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CASE REPORT

Lisdexamfetamine Toxicity with Delayed Hypertensive Emergency

RACHEL F SCHULT[1,*], DOMENIQUE N CIRIELLO[2], EMILY K SCHRANZ[2], MICHELLE MALNOSKE[1], TIMOTHY J WIEGAND[1]

[1]University of Rochester Medical Center, Rochester, New York, USA
[2]John Fisher College Wegmans School of Pharmacy, Rochester, New York, USA

Abstract

Background: Lisdexamfetamine is a stimulant used for the treatment of attention-deficit/hyperactivity disorder. Limited data exist regarding the presentation and management of patients with lisdexamfetamine toxicity.
Case Presentation: A 17-year-old female with history of prior suicide attempt presented to the emergency department after ingestion of 50 lisdexamfetamine 40 mg capsules which belonged to a friend. The patient was asymptomatic until approximately seven hours post-ingestion when she developed hypertension, mydriasis and complained of severe headache, blurred vision, chest pain, nausea, and vomiting. The patient was diagnosed with drug-induced hypertensive emergency and phentolamine was administered after lorazepam failed to adequately control her symptoms.
Discussion: While lisdexamfetamine is a pro-drug, onset of clinical effects after ingestion is typically quicker and often consistent with amphetamine intoxication including many sympathomimetic symptoms, not simply those related to vasoconstriction alone. Benzodiazepines are frequently utilized in the management of stimulant toxicity; however, they were insufficient for our patient. This case highlights a unique presentation of lisdexamfetamine toxicity with primarily alpha adrenergic stimulant effects in addition to altered pharmacokinetics observed in overdose. Phentolamine was effective for management of hypertensive emergency in this patient.
Conclusion: Lisdexamfetamine toxicity may present with delayed onset of clinical effects. Phentolamine may be useful for treating hypertensive emergency resulting from overdose in addition to standard care.

Keywords: Lisdexamfetamine; Phentolamine; Toxicology

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INTRODUCTION

Lisdexamfetamine, a stimulant prodrug of dextroamphetamine, came to market in 2007 for the treatment of attention-deficit/hyperactivity disorder (ADHD) in the United States (1). In 2011, 8.5 million prescriptions of lisdexamfetamine were dispensed (2). To date, few cases of lisdexamfetamine toxicity have been reported. We present a case of lisdexamfetamine overdose with delayed stimulant effects resulting in hypertensive emergency successfully treated with phentolamine.

CASE PRESENTATION

A 17-year-old female with history of borderline personality disorder, depression, and prior suicide attempts presented to the emergency department 30 minutes after ingestion of 50 lisdexamfetamine 40 mg capsules belonging to a friend. Initial vital signs 60 minutes post ingestion included blood pressure 108/65 mmHg, heart rate 76 beats/minute, and temperature 37 degrees Celsius. No adrenergic symptoms such as diaphoresis, tremor, or mydriasis were noted at this time. Within one hour of arrival, the patient received 50 g (approximately 1 g/kg) activated charcoal. The patient remained asymptomatic until six and a half hours after arrival to the emergency department (seven hours post ingestion) when she complained of severe headache, blurred vision, chest pain, nausea, and vomiting. At this time, marked mydriasis and fine tremor were noted on exam while repeat vital signs demonstrated an elevated blood pressure of 170/105 mmHg with no change in heart rate. The patient was administered 2 mg intravenous (IV) lorazepam without improvement in symptoms; blood pressure remained elevated at 172/95 mmHg. Another 2 mg IV lorazepam was administered and blood pressure remained at 158/88 mmHg. At nine hours post ingestion, 1 mg IV phentolamine was given. Within 30 minutes, blood pressure improved to 116/87 mmHg and the heart rate remained relatively unchanged at 77 beats/minute (range 76-96 beats/minute over the preceding nine hours). The patient subsequently received 0.1 mg clonidine by mouth and was admitted to the pediatric intensive care unit approximately 11 hours post ingestion. She received additional doses of medication for recurrent

[*]Correspondence to: Rachel Schult; PharmD. Department of Pharmacy, University of Rochester Medical Center, 601 Elmwood Avenue, Box 638, Rochester, NY 14642.
E-mail: Rachel_Schult@urmc.rochester.edu, Tel/Fax: +1 585 275 2599, +1 585 756 5582
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hypertension and was administered a total of 6 mg IV lorazepam, 4 mg IV phentolamine, and 0.4 mg clonidine by mouth throughout her hospital course. Her symptoms improved and vital signs normalized over a 24-hour period with complete resolution of toxicity approximately 48 hours post ingestion. Serum concentration of amphetamine 16 hours post ingestion was 300 ng/mL (*NMS Labs*); the mean peak concentration in healthy adults is reported as approximately 80 ng/mL after a single dose of 70 mg.

DISCUSSION

Lisdexamfetamine is a prodrug consisting of dextroamphetamine coupled with the amino acid L-lysine. While lisdexamfetamine is inactive, it is rapidly absorbed and extensively metabolized to its active metabolite dextroamphetamine. At therapeutic doses, the peak concentration of the active metabolite occurs at 3 hours with a half-life of 10 hours (1).

Amphetamines promote the release of catecholamines such as dopamine, serotonin, and norepinephrine which directly stimulate both alpha and beta adrenergic receptors. Release of these neurotransmitters results in increased attention, mood regulation, and improved learning, all of which are desirable for treatment of ADHD (3). Release of norepinephrine and stimulation of adrenergic receptors also result in adverse effects and toxicities. Symptoms commonly reported after exposure to lisdexamfetamine are consistent with typical effects of amphetamine toxicity and include hypertension, tachycardia, agitation, and vomiting (4). Initial treatment for stimulant toxicity typically involves supportive care with benzodiazepines which have a sympatholytic effect. In this situation, benzodiazepines are used to combat adrenergic toxicity.

