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Delayed torsades de pointes after massive risperidone overdose with rising paliperidone concentrations: a case report

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Case Report

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Abstract

Background

Risperidone is an atypical antipsychotic associated with QT interval prolongation; however, torsades de pointes (TdP) following overdose is extremely rare. The contribution of its active metabolite, paliperidone, to severe cardiac toxicity is unclear.

Case presentation

A woman in her 40s with schizophrenia was admitted after self-inflicted abdominal stab wounds and a massive risperidone overdose. Following emergency laparotomy and massive transfusion, her condition initially stabilized. Nine and a half hours after admission, she developed TdP requiring cardiopulmonary resuscitation. Recurrent non-sustained ventricular tachycardia and QTc prolongation (517 ms) were subsequently managed with intravenous magnesium sulfate and overdrive pacing. Further investigation revealed ingestion of more than 700 mg of risperidone. Serial serum analyses demonstrated an admission risperidone concentration of 1,185.86 ng/mL. At the onset of TdP, risperidone concentrations were declining, whereas paliperidone concentrations continued to increase and peaked.

Conclusion

The delayed rise in paliperidone concentrations may have contributed to the development of TdP despite declining risperidone concentrations. The risperidone concentration at admission was extraordinarily high and, to our knowledge, among the highest reported in surviving cases of risperidone intoxication. Although postoperative physiological changes and hemorrhagic stress may have influenced pharmacokinetics, this case suggests that accumulation of the active metabolite may contribute to severe cardiac toxicity following massive risperidone overdose. Prolonged cardiac monitoring and early intervention, including magnesium sulfate administration and overdrive pacing, should be considered even after initial clinical stabilization.

1. Introduction

Risperidone, an atypical antipsychotic, effectively treats both the positive and negative symptoms of schizophrenia. It is primarily metabolized in the liver by the cytochrome P450 enzyme CYP2D6 to its active metabolite, 9-hydroxyrisperidone (paliperidone). Paliperidone possesses pharmacological properties similar to those of risperidone and is clinically available under the trade name Invega. Both agents exert their therapeutic effects through combined antagonism of serotonin 5-HT2 and dopamine D2 receptors [1].

Risperidone is an antipsychotic associated with QT interval prolongation. It inhibits the rapid component of the delayed rectifier potassium current. However, QT prolongation is uncommon even after overdose [2], and severe ventricular dysrhythmias, such as torsades de pointes (TdP), are considered exceedingly rare. Consequently, some authors have suggested that the arrhythmogenic risk associated with

risperidone may be overstated [3]. Furthermore, QT prolongation observed following risperidone overdose correlates more strongly with tachycardia than with dose, suggesting that it may not necessarily confer an increased risk of TdP [4].

The present case describes delayed-onset TdP following massive risperidone overdose and provides serial measurements of serum risperidone and paliperidone concentrations throughout the clinical course. Although traumatic injury and perioperative physiological stress may have contributed to the development of TdP in this patient, reports of TdP following isolated risperidone or paliperidone overdose remain exceptionally rare. Moreover, detailed evaluations of the temporal relationship between serum risperidone and paliperidone concentrations and the development of cardiac toxicity in severe intoxication are limited.

2. Case presentation

A woman in her 40s with schizophrenia collapsed in the bathroom of her home with three stab wounds to the abdomen. Empty blister packs of risperidone 1-mg tablets (40 tablets) and a kitchen knife were found at the scene. Upon evaluation by emergency medical services, she was hypotensive, with a blood pressure of 70/40 mmHg, and tachycardic, with a heart rate of 120 beats/min. After arrival at the emergency department, she underwent endotracheal intubation, massive transfusion (six units of packed red blood cells and 10 units of fresh frozen plasma), and emergency laparotomy for hemostasis.

Intraoperative findings revealed injuries to the left inferior epigastric artery and vein, omentum, and right ovary, with an estimated blood loss of approximately 1.5 L. Her vital signs stabilized following surgical hemostasis. Laboratory testing demonstrated anemia, with a hemoglobin level of 8.1 g/dL, whereas electrolyte levels and other laboratory findings were unremarkable. A 12-lead electrocardiogram obtained on admission after surgery showed mild QTc prolongation (427 ms; Fig. 1). Continuous low-dose infusions of fentanyl and midazolam were administered for perioperative management. Throughout this period, acid–base status, electrolyte levels, and body temperature remained within normal ranges.

