An Infant with a Prolonged Sympathomimetic Toxidrome after Lisdexamfetamine Dimesylate Ingestion

Kelly E. Wood¹ · Matthew D. Krasowski²

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Abstract

Introduction Stimulant medications are approved to treat attention deficit hyperactivity disorder (ADHD) in children over the age of 6 years. Fatal ingestion of stimulants by children has been reported, although most ingestions do not result in severe toxicity. Lisdexamfetamine dimesylate, a once daily long-acting stimulant, is a prodrug requiring conversion to its active form, dextroamphetamine, in the bloodstream. Based on its unique pharmacokinetics, peak levels of d-amphetamine are delayed. We describe a case of accidental ingestion of lisdexamfetamine dimesylate in an infant.

Case Report A previously healthy 10-month-old infant was admitted to the hospital with a 5-h history of tachycardia, hypertension, dyskinesia, and altered mental status of unknown etiology. Confirmatory urine testing, from a specimen collected approximately 16 h after the onset of symptoms, revealed an urine amphetamine concentration of 22,312 ng/mL (positive cutoff 200 ng/mL). The serum amphetamine concentration, from a specimen collected approximately 37 h after the onset of symptoms, was 68 ng/mL (positive cutoff 20 ng/mL). Urine and serum were both negative for methamphetamine, methylenedioxymphetamine (MDA), methylenedioxymphetamine (MDMA, Ecstasy), and methylenedioxyamphetamine (MDEA). During the hospitalization, it was discovered that the infant

had access to lisdexamfetamine dimesylate prior to the onset of symptoms.

Conclusion Amphetamine ingestions in young children are uncommon but do occur. Clinicians should be aware of signs and symptoms of amphetamine toxicity and consider ingestion when a pediatric patient presents with symptoms of a sympathetic toxidrome even when ingestion is denied.

Keywords Lisdexamfetamine dimesylate · Attention deficit disorder with hyperactivity · Dextroamphetamine

Abbreviations

ADHD	Attention deficit hyperactivity disorder
GCS	Glasgow Coma Scale
LDX	Lisdexamfetamine dimesylate
LC/MS/MS	Liquid chromatography-tandem mass spectrometry
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymphetamine
MDEA	Methylenedioxyamphetamine
TSH	Thyroid-stimulating hormone

Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most common pediatric psychiatric disorders affecting 10 % of children age 3 to 17 years in the USA [1, 2]. Core symptoms include inattentiveness, hyperactivity, and impulsivity. Stimulant medications are highly effective in reducing core symptoms and are considered first-line therapy for children age 6 and older [3–5].

This data has not been presented previously in any form.

✉ Kelly E. Wood
Kelly-wood@uiowa.edu

¹ Stead Family Department of Pediatrics, University of Iowa Children's Hospital, 200 Hawkins Dr, Iowa City, IA 52242, USA

² Department of Pathology, University of Iowa Hospitals and Clinics, Iowa City, IA 52242, USA

Lisdexamfetamine dimesylate (LDX), Vyvanse®, is a long-acting stimulant approved for once-daily treatment of ADHD in children 6 years and older. It was introduced into the US market in 2007, and prescriptions for the drug tripled between 2007 and 2011 [1]. Unlike other long-acting stimulants, it is a prodrug that is rapidly converted to dextroamphetamine (*d*-amphetamine), its active form, in the blood [6]. Its extended release characteristics provide more consistent effects over a prolonged duration, less pharmacokinetic variability and reduced potential for abuse as peak plasma concentrations of *d*-amphetamine are lower and delayed [1, 6]. Clinical effects after ingestion of a therapeutic dose may last over 12 h [1].

We report a case of an infant who presented with signs and symptoms of sympathomimetic toxicity presumably due to ingestion of LDX.

Case

A previous healthy 10-month old presented to the emergency department (ED) with the acute onset of abnormal movements and behaviors that developed at her grandmother's house. She had been acting normally earlier in the day. She had symptoms of a viral respiratory tract infection but had been afebrile. That evening around 8:00 p.m., the mother noticed that the infant was swaying her head back and forth as if shaking her head "no." At 2:00 a.m., the infant woke up crying and restless. She was darting her tongue in and out of her mouth. She did not respond to her name and was staring off and making strange sounds.

She was a healthy infant with no prior history of such behaviors. She was immunized and did not take medications. Developmentally, she was able to pull herself to stand and crawl well. Earlier in the day, she had rolled off the bed onto a carpeted surface but acted normally afterwards. There was no maternal family history of seizures, movement disorders, or other neuromuscular conditions. The paternal family history was unknown. She was an only child who lived with her mother. She attended daycare during the week and was cared for by her grandmother on evenings and weekends. No one else in the home was ill or having similar behaviors.

