

Case Report

Does risperidone causes life threatening pancytopenia? A case report from Nepal

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Abstract:

Antipsychotic drugs like risperidone are sometimes associated with rare but serious adverse events such as pancytopenia. We describe a 38-year-old man on risperidone for schizophrenia for two months who experienced pancytopenia. There was no prior history of hematological diseases or contact with possible triggers in the patient. Upon admission, he presented with symptoms of generalized weakness, black stool, constipation, and recurrent urinary tract infection. Risperidone was promptly discontinued, and supportive measures including prophylactic antibiotics, blood transfusion, and colony-stimulating factors were initiated. Close hematological monitoring should be considered in patients on risperidone, and awareness of the potential risk of pancytopenia associated with its usage is crucial. Timely identification and management of drug-induced pancytopenia are crucial to ensure favorable patient outcomes and prevent potentially life-threatening complications.

Keywords: Pancytopenia; Risperidone; Schizophrenia.

Introduction:

Schizophrenia is a complex, heterogeneous behavioral, and cognitive syndrome characterized by the presence of delusional beliefs, hallucinations, and disturbances in thought, perception, and behavior.¹ The dysregulation of many neurotransmitters, including dopamine, serotonin, glutamate, and gamma-aminobutyric acid (GABA), results in positive (delusion, hallucination, and paranoia) and negative (anhedonia, avolition, asociality, and flat affect) symptoms of schizophrenia². Thus, the treatment modalities for schizophrenia depend on the modulation of these neurotransmitters with antipsychotic drugs. Among them, second-generation antipsychotic drugs quickly became a first-line treatment for acute and chronic schizophrenia due to their preferential side effect profile. Risperidone has

demonstrated significant benefits as a first-line treatment for the initial episode of psychosis in terms of its effectiveness³. However, the common adverse effects of risperidone include extrapyramidal symptoms (tremors, rigidity, akathisia, dystonia, and tardive dyskinesia), hyperprolactinemia, sedation, gastrointestinal effects, and weight gain⁴. A class warning indicates that antipsychotics may lead to blood dyscrasias, encompassing leukopenia, neutropenia, and agranulocytosis.

Pancytopenia is a hematologic condition characterized by a reduction in all three peripheral blood cell lines. It involves hemoglobin levels below 12 g/dL in women and 13 g/dL in men, platelet counts lower than 150,000 per mL, and leukocyte counts below 4000 per ml (or an absolute neutrophil count below 1800 per ml). However, it is essential to note that these thresholds mainly depend on age, sex, race, and clinical scenarios⁵.

This case report highlights a 38-year-old patient who presented with pancytopenia due to risperidone therapy for schizophrenia, as risperidone causes either leukopenia, neutropenia, anemia, thrombocytopenia, or bicytopenia, according to available scientific studies. The presented case fulfills the criteria for pancytopenia, and the clinical course suggests that risperidone is the most plausible cause for this effect.

Case:

A 38-year-old gentleman was brought in by the emergency medical service due to unstable vitals and drowsiness. His blood pressure was 70/40 mm of Hg, pulse was 127 bpm, SpO₂ was 99% on a face mask, respiratory rate was 30 breaths/min, and temperature was 102.5 F with chills. His presenting complaints included black tarry stool (8 episodes) for 7 days, constipation for 5 days, severe abdominal pain for 3 days, and fever for 1 day (temp max 102.7 F). The patient

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had perianal pain and had self-medicated with NSAIDs (tab. nimesulide 2 tabs) for 3 days. He was admitted to the ICU and intubated with a low Glasgow Coma Scale (GCS) score a day after. Ultrasonography of the abdomen showed no signs of hepatomegaly, splenomegaly, or lymph node enlargement. It is noteworthy that the patient had a history of recently diagnosed schizophrenia 2 months back and was prescribed risperidone 1mg daily. He also had a history of decreased appetite and weight loss for 2 months and recurrent UTIs.

Baseline laboratory values showed pancytopenia with WBC count 150 cells/mm³, ANC 0.9 cells/mm³, lymphocytes 146 cells/mm³, monocytes 1.8 cells/mm³, eosinophil 0.0 cells/mm³, basophil 1.0 cell/mm³, hemoglobin 6.9 gm/dl, hematocrit 18.6%, platelet count 13000 cells/mm³. Peripheral blood smear showed an impression of pancytopenia. One pint of whole blood was transfused. The patient had a continuous fever with a maximum of 103.1° F. He was started with IV inotropes, IV Hydrocortisone, broad-spectrum antibiotics (IV Meropenem, IV Metronidazole), stress ulcer prophylaxis (IV Pantoprazole), and antipyretics (IV Paracetamol).

