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Selected Topics: Toxicology

ACCIDENTAL PEDIATRIC PALIPERIDONE INGESTION RESULTING IN DELAYED PROFOUND TACHYCARDIA

Heather A. Borek, MD and Nathan P. Charlton, MD

Division of Medical Toxicology, Department of Emergency Medicine, University of Virginia School of Medicine, Charlottesville, Virginia
Reprint Address: Heather Borek, MD, Division of Medical Toxicology, Department of Emergency Medicine, University of Virginia School of Medicine, 1222 Jefferson Park Ave, 4th Floor, Charlottesville, VA 22908.

☐ **Abstract—Background: Paliperidone is an atypical antipsychotic that is approved to treat schizophrenia in patients 12 years of age and older. There are minimal data on the clinical effects of exposure in the < 12-year-old age group. Case Report: We report the case of a 7-year-old girl who was accidentally dosed with paliperidone for 3 days. Her clinical course was notable for a dystonic reaction and profound sinus tachycardia, with a heart rate peaking at 201 beats/min. The tachycardia persisted for over 64 h after her last dose. The mechanism of tachycardia has not been elucidated and is likely multifactorial, with alpha blockade and anticholinergic effects probably contributing. Why Should an Emergency Physician Be Aware of This?: Clinicians should be aware that paliperidone ingestion in children may result in delayed, profound tachycardia and may require more prolonged observation times or admission to the hospital.**

☐ **Keywords—pediatric medication error; paliperidone; delayed tachycardia**

INTRODUCTION

Paliperidone is an atypical antipsychotic that was approved in the United States by the Food and Drug Administration in 2006. It is approved for adults, as well as adolescents as young as 12 years of age, to treat schizophrenia. Paliperidone is an active metabolite of risperidone and has antagonistic properties at the dopamine D2 receptor, the serotonin 2A receptor, the histamine 1 receptor, and α1 and α2 adrenoreceptors (1,2). Data from U.S. Poison Center cases over a 5.5-year time period revealed 801 cases related to paliperidone exposures, with only 67 of those patients in the age range of 6–12 years. Only 15% of patients in the study required intensive care unit admission, with approximately 40% able to be discharged from the emergency department, suggesting that serious toxicity is not common (1). However, this study included mainly patients over the age of 13 years. Paliperidone use in younger children is not recommended, and there is scant information on clinical effects in children.

CASE REPORT

A 7-year-old, 31-kg girl with a history of prematurity, patent ductus arteriosus, and attention deficit hyperactivity disorder presented with facial twitching and neck spasms, consistent with a dystonic reaction. It was found that her pharmacy had accidentally dispensed paliperidone 3-mg tablets instead of guanfacine, and she had received this dose daily for 3 days, with her last dose given approximately 13 h prior to presentation. Guanfacine 3 mg nightly was her only prescribed medication, which she had been taking for over a year. Her presenting vital signs showed a heart rate of 170 beats/min, a blood pressure of 108/93 mm Hg, and otherwise normal vital

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signs, including a normal temperature of 37.1°C. Her dystonic reaction resolved with diphenhydramine 30 mg intravenously, however, she had persistent tachycardia, mydriasis, and flushing, all of which were present prior to diphenhydramine administration. She did not have orthostatic changes to her blood pressure, and her heart rate did not decrease with a trial of benzodiazepines. A comprehensive metabolic panel, complete blood count, and chest radiograph were unremarkable. Her heart rate peaked at 201 beats/min 14 h after her last dose. She continued to exhibit sinus tachycardia during an 8-h observation period, and the decision was made to transfer her to a tertiary care facility for pediatric telemetry monitoring. Twenty-six hours after her last dose of paliperidone, shortly after her arrival to the tertiary care hospital, her examination was notable for heart rate of 176 beats/min (up to the 190s with stimulation), blood pressure of 106/69 mm Hg, temperature of 37.2°C, normal mental status, no clonus with testing of deep tendon reflexes, no muscular rigidity, and pupils were 5 mm and reactive.

Her electrocardiogram (ECG) obtained at the initial hospital showed a sinus tachycardia with a QTc of 502 ms, however, a subsequent ECG without any QTc-related intervention at approximately 26 h after last dose showed sinus tachycardia at a rate of 173 beats/min, with a QRS of 60 ms and a QTc of 407 ms without signs of ischemia. A subsequent ECG at 35 h after the last dose continued to show a normal QTc of 428 ms.

She continued to have tachycardia with minimal stimulation during her hospital course. At 64 h since her last dose, she had a heart rate of 136 beats/min. However, at that point she remained otherwise asymptomatic and was discharged with close primary care follow-up the following day.

DISCUSSION

Paliperidone is an atypical antipsychotic that is the active metabolite of risperidone. It has a unique delivery mechanism as a tablet with a tri-layer core that results in a sustained-release delivery system, with peak serum concentration occurring about 24 h after ingestion at therapeutic doses (2).

Overdose data are limited. A case report of an intentional overdose of 3.1 mg/kg of paliperidone in a 14-year-old girl reported a delayed-onset tachycardia that did not begin to manifest until 20 h after ingestion. This progressed to a narrow complex tachycardia with a rate in the 190s upon standing 26.5 h after ingestion (3). Another case, in a 23-year-old woman, involved a mixed ingestion of paliperidone with quetiapine and zopiclone. She had tachycardia, which persisted for about 72 h, with a peak heart rate of 190 beats/min 40 h after ingestion (4). Her weight was not specified in the report, but if one assumes a 70-kg adult, this would have resulted in a 7.2-mg/kg ingestion of paliperidone. In our case, the patient ingested 0.29 mg/kg spaced out over 3 days and still experienced significant tachycardia. To our knowledge, this is the first case that depicts profound tachycardia related to an accidental ingestion and also demonstrates a much lower mg/kg ingestion threshold for developing symptoms than previous reports.

The mechanism of tachycardia is not clear. Peripheral α-adrenergic blockade may play a role, as the previous reports noted lightheadedness or worsening tachycardia with positional change (3,4). However, our patient had no orthostatic changes with vital signs or symptoms and had no hypotension, making this unlikely to be the sole mechanism. Paliperidone has no reported affinity for the muscarinic acetylcholine receptor, but our patient showed some signs consistent with anticholinergic findings (flushing, mydriasis), which may have contributed to her tachycardia; she did not exhibit altered mentation or urinary retention to suggest a full anticholinergic toxidrome (2). It is certainly possible that toxicokinetics and receptor affinities in overdose vary from those studied at therapeutic dosing. Guanfacine withdrawal was also considered, but her lack of hypertension made this less likely. Her guanfacine was held during her hospitalization and restarted at discharge because the concern for withdrawal was low and we did not want to induce hypotension by potentially worsening α-blockade. Her tachycardia seemed out of proportion to any of the above mechanisms alone. Paliperidone has no reported affinity for the β-1 or β-2 adrenergic receptors, but it is possible that there is direct cardiac chronotropic effect or a yet-to-be elucidated mechanism (2). Interestingly, although tachycardia has been reported with risperidone overdoses, it is nowhere near as profound as is seen in the reports of paliperidone-associated tachycardia (3–5). Although it is possible that there was another substance involved, the history was reliable, with pill identification and a phone call to the pharmacy both confirming the error; as such, neither a urine drug screen nor a paliperidone level was performed due to the established error. Additional testing was felt unlikely to change management.

WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?

Paliperidone toxicity in children may result in prolonged, delayed tachycardia from unclear, likely multifactorial mechanisms. Clinicians should consider a conservative approach, such as prolonged observation in paliperidone ingestions in children younger than 12 years of age due to limited clinical data.

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