Upon presentation to the ED at 4:00 a.m., she was tachycardic with a heart rate of 163 beats per minute, hypertensive with a blood pressure of 116/96 mmHg, and afebrile with a temperature of 36.6 °C. Her oxygen saturation was 97 % on room air. She was awake but not interactive nor responsive to voice. She continuously moved her tongue in and out of her mouth. Her head was normocephalic without signs of trauma. Her anterior fontanelle was soft and flat. Her pupils were dilated, symmetric, and minimally reactive to light. Nystagmus was not present. Her heart rate was tachycardic but otherwise normal. On neurologic exam, she was alert and her eyes were open. Her pediatric Glasgow Coma Scale (GCS) score was 12. She did not respond to voice but did to pain. She would

not focus on the examiner and reached for objects that were not present. Her tone, strength, and reflexes were normal. She had truncal instability and would not crawl. Due to concern for seizure versus dyskinesia, she received a single dose of intravenous lorazepam (0.05 mg per kilogram of body weight per dose [mg/kg/dose]) without effect. She was admitted to the general pediatric hospital unit at 7:00 a.m. (5 h after symptom onset) and placed on cardiorespiratory monitoring. Upon admission, she was afebrile and continued to have tachycardia, hypertension, irritability, and atypical movements.

On laboratory evaluation, electrolytes, blood glucose level, liver function tests, whole blood lead level, and thyroid stimulating hormone (TSH) were normal. Serum ethanol level was 0 mg/dL. Acetaminophen and salicylate drug levels were undetectable. Urine drug screen collected approximately 16 h after the onset of symptoms was presumptively positive for amphetamines as analyzed in the University of Iowa Hospitals and Clinics Core Clinical Laboratory (Roche Diagnostics Amphetamine II Assay, cobas c502 analyzer). Confirmatory amphetamine testing using liquid chromatography-tandem mass spectrometry (LC/MS/MS) was performed by a commercial reference laboratory (ARUP Laboratories, Salt Lake City, UT) and showed a urine amphetamine concentration of 22,312 ng/mL (positive cutoff 200 ng/mL). The serum amphetamine concentration, from a specimen collected approximately 37 h after the onset of symptoms, was also analyzed by LC/MS/MS (ARUP Laboratories) and showed a concentration of 68 ng/mL (positive cutoff 20 ng/mL). Urine and serum were both negative for methamphetamine, methylenedioxyamphetamine (MDA), methylenedioxymethamphetamine (MDMA, Ecstasy) and methylenedioxyethamphetamine (MDEA).

At presentation, the mother did not recall the infant ingesting and/or getting into any medications. Because of the new confirmatory lab data, the family was again asked about access to amphetamine products in the home. The grandmother recalled a bottle of LDX (Vyvanse®), a prescription medication for the grandmother, had recently been spilled. The family thought all the pills had been picked up but were unaware of what the total pill count was before the spill.

Throughout the day, her mental status improved but she was irritable and fussy. She began to reach for her mother indicating recognition. She was difficult to console. Holding her would calm her for a short time period. She would sleep for short intervals then wake up crying. She was treated with oral acetaminophen (15 mg/kg/dose) for comfort. Twelve hours after her family first noticed her behavioral changes, she returned to her baseline mental status and demeanor and her dystonic movements resolved. She was discharged the following morning approximately 34 h after symptom onset. At discharge, she was crawling and pulling to stand, but continued to have mild truncal ataxia when sitting upright. Social work was consulted during hospitalization. The family was counseled about the safe storage of medications including the use of a locked

cabinet or storage box. Verbal consent for publication of this case report was obtained from the parent.

In addition to the index case, we analyzed our electronic health record over an 8-year period for other cases involving young children with positive amphetamine screens in urine. Thirty-five cases including the index case were identified including one other similar case, namely a 15-month-old child with accidental ingestion of amphetamine mixed salts (Table 1). This child presented with symptoms of sympathetic activation including tachycardia. All amphetamine-positive urine screens in children between 4 and 8 years old were explainable by known amphetamine mixed salts or LDX prescriptions.

Discussion

Accidental ingestion of medications is most common in children 5 years of age and younger, especially toddlers who are naturally curious, mobile, and use mouthing to explore objects. Ingestions in infants under the age of 1 are less common. Ingestion of stimulants in young children is uncommon, but fatalities have been reported. Between 2007 and 2012, US poison control centers reported 7113 children (≤ 19 years) were exposed to LDX [1]. Of these, 35.8 % (2544) were less than 6 years of age and 2.3 % (162) were less than 1 year of age [1]. No fatalities were reported. Published case reports of naïve children exposed to LDX are rare, and to our knowledge, only one other involving a 6-year old with severe symptoms requiring intensive care admission for 48 h has been published to date [7]. There is also a case report on a 10-year-old boy who experienced protracted toxicity (48 h), including chorea, after accidental double dose of his prescribed LDX [8].