Clinical Course and Outcome: Although reversible, gradual deterioration was noted despite the stopping of risperidone and supportive measures. Despite resuscitation efforts, the patient did not survive beyond 6 hours following admission to the ICU.

Discussion:

Schizophrenia is a serious mental condition that involves a disconnection from reality, including hallucinations and delusions. Medications are the primary approach to treating schizophrenia, with antipsychotic medications being the most commonly prescribed drugs for this condition.

The primary goal of antipsychotic drugs is to effectively manage signs and symptoms at the lowest possible dose using different drugs, doses, or combinations. Antipsychotic drugs are classified as typical (first-generation) and atypical (second-generation) antipsychotics. Typical antipsychotics act exclusively as dopamine-2 (D2) receptor antagonists, while atypical antipsychotics are characterized by serotonin-2A (5-HT_{2A}) antagonists along with potency for serotonin-1A, serotonin-1C, histamine-1, alpha1 adrenergic, and alpha2-adrenergic receptor blockers⁶. These antipsychotic drugs are often associated with adverse effects. These adverse effects can range from mild (e.g., mild sedation or dry mouth) to moderate (e.g., akathisia, acute dystonia, weight gain, sexual dysfunction) to life-threatening (e.g., myocarditis, agranulocytosis)⁷. Therefore, atypical antipsychotic drugs are preferred due to their lower adverse effect profile and higher success rate in treating patients with refractory schizophrenia and tardive dyskinesia. Among the atypical antipsychotics, risperidone is considered the first-line treatment for the initial episode of psychosis in terms of effectiveness. However, risperidone is associated with well-established adverse effects, such as extrapyramidal symptoms, weight gain, hyperprolactinemia, and sedation. Few studies have reported risperidone-induced reversible leukopenia, neutropenia, and thrombocytopenia^{8,9}. Significant hematologic adverse effects

occur in 1 to 2 instances per 100,000 patients each year¹⁰. Different mechanisms, such as bone marrow suppression, immune-related cell destruction, and direct marrow toxicity, have been hypothesized, although a precise understanding of the pathophysiologic basis for these hematologic adverse effects is lacking¹¹. Additionally, it has been suggested that most drug-induced neutropenia is dose-related¹².

A recent study by Chen et al. showed that risperidone, but not haloperidol, affects the immune functions of mature dendritic cells. Risperidone-treated mature dendritic cells have been shown to produce TNF- α , which has the potential to cause the death of neutrophils¹³.

In an African adolescent treated for schizophrenia, risperidone-associated leukopenia developed 10 days after starting risperidone therapy (4 mg/day). The cessation of treatment was followed by a normalization of the white blood cell differential count, and the rechallenge was positive (2 mg/day)¹⁴.

In another report by Semba J, a 48-year-old man with a history of hypertension was admitted to the hospital because of right hemiplegia and was started on risperidone (1 mg twice a day) because he was exhibiting delirium. Two weeks later, he developed thrombocytopenia. His platelets returned to normal 4 days after stopping risperidone⁹.

A similar finding was present in a study by Alrahili NM, where risperidone-induced pancytopenia was found in a 14-year-old female who was started on risperidone 0.75 mg every night for irritable mood and aggression¹⁵. The evaluation hinted towards risperidone being the most likely cause of pancytopenia in this case¹⁵.

In a study by Finkel B, a 40-year-old woman, because of a resistant psychotic state and the presence of extrapyramidal syndrome, risperidone treatment was started, and 2 weeks afterward, it was gradually increased to 4 mg/day in the second week. At that time, a blood sample was drawn, and risperidone was discontinued because of the emergence of agranulocytosis (WBC count=2,400/mm³, neutrophil rate=32%)¹⁶.

