthy<sup>a,1</sup>, Matthew D. Krasowski<sup>b</sup>

<sup>a</sup> Stead Family Department of Pediatrics, University of Iowa Stead Family Children's Hospital, Iowa City, IA, 52242, USA

<sup>b</sup> Department of Pathology, University of Iowa Hospitals and Clinics, Iowa City, IA, 52242, USA

### 1. Introduction

Attention deficit hyperactivity disorder (ADHD) has an estimated prevalence in the United States (U.S) of 4–9% in children and 4% in adults [1]. The first reported cases of adults with ADHD date back to the 1970s [2]. Adult ADHD was formally recognized as a diagnosis in 2013, with revised diagnostic criteria allowing for later age of symptom onset (12 versus 7 years) [3]. Recent evidence suggests that adult onset ADHD and childhood onset ADHD are separate entities rather than a continuum [3,4].

ADHD diagnosis in the U.S. is increasing [5]. The U.S. Food and Drug Administration (FDA) approved stimulants medications to treat adult ADHD in 2004 [6]. A study of commercially insured adults and children found that stimulant prescribing increased in all age groups from 2010 to 2014 but the greatest increase was seen in adults [6]. A similar study reported that stimulants were prescribed in over 70% of office visits for ADHD regardless of age [6]. Overall outpatient prescriptions for amphetamine mixed salts in the U.S. exceeded 4.5 million in 2009 and were approximately 3.0 million in 2014 [7]. Total outpatient prescriptions for lisdexamfetamine (LDX), a pro-drug of amphetamine, exceeded 7.5 million in the U.S. by 2014 [7].

With the rise in the prescribing of stimulants for ADHD, more infants and children may be exposed to environments where amphetamines are present. As such, medical providers must have a high suspicion for amphetamine ingestion for children who present with supportive symptoms without another clear cause. We describe a case series of 5 children under the age of 2 presenting with sympathomimetic toxicity due to confirmed amphetamine ingestion, presumably of amphetamine based stimulants prescribed to a household member for ADHD.

### 2. Materials and methods

We describe five pediatric patients admitted to the University of Iowa Stead Family Children's Hospital with a urine or hair specimen that confirmed positive for amphetamine over a 20-month period (August 2015–March 2017). “Case 3” was previously published as a case report [8]. (Cases 1–5)

We also present the results from a retrospective study of cases that had urine drug testing that was screen positive for amphetamines but without confirmatory testing over a 13-year period (2004–2017). This analysis identified two additional cases where amphetamine ingestion was strongly suspected, although confirmatory toxicology analysis was not performed. (Cases 6–7)

Infants under 1 week of age were excluded. Cases with confirmed methamphetamine exposure or involving children on known prescription mixed amphetamine salts or LDX were also excluded.

Urine drug screening samples were processed using Amphetamines II Assay (positive cutoff 1000 ng/mL) run on cobas c502 analyzer (Roche Diagnostics Indianapolis, IN, USA). Confirmatory urine testing for amphetamines was referred to ARUP Laboratories (Salt Lake City, UT, USA) for a panel that can specifically quantitate amphetamine, methamphetamine, and several amphetamine derivatives by high-performance liquid chromatography coupled to tandem mass spectrometry (HPLC/MS/MS). The limit of quantitation for the analytes for amphetamines confirmation was 200 ng/mL. The screening and confirmatory testing in urine does not distinguish between amphetamine arising from amphetamine mixed salts or LDX pharmaceutical products.

