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Case report

Safety and tolerability of PaliperidonePalmitate: a case report of an accidental overdose

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SUMMARY

Paliperidone is a second-generation antipsychotic used in the treatment of Schizophrenia. It is also available as Paliperidone Palmitate (PP), a long-acting injection that can be administered monthly (PP1M) or every 3 months (PP3M). To our knowledge, only one case of PP accidental overdose has been described in Literature. We report a 55-year-old male who accidentally received a cumulative dose of 200 mg of PP within 5 days. The mistake was promptly recognized and this allowed a careful follow-up over the following hours and days. Clinical evaluation, supported by blood and instrumental tests, showed no medical consequences and the patient never complained of side effects. No additional therapy was required. Our experience, supported by data from the literature, suggests that PP is generally well tolerated and safe. However, a close clinical follow-up during the hours and days following an accidental overdose is recommended.

Key words: paliperidone palmitate, accidental overdose, long-acting injectables, case report

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Conflict of interest
The Authors declare no conflict of interest

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Introduction

Since the end of last century, a new class of antipsychotic drugs named atypical or second-generation antipsychotics (SGAs) was launched on the market: these molecules represent the first choice in the treatment of Schizophrenia, given their efficacy and tolerability. This led to the development, for some of the SGAs, of depot formulations called Long-Acting Injectables (LAIs). Currently, SGAs available in a LAI formulation are Risperidone, Olanzapine, Aripiprazole and Paliperidone. Paliperidone Palmitate (PP) is the only LAI available both in monthly (PP1M) and 3-monthly (PPM3) injection. This paper consists in a case report of PP1M accidental overdose: to our knowledge, such occurrence is reported only once in scientific literature [1]. We followed the CARE guidelines [2] in writing this case report.

Case summary

The patient is a 55-year-old Italian male. He has been under the care of our mental health services since 2019. He initially received a diagnosis of Schizophreniform disorder and Antisocial personality disorder. After 6 months of clinical observation by our team, he met criteria for Schizophrenia. He does not have any medical comorbidities and he does not take any medications other than the prescribed psychiatric therapy. His clinical condition is characterized by positive symptoms (auditory hallucinations) that have been stable for several years. He also complains of low mood and a tendency to experience irritability and anger. His psychiatric history is characterized by severe impulsive behaviour, with episodes of harm toward himself as well as others. The patient was referred to our mental health services after being treated for several years in a psychiatric facility

of another Italian Region, where he was given Haloperidol Decanoate 75 mg monthly and Biperiden hydrochloride. During the first contact with our service, he complained of sexual side effects and lower limb tremors, asking to be switched to a different medication. For that reason, the patient was given oral Paliperidone that was well tolerated; he was then switched to PP1M. After he was given the first 150 mg injection and a second 100 mg injection 7 days later, he was put on a 4-week schedule of 75 mg of PP for 6 months. During this time the patient showed a good response to medication and maintained stable psychiatric conditions. After the outbreak of the COVID-19 crisis and the enactment of restrictive measures across Italy, the patient complained of irritability and severe anxiety. Therefore he was given an adjunctive anxiolytic intramuscular therapy (delorazepam) and, in correspondence of the seventh-month injection, the psychiatrist made the decision to increase PP dose to 100 mg monthly. Five days later the patient visited our mental health center again, asking to be given adjunctive anxiolytic therapy. However, due to a mistake in the interpretation of the prescription order, he was given a 100 mg injection of PP instead. The mistake was promptly recognized and this allowed a careful follow-up: the patient was rapidly evaluated by a physician that performed a complete physical examination and, in the following hours, he was periodically evaluated by a nurse who took vital signs resulting within the normal range all time. The psychiatrist requested an ECG registration with QTc measurement that was performed on the day following the accidental overdose, resulting in a normal trace and a QTc interval of 425 milliseconds. Moreover, a complete blood count, an electrolyte, liver and renal panel were performed. Results were all within range with the exception of a finding of microcytic anemia, unlikely linked to the accidental overdose. Clinical conditions were monitored on a daily basis through visits conducted both in person and by telephone. The patient never reported any side effect and denied to experience symptoms such as stiffness, anxiety or agitation. The psychiatrist administered a new PP injection 4 weeks after the accidental overdose.

Discussion

Paliperidone (9-hydroxyrisperidone) is an active metabolite of Risperidone and it is an antagonist at D2 and 5HT2A receptors, as well as antagonist at α1, α2 and H1 receptors. This pharmacodynamic profile explains the potential occurrence of side effects such as orthostatic hypotension, weight gain and sedation, although to a lesser degree compared to Risperidone [3]. Moreover, Paliperidone has a lower propensity to cause anticholinergic adverse effects and cognitive impairment because of the absence of antagonistic activity at cholinergic receptors [4]. Paliperidone is largely eliminated unchanged in urines. Cytochromes CYP2D6 and CYP3A4 do not seem to play a relevant role in the metabolism of Paliperidone in vivo [4,5]. From a clinical point of view, this translates into a low risk of drug-drug interactions.

