Paliperidone Overdose With Delayed Onset of Toxicity

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Paliperidone, or 9-hydroxy risperidone, is the newest atypical antipsychotic agent to be approved for use by the Food and Drug Administration. Despite being the primary active metabolite of risperidone, paliperidone differs in several ways from risperidone. The most notable difference is that paliperidone is formulated as an extended-release product. We present a case of a 14-year-old, 59-kg girl with a history of psychosis and major depressive disorder who developed toxicity after an ingestion of 180 mg (3.1 mg/kg) of paliperidone. This case is not only one of the first cases of paliperidone overdose described in the literature but also is unique in that it describes delayed onset of toxicity, as well as extended duration of symptoms. [Ann Emerg Med. 2011;58:80-82.]

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INTRODUCTION

In December 2006, paliperidone (9-hydroxy risperidone) became the newest atypical antipsychotic to be approved by the Food and Drug Administration. Although it has approval for treatment of schizophrenia and schizoaffective disorder,[1] off-label uses include management of psychosis and bipolar disorder. Since its release, the number of prescriptions for paliperidone has steadily increased annually.[2]

Risperidone, an atypical antipsychotic, requires metabolism through CYP2D6 to the active metabolite 9-hydroxyrisperidone.[3] Patients who are slow metabolizers of 2D6 because of genetic polymorphisms may experience impaired effectiveness of risperidone. Because paliperidone is the active metabolite of risperidone, impaired 2D6 metabolism is not likely to result in altered pharmacokinetic properties of paliperidone.[3] Like risperidone, paliperidone is primarily metabolized to inactive metabolites and then renally excreted.[4]

Paliperidone has a unique delivery system. The tablet is composed of a trilayer core with 2 drug layers and an osmotic layer to facilitate staged drug delivery.[5,6] This 3-layer model is designed to result in a steady release of drug during a 24-hour period.[6]

CASE REPORT

A 14-year-old, 59-kg girl presented to the emergency department (ED) 1 hour after ingestion of 180 mg of extended-release paliperidone in a suicide attempt. The patient's medical history was notable for major depressive disorder and "psychosis not otherwise specified." She had multiple previous suicide attempts and was most recently discharged from an inpatient psychiatric hospitalization 1 month before. After that most recent psychiatric admission, she was supposed to begin receiving venlafaxine 75 mg daily and paliperidone 6 mg daily. However, she had not been compliant with any of her medications. Specifically, she indicated that she had not begun receiving the venlafaxine and specifically denied ingesting any of the venlafaxine as part of the overdose. She also denied consuming any illicit drugs of abuse. The only other notable medical history was for a benign heart murmur as a child. She denied any history of tobacco, ethanol, or illicit drug consumption.

The patient presented to the ED, where her blood pressure was 130/72 mm Hg, with a pulse rate of 119 beats/min. She was afebrile. Her examination result was notable for mild tachycardia but was otherwise asymptomatic. Specifically, she remained awake and alert without evidence of sedation.

Laboratory studies in the ED revealed a normal CBC count, electrolyte levels, and hepatic functions. Her serum bicarbonate level was 24 mmol/L, with an anion gap of 9. A urine pregnancy test result was negative. A 12-lead ECG revealed mild tachycardia, with a pulse rate of 100 beats/min and normal intervals (Figure, *A*). Serum acetaminophen and salicylate concentrations were nondetectable, and a urine drug screen result for drugs of abuse was negative. The patient remained in the ED for nearly 20 hours postingestion while awaiting an inpatient psychiatric bed. The initial tachycardia resolved 5 hours postingestion. The patient fell asleep, and her pulse rate stayed between 80 and 90 beats/min until approximately 20 hours postingestion, at which time tachycardia developed.

The patient was placed in an ambulance for transfer to an inpatient psychiatric hospital. On arrival at the psychiatric facility, she was observed to have a pulse rate of 130 beats/min, prompting her to return to the initial ED. On return to the ED, the patient was tachycardic, with a pulse rate of 120 beats/min and a blood pressure of 114/61 mm Hg. She remained relatively asymptomatic for the next several hours. Repeated chemistry study results were essentially unchanged, and thyroid study results were normal. Six and a half hours after returning to the