Hair toxicology samples were analyzed by United States Drug Testing Laboratory (Des Plaines, Illinois, USA) using the Childguard<sup>®</sup>

**Abbreviations:** ADHD, attention deficit hyperactivity disorder; AG, anion gap; BMP, basic metabolic panel; BPM, beats per minute; C, Celsius; CBC, complete blood count; CK, creatinine kinase; *d*-amphetamine, dextroamphetamine; DSM-V, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ED, emergency department; EKG, electrocardiogram; ELISA, enzyme-linked immunosorbent assay; FDA, Food and Drug Administration; GC/MS, gas chromatography/mass spectrometry; HPLC/MS/MS, high performance liquid chromatography/tandem mass spectrometry; LC/MS/MS, liquid chromatography/tandem mass spectrometry; LDX, lisdexamfetamine dimesylate; MDA, methylenedioxymphetamine; MDEA, methylenedioxymethylamphetamine; MDMA, methylenedioxymethylamphetamine; mEq/L, milliequivalents per liter; mg, milligram; N/A, not applicable; ng/mL, nanogram per milliliter; pg/mg, picogram per milligram; QNS, quantity not sufficient; 5-HT, serotonin; THC, tetrahydrocannabinol; UA, urinalysis; UDS, urine drug screen; U.S., United States

\* Corresponding author at: University of Iowa Stead Family Children's Hospital, Stead Family Department of Pediatrics, 200 Hawkins Dr, Iowa City, IA, 52242, USA.  
E-mail address: [Kelly-wood@uiowa.edu](mailto:Kelly-wood@uiowa.edu) (K.E. Wood).

<sup>1</sup> Present address: Department of Pediatrics, Children's Hospital of Wisconsin, Milwaukee, WI, 53226, USA.

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test for amphetamines (including amphetamine and methamphetamine), cocaine, opiates, phencyclidine, and tetrahydrocannabinol (THC) [9]. Collection of hair specimens followed chain of custody procedure with documentation of specimen matrix and location, indication for testing, test panel, and patient identification. The reference laboratory only tests the 3.81 cm (1.5 in.) of hair closest to the scalp (root end). Collection methods follow those recommended by reference laboratory. Briefly, hair is inspected to be sure it is not chemically treated or synthetic (either of which would be uncommon in young children). The collection goal is at least 100 mg of scalp hair. Prior to each collection, scissors, clip, and comb are wiped with non-ethanol alcohol pad. For hair longer than 3.81 cm, a section of hair is isolated and secured with a hair clip. Using a rat-tail comb, a section of hair is clipped with cutting shears at scalp level. For patients with thin hair, multiple sites may be used. A printed ruler helps assure adequate collection. For hair shorter than 3.81 cm, smaller amounts of hair are collected from multiple sites around the head.

The protocol for hair analysis can determine both systemic and second-hand (environmental) exposure to drugs. Initial screening utilized enzyme-linked immunoassay (ELISA) analysis of unwashed hair. The screening cutoffs for ELISA was 500 pg/mg for amphetamines and cocaine metabolites, 200 pg/mg for opiates, 300 pg/mg for phencyclidine, and 1 pg/mg for THC and metabolite. Confirmation of hair samples was performed by HPLC/MS/MS or GC/MS. Only drugs or metabolites confirmed by these mass spectrometry-based methods were reported. Amphetamines confirmation in hair utilized HPLC/MS/MS with a lower limit of quantitation of 100 pg/mg for each of the analytes. Similar to the urine toxicology analysis, the screening and confirmatory testing in hair does not distinguish between amphetamine arising from amphetamine mixed salts or LDX pharmaceutical products

This study was reviewed and approved by the institutional review board (study #201612807).

### 3. Results

#### 3.1. Cases with confirmed toxicology testing

##### 3.1.1. Case 1

A previously healthy 10-month-old boy was brought to an outside emergency department (ED) by his parents due to 12 h of marked fussiness and inconsolability. He had an anion gap metabolic acidosis (anion gap [AG] 21 mEq/L); otherwise, laboratory testing was with normal ranges, including the remainder of his basic metabolic panel (BMP), transaminases, complete blood count (CBC), and urinalysis (UA). A urine drug screen (UDS) was obtained. After evaluation, he was given a suppository for presumed constipation and then discharged. After discharge, the UDS returned presumptive positive for amphetamines. The family was contacted, and he was transferred to our institution. Upon admission (approximately 24 h after symptom onset), he was tachycardic (148 beats per minute [bpm]) and hypertensive (110/76 mm Hg) but his irritability had improved. His temperature was 37.1 °Celsius (°C). Physical examination was otherwise normal.