Nine and a half hours after admission, she developed TdP, which required cardiopulmonary resuscitation and administration of 1 mg of epinephrine, resulting in return of spontaneous circulation. Because non-sustained ventricular tachycardia recurred intermittently and the QTc interval further prolonged to 517 ms from 427 ms on admission (Fig. 2), intravenous magnesium sulfate (20 mEq) was administered, and a temporary transvenous pacemaker was inserted for overdrive pacing (Fig. 3). Her hemodynamic status gradually stabilized thereafter.

Subsequent investigation by the family revealed additional empty blister packs, confirming ingestion of more than 700 mg of risperidone rather than the initially suspected 40 mg. No other empty medication packages were identified. After regaining consciousness, the patient reported the ingestion of all risperidone tablets at once, although the exact time of ingestion remained unclear.

Because massive risperidone ingestion was subsequently confirmed, activated charcoal was administered 16 hours after admission. Overdrive pacing was discontinued on hospital day 3. Her mental status gradually improved by hospital day 4; she was extubated on hospital day 6, and was transferred to another psychiatric hospital on hospital day 16.

Serum concentrations of risperidone and its active metabolite, paliperidone, were measured using liquid chromatography–tandem mass spectrometry. On admission, serum risperidone and paliperidone concentrations were 1,185.86 ng/mL and 987.80 ng/mL, respectively. At TdP onset, the risperidone concentration had decreased to 683.05 ng/mL, whereas the paliperidone concentration had peaked at 1,320.83 ng/mL. Elimination half-lives of risperidone and paliperidone were 10.38 hours and 22.97 hours, respectively, with prolongation observed only for risperidone (Fig. 3). Elimination half-lives were calculated by plotting all serum concentrations obtained after the maximum observed concentration (initial concentration for risperidone) on a logarithmic scale, determining the elimination rate constant from the slope of the regression line, and converting it to the corresponding half-life.

3. Discussion

In the present case, delayed-onset TdP developed approximately 10 hours after ingestion of an extremely large dose of risperidone (approximately 700 mg), despite the reported elimination half-life of risperidone being approximately 4 hours. Serum risperidone concentration on admission was markedly elevated at 1,185.86 ng/mL (therapeutic reference range, 20–60 ng/mL [5]). Even after accounting for the potential dilutional effects of hemorrhage and massive transfusion, this concentration was among the highest reported in surviving cases of risperidone intoxication.

During clinical deterioration, the risperidone concentration was decreasing, whereas the concentration of its active metabolite, paliperidone, continued to increase. Because paliperidone has pharmacological activity comparable to that of risperidone [1, 6], the delayed increase in paliperidone concentration may have contributed to the development of TdP. To our knowledge, no previous reports have described a severe risperidone overdose with a clinical course similar to that observed in the present case. Furthermore, no reports have simultaneously evaluated serial serum concentrations of both risperidone and paliperidone.

The patient’s postoperative physiological condition, including hemorrhage, inflammation, stress responses, altered vascular permeability, and the effects of fluid resuscitation and blood transfusion, may have influenced the pharmacokinetics observed in this case. Therefore, definitive conclusions cannot be drawn from a single case. Nevertheless, in cases of massive risperidone overdose, delayed accumulation of paliperidone in addition to persistently elevated risperidone concentrations may contribute to severe toxicity and life-threatening dysrhythmias. Further reports incorporating detailed pharmacokinetic analyses are needed.

In this case, the elimination half-life of risperidone was prolonged, whereas that of paliperidone was not. Risperidone metabolism is influenced by CYP2D6 genetic polymorphisms, drug interactions, and renal

function, whereas paliperidone pharmacokinetics may also be affected by enzyme inducers and renal impairment [1, 5, 7]. Approximately 7% of White individuals are estimated to be poor metabolizers of CYP2D6 po [5]. In this case, no concomitant CYP2D6 inhibitors were identified, and renal dysfunction was absent. Therefore, saturation of CYP2D6-mediated metabolism or an underlying poor-metabolizer phenotype may have contributed to the prolonged elimination of risperidone. Delayed gastrointestinal absorption related to the extremely large ingestion and postoperative gastrointestinal dysfunction may have been involved. This case demonstrates that marked pharmacokinetic alterations following massive risperidone overdose may result in delayed life-threatening dysrhythmias, highlighting the need for prolonged and careful cardiac monitoring even after initial clinical stabilization.