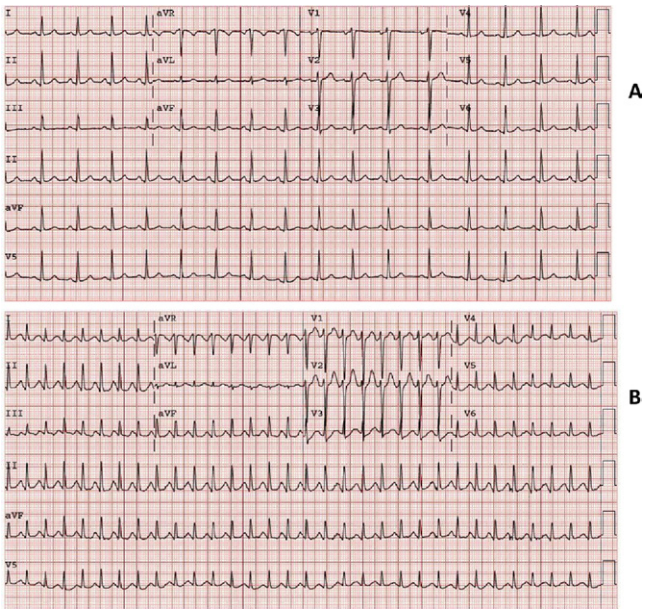

Figure. Initial and delayed ECG results after paliperidone overdose.

ED (26.5 hours postingestion), the patient stood up and developed a narrow complex tachycardia at 190 beats/min (Figure, *B*). She received 6 mg of adenosine, followed by 12 mg of adenosine, without any immediate change in her symptoms. She also received 1 L of normal saline solution. The pulse rate gradually decreased to 120 beats/min during the next 30 minutes. She was ultimately transferred to a pediatric ICU. On arrival in the ICU, she was lightheaded with positional changes. Her examination result was notable for tachycardia without any murmurs or rubs. Her pupils were 3 mm and reactive bilaterally. No lower-extremity rigidity or clonus was observed. She was fully oriented and had a nonfocal neurologic examination result. No hyperreflexia was appreciated. An echocardiogram was obtained and the result was normal. Comprehensive urine drug testing by gas chromatography/mass spectrometry, which was obtained on her arrival in the pediatric ICU, revealed only the presence of 9-hydroxyrisperidone. No venlafaxine was detected. A serum paliperidone concentration result obtained 40.5 hours postingestion was 170 ng/mL (therapeutic 4.8 to 16.5 ng/mL).

Thirty-nine hours postingestion, orthostatic vital signs were again obtained, and the patient developed a narrow complex tachycardia, with a pulse rate of 190 beats/min. At this time, her blood pressure was 97/44 mm Hg and she experienced lightheadedness. Mild tachycardia persisted for nearly 90 hours postingestion. She remained lightheaded with positional changes for the first 2 days in the hospital. Throughout her hospitalization, she received supportive care, including intravenous fluids, but did not receive any specific antidotal therapy. She was medically cleared after her symptoms and tachycardia had resolved and was ultimately transferred back to inpatient psychiatry, without any long-term sequelae.

DISCUSSION

Owing to its exclusive delivery system, a gradual release of paliperidone is achieved during a 24-hour period.[6] After administration of a single tablet of paliperidone, the maximal serum concentration is achieved after 25 hours. A steady-state serum concentration is achieved after 4 to 5 days.[4] Paliperidone is metabolized to several inactive metabolites, although the majority of the drug is excreted unchanged in the urine.[4]

The typical dosing of paliperidone for adults with schizophrenia or schizoaffective disorder is 6 mg per day. This dose can be increased in increments of 3 mg per day until a maximal daily dose of 12 mg per day is reached. Because the drug is not recommended for patients younger than 18 years, no pediatric dosing ranges are available.[1] Paliperidone is an antagonist of the dopamine 2, serotonin 2a, histamine 1, and α_1 and α_2 receptors.[4,7] At therapeutic dosing, there is no affinity for the β-receptors and virtually no affinity at the Muscuranic 1 receptor.[7] Antagonism of the serotonin 2a and dopamine 2 receptors is responsible for the therapeutic effects on the negative and positive symptoms of schizophrenia, respectively. Antagonism of the dopamine 2 receptors can also lead to extrapyramidal symptoms, however. Antagonism of the histamine 1 receptors results in sedation, whereas antagonism of the α_1 receptor results in orthostasis and reflex tachycardia.[8]

In several studies, tachycardia was one of the most common adverse events observed.[9,10] Boom et al[11] examined the pharmacodynamic effects of various dosing regimens of paliperidone. After administration of a single dose of 15 mg of paliperidone, the mean pulse rate increased by 22 beats/min, and the maximal mean pulse rate occurred nearly 36 hours postingestion. In this case report, the patient's initial pulse rate was mildly tachycardic, at 119 beats/min, but this had resolved within 4 hours of admission to the ED (5 hours postingestion). Further tachycardia was not observed while the patient was waiting for an inpatient psychiatry bed but again was observed nearly 20 hours postingestion. The patient did not ambulate while in the ED on her first visit. Some of the tachycardia observed on her arrival at the psychiatric hospital may have been related to positional changes. However, given that the tachycardia was sustained and not only associated with positional changes, it is unlikely that the tachycardia observed was strictly due to the α-1 antagonism with resultant orthostasis. As such, the primary reason for the delayed onset of the tachycardia was likely due to the delayed absorption of the drug, which was a result of paliperidone's delivery matrix.