A UDS was presumptively positive at our institution for amphetamines. Confirmatory urine testing was positive for amphetamines with amphetamine concentration of 25,533 ng/mL. (see Table 1) Urine drug screen from the outside ED was negative for benzodiazepines, cocaine, opiates, methamphetamine, propoxyphene, THC, and tricyclic antidepressants. UDS at our institution was negative for benzodiazepines, cocaine, opiates, oxycodone and THC. Repeat laboratory studies, including creatine kinase (CK), were normal. A child abuse evaluation was conducted, including skeletal survey, which was negative. Hair toxicology testing was sent, and was positive for amphetamines. (see Table 1) Telemetry showed multiple premature ventricular contractions, but electrocardiogram (EKG) was normal.

There was no history of observed ingestion. Developmental history was normal. He was able to crawl and cruise. The patient had an older

**Table 1** Demographic information, creatinine kinase levels and quantitative amphetamine assay results for five cases of confirmed amphetamine ingestion and two cases of suspected ingestion.

Case	Age	Sex	Creatine kinase (39-308 units/L)*	Urine amphetamine (ng/mL)**	Hair amphetamine (pg/mg) †	Suspected drug
Case 1	10 months	M	175	25,533	3,777	Lisdexamfetamine
Case 2	11 months	F	637	45,751	844	Lisdexamfetamine
Case 3	10 months	F	N/A	22,312	Presumptive positive for amphetamines by ELISA ††, QNS‡ for confirmatory testing	Lisdexamfetamine
Case 4	26 months	M	1122	2,067	N/A§	Lisdexamfetamine
Case 5	15 months	M	121	19,618	Negative	Amphetamine-dextroamphetamine
Case 6	15 months	M	N/A§	Presumptive positive (> 1,000 ng/mL); confirmatory testing not performed	N/A§	Amphetamine-dextroamphetamine
Case 7	7 years	M	N/A§	Presumptive positive (> 1,000 ng/mL); confirmatory testing not performed	N/A§	Amphetamine-dextroamphetamine

\* units per liter reported as peak levels, \*\*nanogram per milliliter, † picogram per milligram, †† enzyme linked immunoassay, ‡quantity not sufficient, § not applicable. Urine amphetamine confirmatory testing was performed by liquid chromatography/tandem mass spectrometry (LC/MS/MS) with a lower limit of quantitation of 200 ng/mL for the amphetamine drugs. Concentrations below 200 ng/mL are not reported. Hair amphetamine testing utilized ELISA for screen and then quantitation by LC/MS/MS for specific amphetamines. The confirmatory testing has lower limit of quantitation of 500 pg/mg. Concentrations below 500 pg/mg are not reported.

sibling with ADHD and developmental delay, who was prescribed amphetamine-dextroamphetamine and LDX. The patient was discharged following symptom resolution on hospital day 2, with no pharmacologic treatment required during hospitalization.

### 3.1.2. Case 2

An 11-month-old previously healthy boy was brought to an urgent care clinic with an abrupt onset (3 h) of agitation, continual movements, and self-injurious biting of his hands. He was transferred to our hospital inpatient unit. Upon arrival, he was tachycardic (172 bpm) and inconsolable. His temperature was 35.6 °C. A blood pressure measurement was unable to be obtained due to lack of cooperation. His face was flushed and he had open bite wounds on his hands. He continued to bite his hands and was noted to have continual non-rhythmic shaking of his extremities.

Laboratory evaluation, including CBC, transaminases, acetaminophen level, and salicylate level were normal and/or negative. (see Table 1) Total CK was elevated and he had an anion gap metabolic acidosis (AG 22 mEq/L). (see Table 1) UDS was presumptive positive for amphetamines and confirmed positive with a quantitative amphetamine concentration of 45,751 ng/mL. UDS was negative for benzodiazepines, cocaine, opiates, oxycodone and THC. An EKG was significant for sinus tachycardia but was otherwise normal. Hair toxicology was ordered, which ultimately returned positive for amphetamines. (see Table 1)

Upon further history, he had been at an in-home daycare when symptoms began. An older child, whom lives in that home, has ADHD and takes LDX. This older child had been known to throw or spit out pills occasionally. During the hospitalization, the infant was treated with benzodiazepines (midazolam and diazepam). Following symptom resolution, he was discharged the next day.

