

# Pancytopenia associated with risperidone use: case report

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## ABSTRACT

85-year-old woman with multiple comorbidities: Chronic Obstructive Pulmonary Disease (COPD) and heart failure. Hospitalization one month ago for pulmonary embolism (PE) managed with rivaroxaban 20 mg/day; mixed delirium and dementia treated with risperidone initially 0.5 mg/day and then 1 mg/day upon discharge. Rehospitalized for urinary septic shock caused by *Klebsiella pneumoniae* (KPC), treated with ceftazidime/avibactam 2.5 g every 8 hours. Admission blood count (CBC) showed 770 leukocytes/mm<sup>3</sup>, hemoglobin 6.3 g/dl, hematocrit 18.9%, and platelets 61,000/mm<sup>3</sup>. We suspended risperidone and started haloperidol, 2 units of red blood cells were transfused, showing improvement on the fourth day; CBC showed leukocytes 1,840/mm<sup>3</sup>, neutrophils 740/mm<sup>3</sup>, hemoglobin 9.8 g/dl, hematocrit 29.3%, and platelets 227,000/mm<sup>3</sup>. The causality of the adverse drug reaction (ADR) evaluated with the World Health Organization (WHO) algorithm ranked as “possible.” It is relevant to have a high index of suspicion about the adverse effects of drugs in patients and their clinical relevance from the perspective of healthcare personnel, applying active pharmacovigilance, mainly in the management of patients with polypharmacy.

**Key words:** Risperidone, pancytopenia, leukopenia, adverse drug reaction, case report.

## Pancitopenia asociada al uso de risperidona: informe de caso

### RESUMEN

Mujer de 85 años con múltiples comorbilidades: enfermedad pulmonar obstructiva crónica (EPOC) y fallo cardíaco. Fue hospitalizada el mes previo por tromboembolismo pulmonar (TEP) manejado con rivaroxabán 20 mg/día; *delirium* mixto y demencia en tratamiento con risperidona inicialmente 0,5 mg/día y luego 1 mg/día al egreso. Reingreso hospitalario por choque séptico urinario por *Klebsiella pneumoniae* (KPC), tratado con ceftazidima/avibactam 2,5 g c/8 horas. Cuadro hemático (CH) de ingreso con 770 leucocitos/mm<sup>3</sup>, hemoglobina 6,3 g/dL, hematocrito 18,9% y plaquetas 61 000/mm<sup>3</sup>. Se suspende risperidona e inicia haloperidol; además se le transfunden 2 unidades de glóbulos rojos, y presenta mejoría al cuarto día. En el día 11 de hospitalización el CH muestra leucocitos 1840/mm<sup>3</sup>, neutrófilos 740/mm<sup>3</sup>, hemoglobina 9,8 g/dL, hematocrito 29,3% y plaquetas 227 000/mm<sup>3</sup>. La causalidad de la reacción adversa al medicamento (RAM) evaluada con algoritmo de la Organización Mundial de la Salud (OMS) fue clasificada como “posible”. Es relevante tener un elevado índice de sospecha sobre los

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efectos adversos de los medicamentos en los pacientes y su relevancia clínica desde la perspectiva del personal sanitario, aplicando una farmacovigilancia activa, principalmente en el manejo del paciente con polifarmacia.

**Palabras clave:** risperidona, pancitopenia, leucopenia, reacción adversa a medicamento, informe de caso.

## INTRODUCTION

Psychiatric disorders are increasingly common, with an estimated global prevalence of 1 in 8 as calculated by the WHO<sup>1</sup>. Among this group of illnesses, delirium occurs more frequently in hospitalized elderly patients, and for its pharmacological management, typical and atypical antipsychotics tend to dominate. The latter is associated with fewer extrapyramidal effects and lower hematological toxicity than the former. Risperidone is an atypical antipsychotic indicated for schizophrenia, delirium, aggression, and bipolar affective disorder<sup>2</sup>.

Hematological toxicity, specifically thrombocytopenia and pancytopenia, is an uncommon but feared and potentially dangerous adverse drug reaction (ADR) that can occur in 0.8% of patients receiving this type of medication, as observed with clozapine. Therefore, the appearance of a blood disorder before starting this medication and periodic monitoring with this lab test is vital during its administration.

Pancytopenia as a specific adverse reaction to risperidone is not well known, which motivated us to prepare this report as a learning experience about this severe and difficult-to-manage adverse reaction for the practice of pharmacovigilance. It is also relevant to raise awareness of this adverse reaction, which is of high clinical significance, for the entire scientific community to promote the prevention and detection of adverse reactions within the framework of the use of this medication and other atypical antipsychotics that may also cause it.

## CLINICAL CASE

### Background

An 85-year-old woman with multiple comorbidities: chronic heart failure with a left ventricular ejection fraction (LVEF) of 62%, dermatomyositis (DM), type 2 diabetes mellitus (T2DM), and hypertension (HTN).