With positional changes, the pulse rate did increase to greater than 180 beats/min. The gradual decrease to approximately 130 beats/min, along with the lack of response to adenosine, led the pediatric cardiologists to determine that both the marked increase in pulse rate and the underlying tachycardia were sinus in origin. Although the abrupt increase in pulse rate to approximately 190 beats/min was likely partially reflex tachycardia caused by positional changes, the underlying tachycardia was not due to orthostasis. Although there is no

affinity for the M1 receptor in therapeutic dosing, we hypothesize that there may be some M1 receptor antagonism in the overdose setting.

To our knowledge, there has been only 1 case of paliperidone overdose published since its approval.[12] In that case, the patient ingested 81 mg during a 3-day span. The patient was mildly tachycardic and hypertensive but was relatively asymptomatic. In that report, the patient's weight was not published, but this case probably involved substantially more drug on a milligram-per-kilogram basis. Furthermore, unlike the case by Chang et al,[12] this case involves a single acute ingestion rather than a subacute overdose. Thus, to our knowledge, this is the first true acute overdose reported with paliperidone.

The patient never received any form of gastrointestinal decontamination. Specifically, she did not receive any activated charcoal. It is possible that if she had received charcoal, decreased absorption would have occurred. However, we believe it is unlikely that enough drug would have been absorbed to significantly alter the course of events that transpired.

This patient remained relatively asymptomatic for nearly 24 hours before symptomatic toxicity developed. The drug's delivery matrix likely contributed to the delayed onset of symptoms and extended duration of symptoms. According to the limited experience with overdose, along with the findings in this case, it may be prudent to recommend prolonged observation after overdose of paliperidone.

Paliperidone, 9-hydroxyrisperidone, is the active metabolite of risperidone. A case of a 14-year-old girl who ingested 180 mg is presented. Owing to its unique design of the tablet, this patient experienced both a delayed onset of toxicity and sustained toxicity. The patient made a full recovery, with no long-term sequelae.

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REFERENCES

1. Invega extended release oral tablets, paliperidone extended-release oral tablets [package insert]. Titusville, NJ: Janssen; 2009.
2. Governale L, Mehta H. Outpatient use of atypical antipsychotic agents in the pediatric population years 2004-2008. Food and Drug Administration Web site. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM193204.pdf. Accessed October 8, 2010.
3. de Leon J, Wynn G, Sandson NB. The pharmacokinetics of paliperidone versus risperidone. *Psychosomatics*. 2010;51:80-88.
4. Yang PL, Plosker GL. Paliperidone extended release. *CNS Drugs*. 2007;21:417-425.
5. Hussar DA. New drugs: paliperidone, dasatinib, and decitabine. *J Am Pharm Assoc*. 2007;47:298-302.
6. Dlugosz H, Nasrallah HA. Paliperidone: a new extended-release oral atypical antipsychotic. *Expert Opin Pharmacother*. 2007;8:2307-2313.
7. Dolder C, Nelson M, Deyo Z. Paliperidone for schizophrenia. *Am J Health Syst Pharm*. 2008;65:403-413.
8. Richelson E. Receptor pharmacology of neuroleptics: relation to clinical effects. *J Clin Psychiatry*. 1999;60(suppl 10):5-14.
9. Kramer M, Simpson G, Maciulis V, et al. Paliperidone extended-release tablets for prevention of symptom recurrence in patients with schizophrenia: a randomized, double-blind, placebo-controlled study. *J Clin Psychopharmaol*. 2007;27:6-14.
10. Tzimos A, Samokhvalov V, Kramer M, et al. Safety and tolerability of oral paliperidone extended-release tablets in elderly patients with schizophrenia: a double-blind, placebo-controlled study with six-month open-label extension. *Am J Geriatr Psychiatry*. 2008;16:31-43.
11. Boom S, Talluri K, Janssens L, et al. Single and multiple dose pharmacokinetics and dose proportionality of the psychotropic agents paliperidone extended release. *J Clin Pharmacol*. 2009;49:1318-1327.
12. Chang JP, Huang CC, Su KP. Paliperidone overdose in a patient with schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010;34:418.