### 3.1.3. Case 3

As we previously reported, a 10-month-old previously healthy girl was brought to the ED due to 2 h of agitation and dyskinetic movements of the face, tongue, and upper extremities [8]. She had been behaving normally the evening prior. She was making odd vocalizations, and did not seem as interactive, though she was awake. Upon presentation to the ED, she was tachycardic (163 bpm), hypertensive (116/96 mm Hg) and unresponsive to voice. Her temperature was 36.6 °C. She was unable to focus and her tongue was darting while she reached for objects not present. CBC, transaminases, UA, ethanol level, salicylate level, acetaminophen level, and nicotine level were all normal. BMP was notable for an anion gap metabolic acidosis (AG 18 mEq/L). UDS returned presumptive positive for amphetamines by immunoassay. Confirmatory urine amphetamine testing was positive with a quantitative amphetamine concentration of 22,312 ng/mL. (see Table 1) UDS was negative for benzodiazepines, cocaine, opiates, oxycodone and THC. Due to abnormal movements, there was concern for seizure activity and lorazepam was given, with minimal improvement.

After admission, further history revealed that the child was cared for at her grandmother's home the day prior to admission. No witnessed drug exposures occurred, though the maternal aunt was known to take LDX, and the drug was present in the home in a secure location. A child abuse evaluation, including a negative skeletal survey and negative retinal exam was conducted. Hair toxicology was presumptively positive for amphetamines but with insufficient sample to confirm. No further benzodiazepines were administered. Discharge occurred the following day.

### 3.1.4. Case 4

A previously healthy 26-month-old boy presented to an outside ED with a 2 h history of irritability and uncoordinated gait. The family had been camping, and after the child had become symptomatic, they noted that a LDX pill was missing from a relative's pill box. He was admitted at the outside hospital, and developed worsening agitation,

tachycardia, and dystonia despite pharmacotherapy with diphenhydramine and lorazepam.

Upon transfer to our institution, he was tachycardic (193 bpm), hypertensive (138/69 mm Hg), agitated and exhibited dystonic movements. His temperature was 37.2 °C. Laboratory studies showed CBC with neutrophilia [white blood cell count (WBC) of 23,100 K/mm<sup>3</sup>], an anion gap metabolic acidosis (AG 20 mEq/L), elevated CK and a UDS presumptively positive for amphetamines and benzodiazepines. (see Table 1) Confirmatory urine testing was positive for amphetamines with a quantitative amphetamine concentration of 2067 ng/mL. (see Table 1) The positive benzodiazepine screen was thought to be reflective of the lorazepam given prior to transfer. UDS was negative for cocaine, opiates, oxycodone and THC. Acetaminophen level, salicylate level, and transaminases were normal. Hair toxicology was not performed. The patient was moved to the pediatric intensive care unit and medicated with intravenous dexmedetomidine. No further benzodiazepines were administered, and patient was discharged the following day.

### 3.1.5. Case 5

A 15-month-old previously healthy boy presented to the ED following 2 h of inconsolability. He was crying and swinging his arms, seemingly at unseen objects, suggestive of hallucinations. Exam in the ED yielded no specific cause of his symptoms. His heart rate (98 bpm) was normal and blood pressure was not obtained at presentation. His temperature was 35.4 °C. An abdominal X-ray was done, to assess for obstruction as a source of discomfort. A mild stool burden was seen, and an enema was given, with no improvement. He was treated with morphine and ibuprofen, without improvement. He was then treated with midazolam which helped calm him. Laboratory studies revealed an anion gap metabolic acidosis (AG 26 mEq/L), neutrophilia (WBC of 20,400 K/mm<sup>3</sup>) and a normal CK. (see Table 1) EKG demonstrated sinus tachycardia. UDS was presumptively positive for opiates and amphetamines. Confirmatory testing yielded a quantitative amphetamine concentration of 19,618 ng/mL. (see Table 1) Confirmatory opiates testing was not performed but was explained by the morphine he had received previously. UDS was negative for benzodiazepines, cocaine, oxycodone and THC. He was admitted for observation.