This case is unique due to the delayed onset of toxicity as well as the limited range of effects seen compared to other cases of lisdexamfetamine intoxication. Typical symptoms of stimulant toxicity, such as tachycardia and hypertension, have been reported with previous cases involving lisdexamfetamine ingestion (5-7). The primary symptoms in our patient were related to hypertensive effects along with marked mydriasis suggesting predominantly alpha-1 agonist effects instead of combined toxicity with beta-1 receptor mediated effects. In fact, our patient did not develop tachycardia at any point during her treatment as would be expected with beta-1 receptor stimulation. Additionally, the timing of sympathomimetic effects was delayed until about seven hours post ingestion and not at the expected time of peak levels for the active metabolite. This suggests the presence of altered kinetics of lisdexamfetamine in overdose and supports the use of prolonged monitoring in these patients. Given the acuity of the patient's ingestion and the fact that the prescription was not her own, we can infer that these delayed effects were not a result of medication tolerance from prolonged use.

Traditional management for amphetamine overdose with benzodiazepines was not sufficient in treating the patient's symptoms in the case presented. Although two doses of lorazepam were administered with slight improvement in blood pressure, the patient had persistent complaints of headache prompting the decision for a more targeted

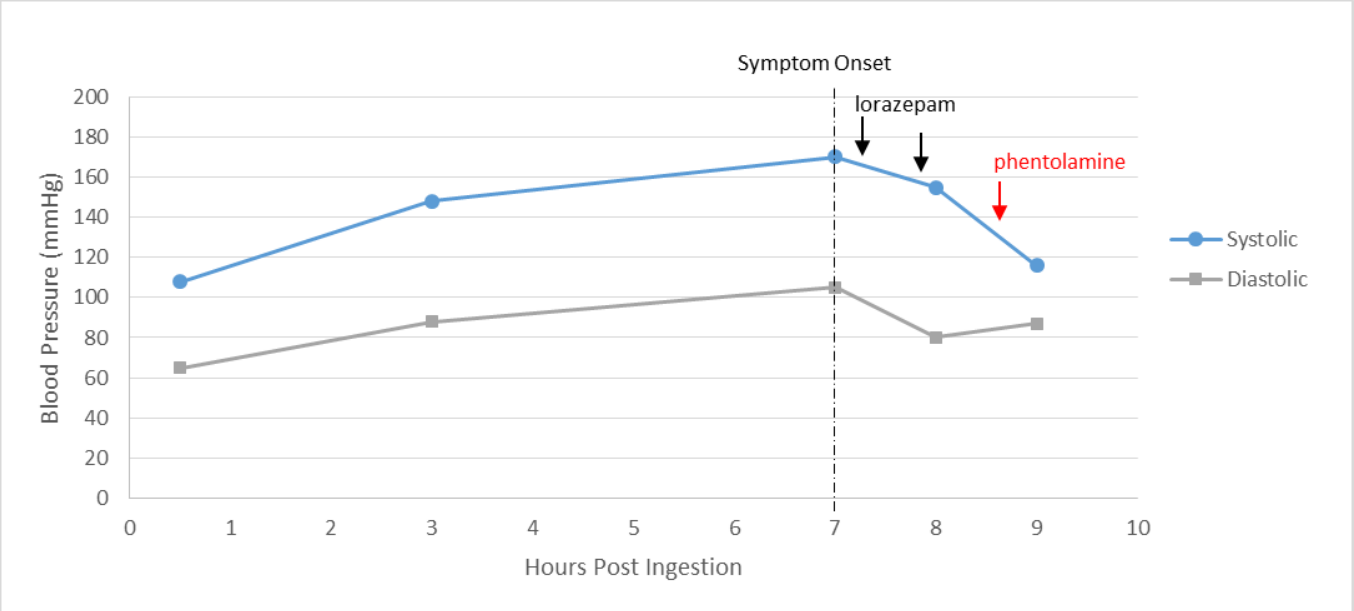

Figure 1. Blood Pressure with Medication Administration

approach to facilitate blood pressure management. As symptoms appeared predominantly related to alpha adrenergic toxicity in the absence of beta adrenergic effects, phentolamine was administered. Phentolamine is an alpha-1 antagonist. It has been used successfully to treat alpha-adrenergic overstimulation in toxicity from phenylpropanolamine, an analog of amphetamine with predominantly alpha-1 receptor mediated effects (8). Our patient's blood pressure temporarily improved after the initial dose of phentolamine (Figure 1); however, multiple doses were required in addition to lorazepam throughout the patient's admission to stabilize her blood pressure. The need for repeat dosing may be required due to the short half-life of IV phentolamine, reportedly 19 minutes, compared to the longer half-life of dextroamphetamine (9). Clonidine, an alpha-2 adrenergic agonist causing decreased sympathetic outflow from the central nervous system, was also used adjunctively in our patient. Dexmedetomidine is a parenteral alpha-2 adrenergic agonist similar to clonidine and has been effectively utilized in a previously reported case of lisdexamfetamine toxicity (7).

CONCLUSION

We present a case of lisdexamfetamine toxicity after intentional overdose in a stimulant-naive adolescent female. Our patient had delayed onset of clinical effects with predominantly alpha-1 adrenergic toxicity compared with typical amphetamine overdoses. Additionally, this case demonstrates that phentolamine may be useful for treating hypertensive emergency resulting from lisdexamfetamine overdose in combination with other interventions such as benzodiazepines and clonidine. Further studies are needed to confirm the safety and efficacy of phentolamine in lisdexamfetamine toxicity.

Conflict of interest: None to be declared.
Finding and Support: None.

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