

Non-Fatal Paliperidone Overdose: A Case Report.

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Abstract

Paliperidone, a novel serotonin and dopamine antagonist, is one of the newest atypical antipsychotics on the market. It is an orally administered drug that is indicated for the treatment of schizophrenia, and is considered to be safe and well tolerated. A 37-year-old female with a long-standing history of schizophrenia had been taking paliperidone 12 mg d⁻¹ for about 1.5 years. She overdosed on a total of 756 mg of paliperidone in response to auditory command hallucinations. She was promptly hospitalized, and fortunately did not suffer any major adverse clinical events, adverse laboratory parameters, or long lasting sequelae. Herein we discuss the inherent characteristics of paliperidone that limit the danger associated with overdosing.

Key Words: Paliperidone; overdose; side effects.

INTRODUCTION

Paliperidone, the active metabolite of risperidone, is one of the newest atypical antipsychotics on the market. It is indicated for the treatment of schizophrenia, and has been shown to improve both positive and negative symptoms in controlled clinical trials. Its therapeutic activity is thought to be mediated through a combination of central dopamine type-2 (D₂) and serotonin type-2 (5HT_{2A}) receptor antagonism. It also antagonizes both adrenergic and histaminergic receptors, which may explain some of its known side effects. In clinical trials side effects that were reported in more than 2% of subjects included tachycardia, abdominal pain, nausea, dry mouth, extrapyramidal symptoms, dizziness, somnolence, and anxiety. Oral paliperidone utilizes the osmotic-controlled release oral delivery system, making it a long-acting drug with a half-life of 23 h. As it is the active metabolite of risperidone (9-hydroxy-risperidone), it is unique in that it is minimally metabolized in the liver and is excreted largely unchanged. This makes it relatively safe for use in patients with mild to moderate hepatic impairment (Invega Product Monograph, 2009).

Herein we report a female schizophrenic patient that overdosed on 756 mg of paliperidone and experienced no severe adverse sequelae. A review of the literature revealed only 1 previous report of paliperidone overdose; however, that case overdosed on 81 mg of paliperidone over a 3-day period (Chang et al., 2010). To the best of our knowledge the presented case is the highest paliperidone overdose reported to date.

CASE

A 37-year-old female overdosed on paliperidone in response to auditory command hallucinations. She was diagnosed with schizophrenia at the age of 20 years and had used several antipsychotics in the past. She had 4 previous hospitalizations due to exacerbation of her illness; the last occurred 3 years earlier. Although she had expressed suicidal ideation in the past, there was no history of suicidal attempts or overdose. About 18 months before she presented her medication was changed from trifluoperazine to paliperidone due to persistent symptoms. She was started on paliperidone 6 mg d⁻¹ and the dose was gradually increased to 12 mg d⁻¹. She was stable

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on this dose, except for occasional hallucinations that occurred once or twice a month. She did not exhibit or report suicidal ideation during this period.

On the day of admission she heard voices commanding her to kill herself. She then ingested all of the paliperidone capsules she had stored in her kitchen. She then informed her family about what she had done, and they subsequently discovered the empty strips of paliperidone that amounted to 126 capsules (6 mg). She was brought to the emergency department 4 h after ingesting the capsules. She was fully alert with stable vital signs (blood pressure: 113/73 mmHg; heart rate: 91 beats min^{-1} ; respiratory rate: 20 breaths min^{-1}). Electrocardiography showed a normal sinus rhythm with no QT prolongation.

Gastric lavage was performed and she was then administered activated charcoal. Blood investigations on admission (blood gases, blood counts, renal function, liver function, creatinine kinase) were all within normal limits. Repeated electrocardiograms and blood investigations over the following week were also normal. Upon admission to the medical ward her vital signs remained stable, except for mild tachycardia during the second 24 h (heart rate fluctuated between 100 and 110 beats min^{-1}). Abnormal rhythms were not noted and her heart rate returned to normal by the third day. The only complaint she had was mild to moderate dizziness during the first 2 days; however, her blood pressure, while both supine and standing remained stable. She was then transferred to the psychiatric ward and discharged in good condition with no physical sequelae 1 week later.

DISCUSSION

We presented a non-fatal paliperidone overdose case with no long-term or serious sequelae. To the best of our knowledge this is the first reported case of overdose due to a high dose of paliperidone. Due to the lack of data on paliperidone overdose, a literature review on risperidone overdose was conducted. As risperidone is the "parent drug" of paliperidone, it may provide some idea of what to expect in cases of paliperidone overdose. Risperidone over-dosage has been associated with drowsiness, sedation, tachycardia, hypotension, seizures, extrapyramidal symptoms, hypokalemia, hyponatremia, prolonged QTc, and occasionally death (Springfield and Bodiford, 1996; Keck and McElroy, 2002).

The presented case suffered only minor adverse events despite overdosing on a very high dose of paliperidone. Her elevated heart rate, and possibly headache

may have been due to blockade of alpha-2 adrenergic receptors (Schotte et al., 1996). Several factors could have contributed to this patient's good outcome. Firstly, the relatively short time her relatives took to bring her in for treatment was a contributing factor. Oral paliperidone utilizes the osmotic-controlled release oral delivery system, which gradually releases the drug over a 24-h period. This slow release would allow gastric lavage or the administration of charcoal to remove most of the active drug before it reaches the circulation. In the presented case gastric lavage was performed about 4 h after the ingestion of paliperidone. Laxatives, though not administered to this patient, would have also been beneficial. Secondly, the slow release probably minimized the peak drug concentration level in the blood, unlike fast-acting drugs with which one can expect a sudden surge in serum levels. Thirdly, minimal involvement of the liver in the metabolism of paliperidone reduced the risk of liver damage due to overdose. Another factor is the possibility of anticholinergic-mediated delayed gastric emptying. This might have minimized the amount of drug entering the circulation. Although both paliperidone and risperidone are said to have negligible muscarinic blockade, there have been reports of anticholinergic side effects with risperidone (Kennedy et al., 2000).

Did paliperidone play a role in the presented patient's impulsive act or her command hallucinations? Being a relatively new drug, there are no data on the role of paliperidone in impulsivity; however, risperidone has been shown to reduce impulsive behavior (Rocca, 2002; Saxena et al., 2006). Though it is well established that both paliperidone and risperidone reduce hallucinations, no studies have looked at their role in command hallucinations. Nevertheless, it is unlikely that paliperidone had propagated the impulsive behavior or command hallucinations in our patient. If anything, paliperidone would have protected her against such symptoms.

The presented case's outcome was good, with only mild tachycardia that lasted 1 day and self-limiting giddiness. Does this case illustrate that paliperidone, due to its unique properties and novel mechanism of delivery, minimize the risks associated with overdosing? It is probably too early to conclude, as only time and further clinical experience and evidence can help us determine if paliperidone can be recommended as an option for patients in whom suicidality or over-dosage is a concern. Yet, it is also important to realize that the toxicity of atypical antipsychotics is variable and not always dose dependant (Trenton et al., 2003); therefore, one should always be concerned and cautious with every overdose

case, regardless of the amount of drugs taken. We do recognize the possibility that because the presented case was actively psychotic she could have claimed to have overdosed when she really had not done so. Clinicians should always err on the side caution when overdose may

be a possibility. In conclusion, the presented case illustrates the importance of timely intervention in cases of over-dosage, and the possibility that paliperidone may be a safer option in patients with a high risk of overdosing themselves.

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