Symptoms started while the toddler was at his grandparent's house, and his grandfather's prescription medications included amphetamine-dextroamphetamine. Hair toxicology was negative for amphetamine or other drugs of abuse. (see Table 1) No further benzodiazepines were required during admission. After improvement in symptoms, he was discharged on hospital day 2.

## 3.2. Cases without confirmatory toxicology testing

Over a 13-year period (2004–2017) we identified 2 additional cases. (see Table 1) Both cases had UDS presumptive positive immunoassay screens for amphetamine. However, neither confirmatory urine nor hair toxicology testing was performed for either child. For both children, UDS was negative for barbiturates, benzodiazepine, cocaine, opiates, phencyclidine, THC, tricyclic antidepressants, and methamphetamine.

### 3.2.1. Case 6

A 15-month-old was observed to accidentally ingest mixed amphetamine salts from the 5 year old sibling's prescription for Adderall XR® (Shire US Inc.), with evidence of three partially chewed 20 mg pills. This child presented with a normal temperature (36.5 °C), tachycardia (220 bpm) and mydriasis and required lorazepam for sedation.

### 3.2.2. Case 7

A 7-year-old child took another child's prescription mixed amphetamine salts, with estimated ingestion of at least 30 mg. This child presented with a temperature of 35.7 °C, a normal heart rate, visual hallucinations and confusion. Multiple doses of risperidone were administered.

#### 4. Discussion

In 1937, Charles Bradley, a psychiatrist, was the first to report the behavioral effect of stimulants in children after observing improved school performance in children taking benzedrine (*d,l*-amphetamine) [10,11]. Subsequently, stimulant medications have become the first line pharmacotherapy for ADHD in older children [11,12]. A systematic ranking of ADHD medications based upon current evidence of efficacy and tolerability is in process [13].

Amphetamines and dextroamphetamine (*d*-amphetamine) are central and sympathetic nervous system stimulants [1,8]. Overdose results in sympathomimetic toxicity producing cardiovascular, neurologic and psychiatric signs and symptoms. Hypertension, tachycardia and agitation are most common [8]. Severe toxicity may cause seizures, hemorrhagic or ischemic stroke, myocardial infarction, hyperthermia, coma and even death [1,8]. Psychiatric manifestations may include confusion, altered mental status, aggression, hallucinations, delirium, paranoia and psychosis [1,8]. In our patients, all were described as irritable, suggesting irritability may be the predominant neuropsychiatric manifestation in infants and young children.

One child exhibited self-mutilating biting behaviors. In 1969, Fog observed that rats treated with *d*-amphetamine and methylphenidate developed stereotypical behaviors of biting / gnawing, sniffing and licking [14]. This effect on laboratory animals has been shown in multiple subsequent studies. Roffman et al. found that pretreatment with a drug to decrease serotonin (5-HT) synthesis diminished these behaviors supporting the important role of central 5-HT activity [15].

Movement disorders including orofacial and limb dyskinesia and dystonia may develop due to the increased dopaminergic transmission caused by psychostimulants [2,16,17]. Chorea has been well described in adults taking amphetamine based stimulants for ADHD, but pediatric data is sparse [18]. Ford et al. described 2 pediatric cases of abrupt onset chorea involving resulting from accidental ingestion of amphetamine mixed salts in an infant and overdose of LDX in an 8 year old [18]. Symptoms were prolonged lasting 48–72 hours [18]. Bruxism, ataxia, tics and tremor have also been described [16,19].

An increased anion gap metabolic acidosis was detected at presentation in all 5 cases.