Amphetamines stimulate the central and sympathetic nervous system by increasing the concentration of dopamine and norepinephrine at the neuronal synapses [1]. Amphetamines compete

for cellular monoamine transporters by blocking reuptake of dopamine and norepinephrine into the presynaptic neuron as well as by stimulating the transporters to work in reverse [9, 10].

Amphetamines are rapidly absorbed from the intestinal tract and cross the blood-brain barrier [10]. Overdose causes a sympathomimetic toxidrome primarily affecting the cardiovascular and neurologic systems. The most common clinical effects include agitation, tachycardia, and hypertension [1]. Psychiatric effects are common and may be explained by the strong dopaminergic effect of amphetamines [10]. Severe effects are rare and associated with large overdoses [11]. Signs and symptoms of mild to moderate toxicity may include tachycardia, hypertension, tachypnea, hyperreflexia, diaphoresis, mydriasis, flushing, palpitations, headache, tremors, dyskinesias, and confusion. Severe toxicity may cause hyperthermia, severe hypertension, arrhythmias, myocardial infarction, intracranial hemorrhage, ischemic stroke, seizures, rhabdomyolysis, multisystem organ failure, and even death. Neuropsychiatric signs include mental status changes, confusion, agitation, aggression, hallucinations, delirium, paranoia, and psychosis. The mainstay of treatment is intravenous benzodiazepines [10].

The pharmacokinetics of LDX have been studied in children as young as 6 years [12]. LDX itself is therapeutically inactive. It is made up of *d*-amphetamine bonded to the amino acid *l*-lysine. Approximately 30 % of the drug is hydrolyzed to its active form *d*-amphetamine [12]. This conversion occurs primarily in the blood with a small amount occurring in the gastrointestinal tract [12]. The peak effect of LDX ingestion is delayed with peak plasma concentration ($C_{\max}$) of LDX-derived *d*-amphetamine reached at 3.5 h ($T_{\max}$) after ingestion compared to 2 h for *d*-amphetamine immediate-release products [10, 11]. The $C_{\max}$ and area under the plasma concentration-time curve (AUC) of *d*-amphetamine increase linearly and proportional to the dose of LDX ingested [12]. LDX is renally cleared with an elimination half-life of 1 h compared to its active form, *d*-amphetamine,

Table 1 Drug exposures associated with amphetamine-positive urine screens in children less than 8 years old at the University of Iowa Hospitals and Clinics

	Drug exposure					
	Amphetamine mixed salts	Lisdexamfetamine	Methamphetamine	Labetalol	Vilazodone	Unexplained
Newborn (up to 1 week old) ^a	2	1	3	1	0	2
1 week to 3 years old ^b	1	1	3	0	1	2
4–8 years old ^c	13	4	0	0	0	1

^a For the newborn cases, four involved newborns whose mothers had known prescriptions during pregnancy for amphetamine mixed salts ($n = 2$), lisdexamfetamine ($n = 1$), or labetalol ($n = 1$; known cause of positive amphetamine urine drug screens). Three cases involved methamphetamine abuse during pregnancy. Two of the amphetamine-positive screens in newborns were unexplained by known maternal or newborn drug use

^b For the 1 week to 3 years old range, in addition to the index case of this report, there was also a 15-month old with suspected accidental ingestion of amphetamine mixed salts. The remaining cases with known drug exposures were methamphetamine exposure ($n = 3$) and vilazodone overdose ($n = 1$). Two cases were unexplained by known drug exposure

^c For the 4–8 years old range, 16 of 18 cases were in children prescribed amphetamine mixed salts ($n = 12$) or lisdexamfetamine ($n = 4$). One was a child who took another child's amphetamine mixed salts medication. There was one additional case unexplained by known drug exposure

which has a half-life of 10.25 h [10]. Approximately 42 % of the drug is excreted in the urine as amphetamine, 25 % as hippuric acid, and 2 % unchanged.

The toxicity of LDX depends on the rate of conversion to *d*-amphetamine [10]. The conjugation of *d*-amphetamine with lysine may be protective against severe toxicity. In animal studies, the lethal dose of LDX was five times higher than that of *d*-amphetamine [1]. Compared to *d*-amphetamine/amphetamine extended release and immediate release, children who ingested LDX had less serious toxicity/outcomes and were less likely to be admitted to the hospital [1].

In summary, clinicians should be aware of the potential for young children to ingest amphetamine or LDX prescription medications and show toxic symptoms. Children who ingest LDX may experience prolonged symptoms due to the long half-life of LDX.

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Compliance with Ethical Standards

Conflict of Interest The authors, Kelly E. Wood and Matthew D. Krasowski, have no conflicts of information to disclose.

Informed Consent Informed consent for publication of this case was obtained and provided to the journal in accordance with the *Journal of Medical Toxicology* policy.

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