In this case, intravenous magnesium sulfate and overdrive pacing were used to prevent recurrence of TdP and to stabilize hemodynamic status. The effectiveness of magnesium sulfate and overdrive pacing in the management of drug-induced QT prolongation and TdP has been documented [8, 9]; these interventions were therefore considered appropriate treatment strategies in this case.

In general, progression from QT prolongation to TdP is associated with several predisposing factors, including electrolyte abnormalities such as hypokalemia, hypothermia, bradycardia, underlying cardiac disease, and concomitant use of QT-prolonging medications [2, 10]. In addition to these factors, the risk of TdP may be further increased in cases such as the present one, in which massive overdose and delayed drug metabolism lead to progressive QT prolongation. Therefore, for patients with severe risperidone intoxication, strict cardiac monitoring and early intervention, including magnesium sulfate administration and overdrive pacing, may be important for both the prevention and management of recurrent TdP.

Abbreviations

TdP: torsades de pointes

Declarations

Ethics declaration: not applicable

Consent for publication: The patient provided consent for the publication of this case report.

Availability of data and materials:

Competing interests: The authors declare that they have no competing interests

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Authors' contributions: Saeko Kohara: Writing – original draft. Ryoko Kyan: Writing – review &editing. Masamune Miyamoto: Writing – investigation & review & editing. Taiki Yamataka: Writing – review &editing. Yoshito Kamijo: Writing – Supervision.