Toxic ingestions including amphetamines are a well-known cause of an increased AG metabolic acidosis [20]. The mechanism by which this occurs is from rhabdomyolysis and release of lactic acid and other organic acids from myocytes [21]. CK values were normal in our patients, but ketonuria was present in some, therefore; we hypothesize that the AG metabolic acidosis we observed was from ketoacidosis. Obtaining basic chemistry testing can be useful in suspected toxic ingestions to look for the presence of an AG metabolic acidosis.

Four of the cases we described likely involved the medication LDX (Vyvanse®), making the present study the largest published series of naïve pediatric patients exposed to LDX [8,22]. LDX was the first pro-drug stimulant to be developed for the treatment of ADHD and was introduced to U.S. markets in 2007 [23,24]. LDX is converted to its active metabolite, *d*-amphetamine, by red blood cell hydrolysis [1]. The rate of conversion determines its toxicity [1]. The peak plasma concentrations and time to peak concentration of *d*-amphetamine are lower after ingestion of oral LDX compared to extended-release amphetamine prescriptions [23,24]. The therapeutic effect of LDX after a single oral dose has been reported to last over 13 h in children and 14 h in adults [25]. This is consistent with the protracted symptoms experienced by the infants in our cases and that reported by others [8,18,22].

Hair toxicology testing was positive for amphetamines in two of the cases described. In both cases, hair was collected within 12 h of presentation to our ED and the ingestions were believed to be acute and novel. Drugs can be incorporated into hair via blood, sweat and sebum [26]. Sebaceous glands secrete directly into the follicle and sweat glands secrete on the skin surface near the follicle [26]. Studies have shown that drugs can diffuse into sweat and coat hair follicles within

hours of ingestion [27]. The hair toxicology procedure employed in the present study used unwashed hair and thus can detect drug or metabolite coating the hair surface. This allows for detection of drug or metabolite introduced by sweat or sebum, or by environmental exposure. The interpretive challenge is that the testing cannot distinguish between longer-term systematic exposure to drug (with incorporation into hair follicle) or more acute exposure. Concentrations of analyte in hair are also difficult to interpret and have not been shown to clearly correlate with level of exposure [26,27]. When introduced by blood at the hair follicle level, it takes 5–10 days for hair to grow and emerge above the scalp's surface [26,27].

Little data is available regarding the clinical correlation of symptoms and urine quantitative drug levels in pediatric patients with amphetamine ingestions. In our series, five cases had quantitative amphetamine concentrations in urine ranging from 2067 to 45,751 ng/mL with four of the five cases exceeding 19,500 ng/mL. For comparison, these four children had higher amphetamine concentrations in urine than the maximum urine amphetamine concentrations achieved in a detailed pharmacokinetic study of amphetamine mixed salts in adults [28]. Given that only single urine specimens were obtained for the five children, it is likely that the peak concentrations may have been substantially higher. In a study of 90 children under the age of 13 with a symptomatic ingestion of amphetamines and/or methamphetamines, higher urine drug levels were associated with seizures (methamphetamine only) and rhabdomyolysis [29]. In that study, the highest reported median urine drug concentration was 4837 ng/mL. In our cases, urine concentration did not appear to correlate with symptom severity.

#### 5. Conclusions

With the increasing prescribing of stimulant medications for both children and adults, clinicians should consider stimulant ingestion in infants and children presenting with signs and symptoms of sympathetic toxicity and/or movement disorders. Symptoms can be protracted with ingestion of long acting stimulants notably LDX. Treatment for symptomatic ingestions is largely targeted at reducing sympathomimetic activity via the use of central nervous depressants, such as benzodiazepines. Though toddlers (age 1 and 2) are at highest risk for accidental ingestion, infants under the age of 1 can be affected as well.

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No funding was used for this study / case series.

#### Conflicts of interest

Dr. Wood has a financial relationship with McGraw-Hill Professionals. She receives royalties for a pediatric board review textbook she co-edited. Drs. Krasowski and McCarthy have no conflicts of interest to report. No funding was used for this study.

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