### Previous Hospitalization

There is a history of hospitalization in a fourth-level hospital in Bogotá (Colombia) due to pulmonary thromboembolism (PTE) and mixed *delirium*, which required pharmacological treatment with risperidone 1 mg orally (PO, *per os*) every 24 hours at night, rivaroxaban 20 mg PO every 24 hours, omeprazole 20 mg PO every 24 hours, metoprolol 50 mg PO every 24 hours, pregabalin 75 mg PO every 24 hours, prednisolone 30 mg PO every

24 hours, azathioprine 50 mg PO every 8 hours, and ipratropium bromide, four puffs every 8 hours. The complete blood count (CBC) performed on 01/09/2023 showed leukocytes 6980 cells/mm<sup>3</sup>, hematocrit 40.4%, and platelets 159,000/mm<sup>3</sup>. After starting risperidone, a follow-up complete blood count (CBC) was performed on 01/27/2023, which reported leukocytes 6270 cells/mm<sup>3</sup>, hemoglobin (Hb) 8.6 g/dL, hematocrit 25.2%, and platelets 160,000/mm<sup>3</sup>. Eleven days later, before hospital discharge on 02/07/2023, another follow-up test was conducted, showing the following results: leukocytes 2900 cells/mm<sup>3</sup>, Hb 7.4 g/dL, hematocrit (HCT) 22%, and platelets 113,000/mm<sup>3</sup>.

### Last Hospitalization

The patient presented to the Emergency Department of the same institution 15 days later with symptoms suggestive of septic shock of urinary origin caused by carbapenemase-producing *Klebsiella pneumoniae* (KPC) and was referred to the Critical Care Unit, where she received treatment with ceftazidime/avibactam, vasopressor support (epinephrine), and intravenous fluids. The complete blood count (CBC) showed depletion of cellular lines: leukopenia (770 leukocytes/mm<sup>3</sup>) associated with grade III normocytic anemia (Hb 6.3 g/dL, HCT 18.9%, MCV 95.5 fL, MCH 38.8 mg/dL) and thrombocytopenia (61,000 platelets).

We consulted with the Clinical Toxicology Service due to a possible drug interaction associated with the patient's polypharmacy as the cause of the pancytopenia. The consulting service reviewed the clinical history and found the following in the pharmacological management: ceftazidime/avibactam, acyclovir, omeprazole, azathioprine, and risperidone metabolized by the cytochrome CYP2D.

Using the World Health Organization (WHO) causality algorithm, the association of risperidone and acyclovir as triggering agents of the decrease in blood cell line counts was analyzed, leading to the discontinuation of these medications. The primary etiology of the pancytopenia was likely the chronic administration of risperidone, initiated during the previous hospitalization; acyclovir was also administered during the last hospitalization, which could have contributed to some extent to the hematologic toxicity.

The Naranjo scale was also applied to evaluate the causal association between risperidone and pancytopenia, yielding a score of 3, categorizing it as "possible."

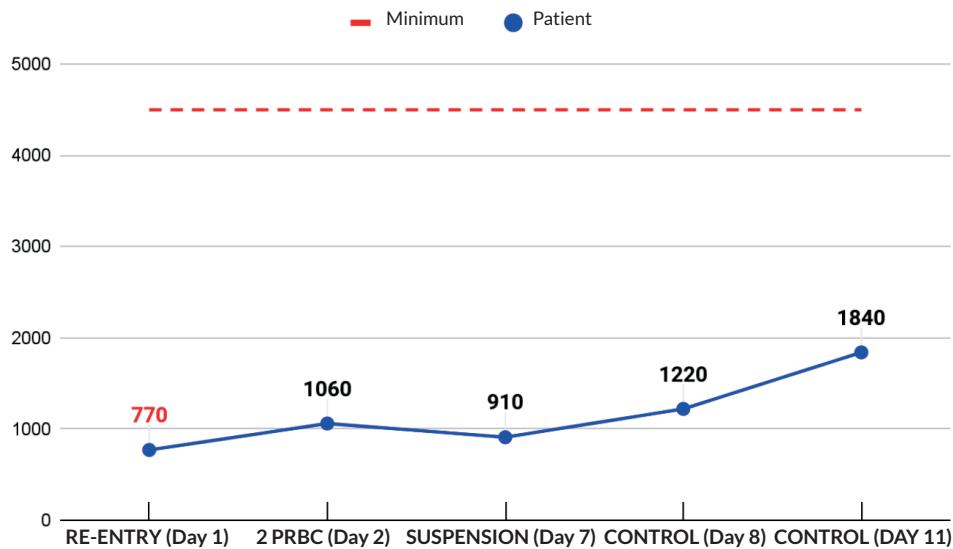


Figure 1. Leukocyte count changes during hospitalization. PRBCU: packed red blood cell unit.