PP formulation consists in nanocrystal molecules in an aqueous suspension that allows a slow dissolution after intramuscular injection: molecules are then hydrolyzed to Paliperidone and absorbed into the systemic circulation [6]. After a single dose, median time to reach C_{max} ranges from 13 to 17 days. The release of the active principle starts from day 1 and lasts for at least 4 months, while the median apparent half-life ranges from 25 to 49 days [7-9].

PP most frequent side effects include insomnia, headache, dizziness, sedation, agitation, weight gain, tachycardia and extrapyramidal symptoms. Among these, akathisia and sedation/somnolence seem to be related to dose [4,7]. Although several cases of Paliperidone overdose are described in Literature, reporting consequences such as dystonia, acute renal failure, akathisia, and tachycardia [10,11], there is only one PP overdose case description that reports no relevant consequences [1]. Moreover, several clinical studies showed that PP is a safe treatment even when used in high doses [9,12,13], in addition to resulting well-tolerated and with low rates of discontinuation, mostly due to weight gain and increase in prolactin levels [14].

This case report provides further evidence on the safety of PP, as no clinical consequences resulted in the administration of a total dose of 200 mg of PP within 5 days, requiring no additional or specific therapy. Specifically, we found no ECG alterations nor QT prolongation. However, we acknowledge some limitations to our case report. Firstly, compared to the other PP overdose case report [1], the cumulative PP dose was lower and much closer to therapeutic dosages, so the fact we didn't find any clinical consequences could be expected, but not certain. Secondly, although the patient did not refer any symptoms ascribed to hyperprolactinemia, an evaluation of prolactin levels would have been useful. Unfortunately, the concurrent COVID-19 health crisis did not permit more tests than the ones already performed.

Conclusions

Our experience, supported by data from Literature, suggests that PP is generally well tolerated and safe, especially when used as monotherapy. However, as in some cases Paliperidone side effects can be fatal, a close clinical follow-up during the hours and days following an accidental overdose is recommended.

Consent

Oral informed consent was obtained from the patient for publication of this case report.

References

1. Ojimba C, Oyelakin A, Khandaker T. Accidental overdose of paliperidone palmitate. Case Rep Psych 2019:10-2. https://doi.org/10.1155/2019/7406298
2. Gagnier JJ, Kienle G, Altman DG, et al. The CARE guidelines: consensus-based clinical case reporting guideline development. J Med Case Rep 2013;7:223. https://doi.org/10.1111/head.12246
3. Stahl SM. Stahl's essential psychopharmacology neuroscientific basis and practical applications (4th ed.). Cambridge: Cambridge University Press 2013.
4. Bishara D. Once-monthly paliperidone injection for the treatment of schizophrenia. Neuropsych Dis Treat 2010;561. https://doi.org/10.2147/ndt.s8505
5. Yasui-Furukori N, Hidestrand M, Spina E, et al. Different enantioselective 9-hydroxylation of risperidone by the two human CYP2D6 and CYP3A4 Enzymes. Drug Metabol Dispos 2001;29:263-1268.
6. Chue P, Chue J. A review of paliperidone palmitate. Exp Rev Neurotherap 2012;12:1383-97. https://doi.org/10.1586/ern.12.137
7. AIFA. Allegato i riassunto delle caratteristiche del prodotto, Xeplion, 2018. https://doi.org/10.1111/j.1744-6570.1985.tb00563.x
8. Emsley R, Kilian S. Efficacy and safety profile of paliperidone palmitate injections in the management of patients with schizophrenia: an evidence-based review. Neuropsych Dis Treat 2018;14:205-23. https://doi.org/10.2147/NDT.S139633
9. Pandina GJ, Lindenmayer JP, Lull J, et al. A randomized, placebo-controlled study to assess the efficacy and safety of 3 doses of paliperidone palmitate in adults with acutely exacerbated schizophrenia. J Clin Psychopharmacol 2010;30:235-44. https://doi.org/10.1097/JCP.0b013e3181dd3103
10. Liang CS, Bai YM, Liou YJ, et al. Acute renal failure after paliperidone overdose: a case report. J Clin Psychopharmacol 2012;32:128. https://doi.org/10.1097/JCP.0b013e31823f9101
11. Wong LY, Greene SL, Odell M, et al. Severe prolonged posture-evoked tachycardia after massive overdose of paliperidone. Clin Toxicol 2016;54:535. https://doi.org/10.3109/15563650.2016.1169283
12. Citrome L. Paliperidone palmitate – review of the efficacy, safety and cost of a new second-generation depot antipsychotic medication. International J Clin Pract 2010;64:216-39. https://doi.org/10.1111/j.1742-1241.2009.02240.x
13. Fernández-Miranda JJ, Díaz-Fernández S. Tolerability of effective high doses of paliperidone palmitate in patients with severe resistant schizophrenia. Int Clin Psychopharmacol 2017;32:6-12. https://doi.org/10.1097/YIC.0000000000000151
14. McEvoy JP, Byerly M, Hamer RM, et al. Effectiveness of paliperidone palmitate vs haloperidol decanoate for maintenance treatment of schizophrenia: a randomized clinical trial. Bone 2014;311:1978-87. https://doi.org/10.1001/jama.2014.4310