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Figures

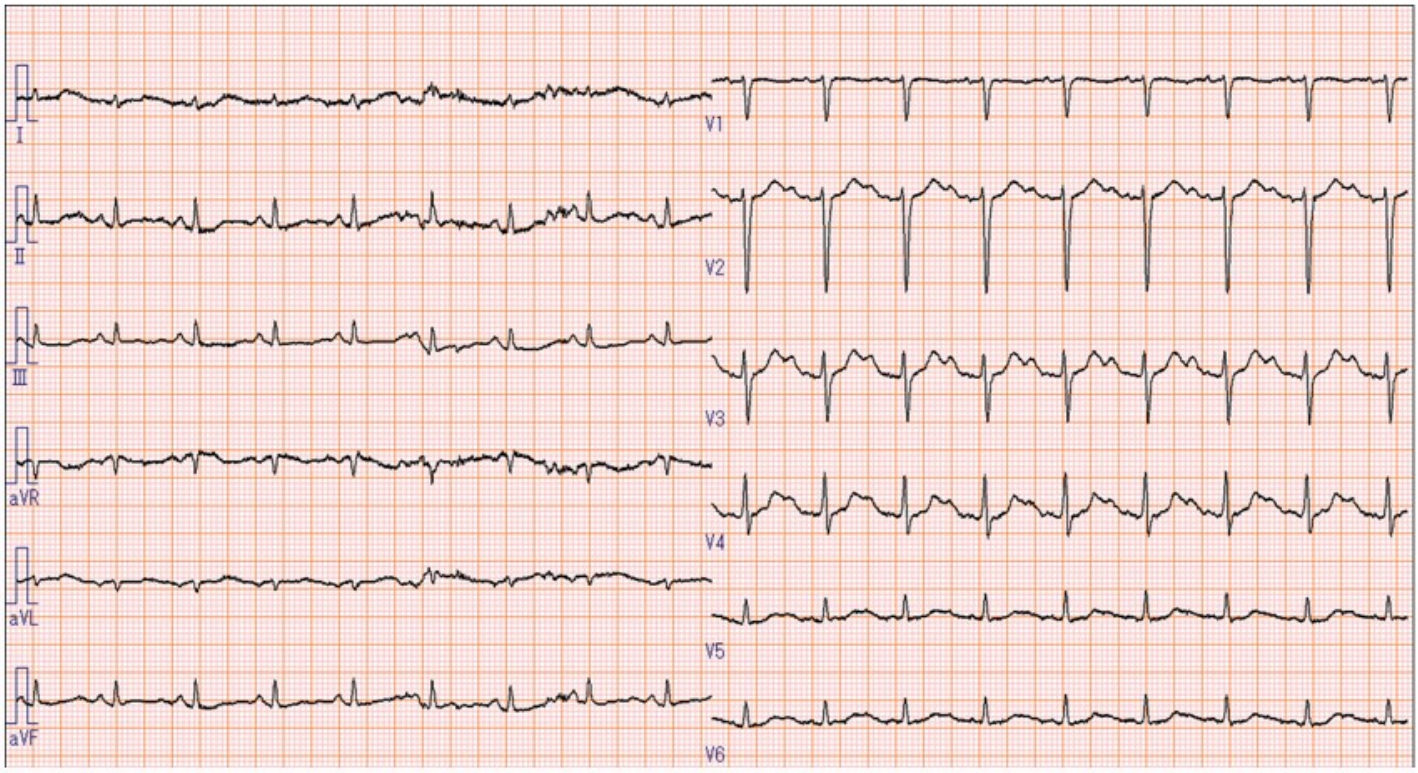


Figure 1.

Figure 1

Twelve-lead electrocardiogram obtained immediately after surgery on admission

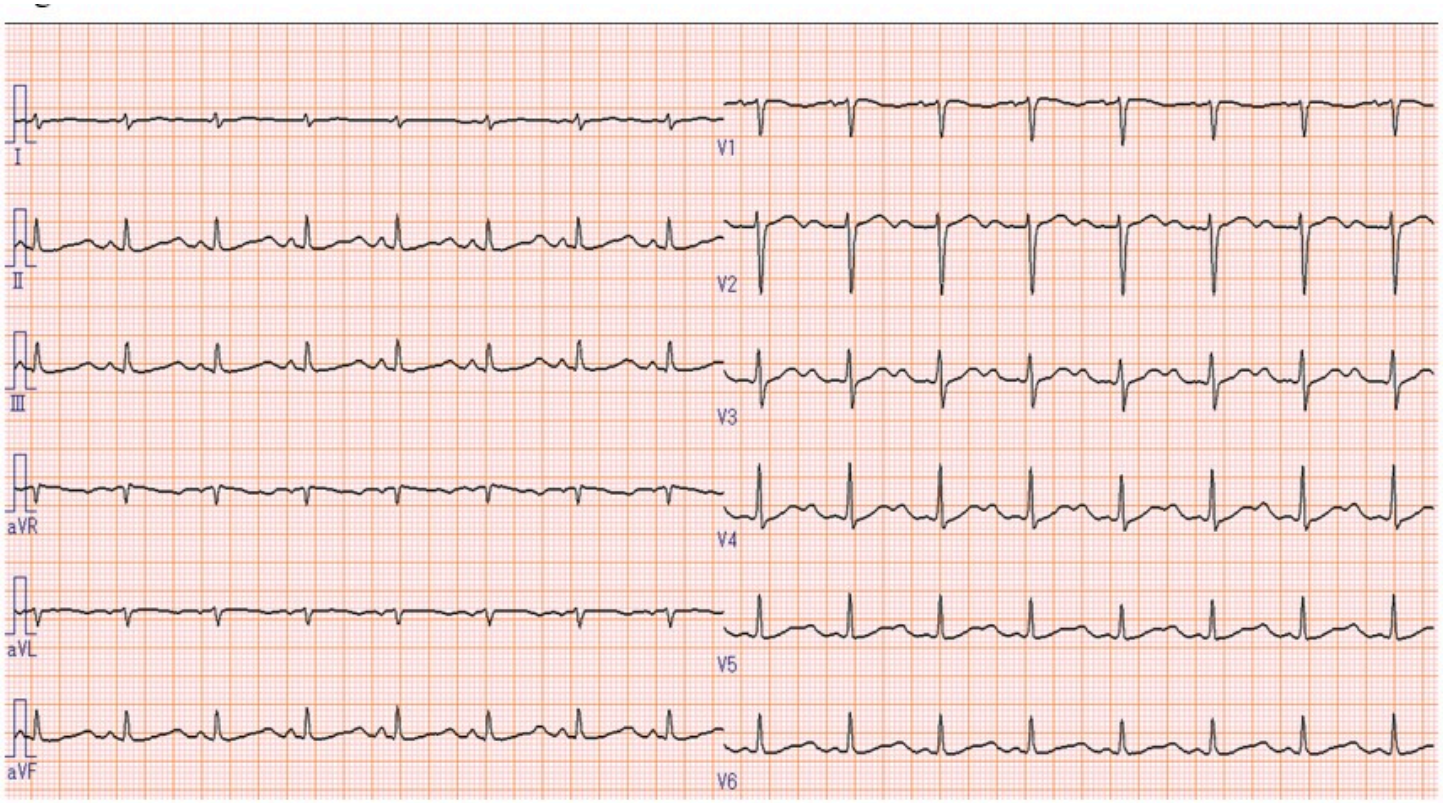


Figure 2.