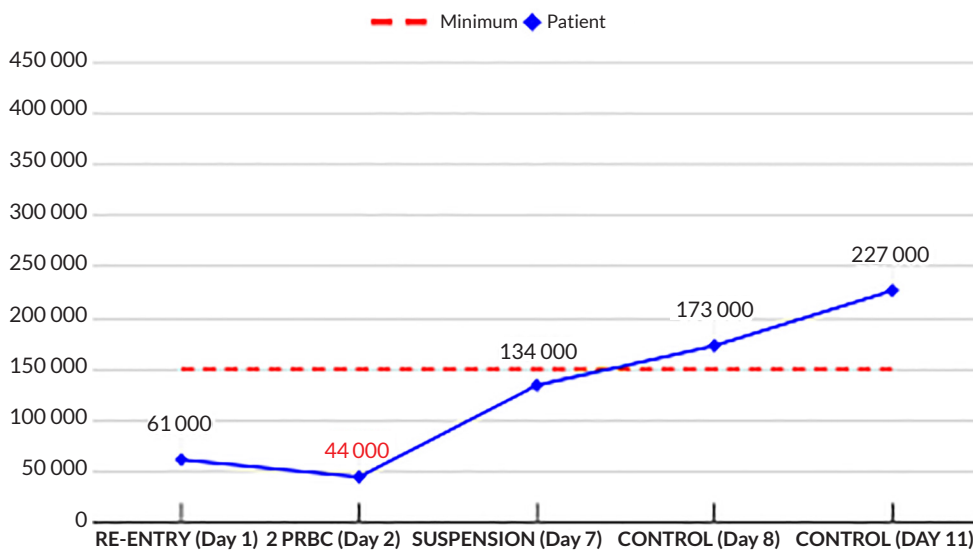


Figure 2. Platelet count changes during hospitalization.

While hospitalized, we administered two units of red blood cells to manage pancytopenia. We conducted a follow-up blood analysis four days after discontinuation of the treatment, which showed improvement in hematologic parameters, with values of leukocytes 1,840 cells/mm<sup>3</sup>, hemoglobin 9.8 g/dL, hematocrit 29.3%, and platelets 227,000/mm<sup>3</sup>, as detailed in Table 1.

The patient was discharged on March 8 and passed away on March 19 (at home), apparently due to complications related to the infection, as reported by the family member over the phone, who did not provide further details about the cause of death.

## DISCUSSION

Risperidone is an atypical antipsychotic belonging to the pyridopyrimidine group, whose primary mechanism of action is to inhibit dopamine synthesis by blocking D2 autoreceptors and postsynaptic receptors, in addition to acting on 5HT<sub>2A</sub> serotonergic receptors in the basal ganglia and prefrontal cortex<sup>5</sup>.

Its main indications are related to the management of psychotic syndrome and bipolar affective disorder<sup>6</sup>.

In this group of medications, extrapyramidal manifestations such as akathisia, dystonia, and tardive dyskinesia have been described as frequent adverse

**Table 1.** Paraclinical evolution after risperidone discontinuation

Clinical evolution	Leukocytes	Neutrophils	Hemoglobin	Hematocrit	Platelets
Day 1 (re-entry)	770	500	6,3	18,9	61 000
Day 7 (suspension)	910	382	10,1	29,4	134 000
Day 11 (control)	1840	740	9,8	29,3	227 000

drug reactions (ADRs). The latter has a prevalence of 20% in patients undergoing treatment with atypical antipsychotics<sup>2</sup>. Less frequent ADRs include cardiovascular manifestations such as orthostatic hypotension, angioedema, pulmonary embolism, and venous thrombosis<sup>7-9</sup>.

In the case under analysis, there was evidence of pancytopenia associated with the use of risperidone—a rare and poorly described ADR in the literature. In Saudi Arabia, Alrahili et al. reported the case of a 14-year-old patient who developed thrombocytopenia, lymphopenia, and neutropenia as adverse effects attributed to the use of risperidone. They reached this conclusion after observing an improvement in blood cell lines two weeks after discontinuing this medication<sup>14</sup>. The causal mechanism is not very clear. It can appear from a few weeks to a month after starting the administration of the drug<sup>11,12</sup>. In the patient, this clinical situation was reversible and improved after four days of discontinuing risperidone, requiring the transfusion of 2 RBC units. The causality classification of ADR with the WHO algorithm was “possible”<sup>12</sup>, considering that other medications the patient received (acyclovir, ceftazidime/avibactam, azathioprine, and omeprazole) can also cause alterations in different blood cell lines.

Hematological toxicity is described for all atypical antipsychotics but mainly for olanzapine and clozapine in 0.8% of patients<sup>10</sup>; in our study, pancytopenia associated with the use of risperidone (another atypical antipsychotic) was identified. For clozapine, the literature describes that blood cell monitoring should be carried out weekly during the first four weeks, then monthly during the first 18 weeks of treatment; after that, at least once every four weeks while the medication continues, and, after discontinuing this medication, monitoring should continue for at least four weeks<sup>15</sup>. For risperidone, the literature does not describe strict monitoring of hematologic lines; however, the scheme described for clozapine can be part of a comprehensive management and active pharmacovigilance for this drug.

## CONCLUSION

Pancytopenia is a rare but very severe adverse drug reaction because it can lead to complications of infectious origin, including sepsis or septic shock. Early detection and timely treatment of this adverse reaction is crucial. Blood panel controls in patients receiving risperidone should occur routinely.

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**Conflicts of interest:** the authors declare no conflicts of interest.

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