Figure 2

Twelve-lead electrocardiogram obtained 13 hours after admission

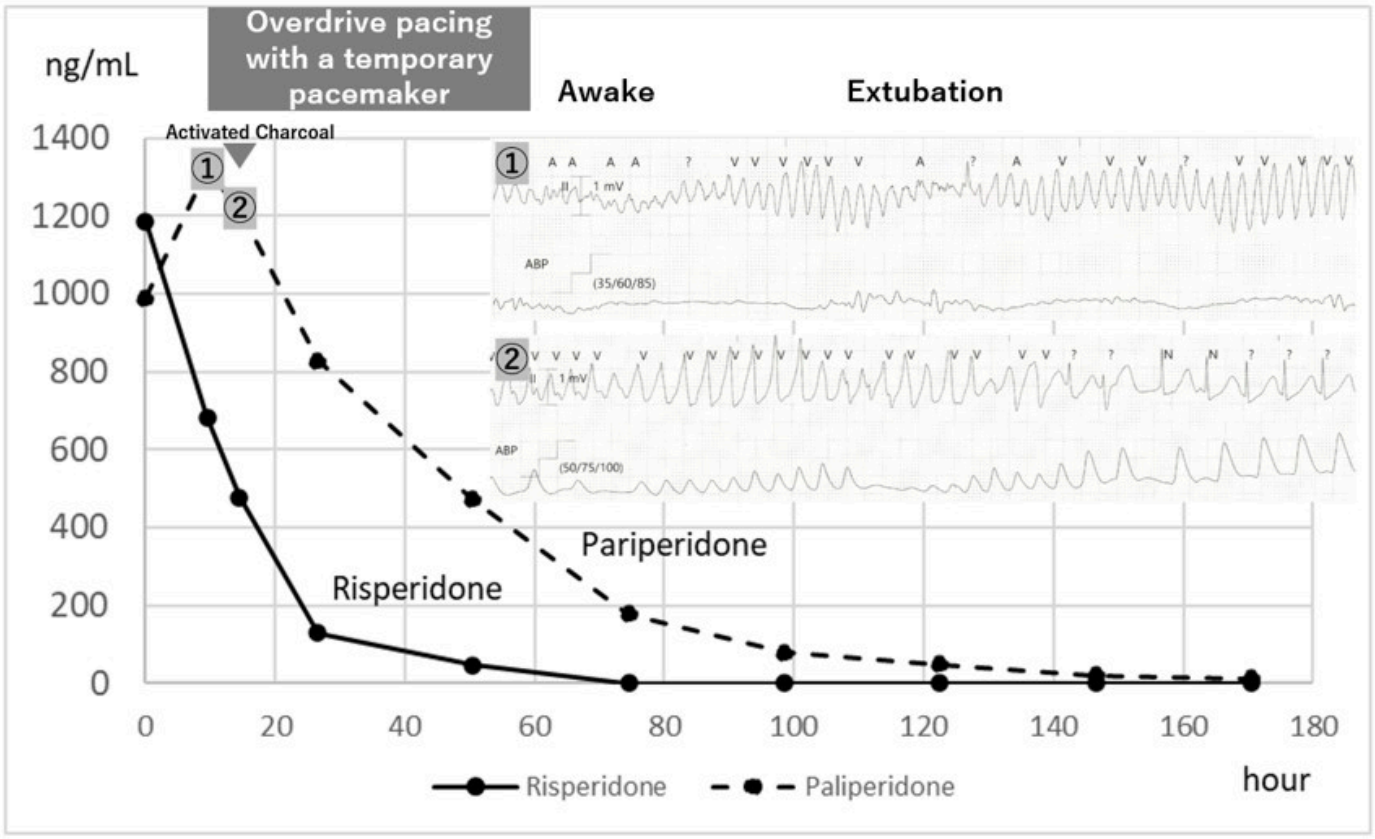


Figure 3.

Figure 3

Clinical course and serial serum concentrations of risperidone and paliperidone