However, our patient was initiated on a low dose of risperidone and subsequently developed pancytopenia, as evidenced by laboratory panels showing a WBC count of 150 cells/mm³, absolute neutrophil count of 0.9 cells/mm³, lymphocytes at 146 cells/mm³, hemoglobin at 6.9 gm/dl, and platelets at 13,000 cells/mm³. Moreover, studies have also shown that risperidone may affect iron reserves and inhibit iron absorption, potentially leading to anemia¹⁷. These cumulative mechanisms may have been the cause of pancytopenia in our patient, as there were no known documented risk factors that could have caused the pancytopenia.

Furthermore, nonsteroidal anti-inflammatory medications (NSAIDs) inhibit platelet cyclooxygenase, preventing thromboxane A₂ production. These medicines cause systemic bleeding by inhibiting thromboxane-dependent platelet aggregation and hence increasing bleeding time¹⁷. Our patient

was taking nimesulide, a NSAID for pain management which may also play an important role in thrombocytopenia but it lacks the evidence that it might cause the pancytopenia. Haematopoietic adverse effects such as thrombocytopenia following ibuprofen ingestion is <1%¹⁸. Very rarely has nimesulide been associated with thrombocytopenia.

This case report holds significant importance in this regard, as reports of risperidone-induced pancytopenia are very rare or under-reported. In this case, the patient was diagnosed with Schizophrenia just 2 months before and was started on risperidone. The patient has no personal or family history of hematological disease. The clinical evaluation and blood workup were not significant for alternative causes. Hence, we considered that Risperidone was the most likely cause of the patient's pancytopenia. No significant studies are available signifying pancytopenia due to risperidone alone, as it may cause either leukopenia, neutropenia, anemia, thrombocytopenia, or bicytopenia.

Continuing research into the mechanism of antipsychotic drug-induced blood dyscrasias alone or its drug interaction with the NSAIDs may further enhance safe day-to-day practices.

Limitations of the study:

Bone marrow analysis could not be performed. Additionally, we could not follow the response after stopping the medication, as the patient's clinical course resulted in his immediate demise.

Conclusion:

This case report could be useful for clinicians working in outpatient and inpatient settings to prompt follow-up with routine blood tests, especially CBC, in patients under risperidone therapy. Patients should also be educated about potential side effects like pancytopenia, although it occurs rarely. To determine if the recommendations need to be revisited, additional research on the risperidone adverse effect profile will be awaited.

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References:

1) Hany M, Rehman B, Azhar Y, Chapman J. Schizophrenia. 2023 Jan 30. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. PMID: 30969686.

2) Park HJ, Choi I, Leem KH. Decreased Brain pH and Pathophysiology in Schizophrenia. *Int J Mol Sci.* 2021 Aug 4;22(16):8358. doi: 10.3390/ijms22168358. PMID: 34445065; PMCID: PMC8395078. https://doi.org/10.3390/ijms_22168358

3) Gómez-Revuelta M, Pelayo-Terán JM, Juncal-Ruiz M, Vázquez-Bourgon J, Suárez-Pinilla P, Romero-Jiménez R, et al. Antipsychotic Treatment Effectiveness in First Episode of Psychosis: PAFIP 3-Year Follow-Up Randomized Clinical Trials Comparing Haloperidol, Olanzapine, Risperidone, Aripiprazole, Quetiapine, and Ziprasidone. *Int J Neuropsychopharmacol.* 2020 Apr 23;23(4):217-229. doi: 10.1093/ijnp/pyaa004. PMID: 31974576; PMCID: PMC7177160. <https://doi.org/10.1093/ijnp/pyaa004> PMID:31974576 PMCID:PMC7177160

4) Alladi CG, Mohan A, Shewade DG, Rajkumar RP, Adithan S, Subramanian K. Risperidone-Induced Adverse Drug Reactions and Role of DRD2 (-141 C Ins/Del) and 5HTR2C (-759 C>T) Genetic Polymorphisms in Patients with Schizophrenia. *J Pharmacol Pharmacother.* 2017 Jan-Mar;8(1):28-32. doi: 10.4103/jpp.JPP_197_16. PMID: 28405133; PMCID: PMC5370325. https://doi.org/10.4103/jpp.JPP_197_16 PMID:28405133 PMCID:PMC5370325

5) Chiravuri S, De Jesus O. Pancytopenia. 2023 Feb 12. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. PMID: 33085293.

6) Grinchii D, Dremencov E. Mechanism of Action of Atypical Antipsychotic Drugs in Mood Disorders. *Int J Mol Sci.* 2020 Dec 15;21(24):9532. doi: 10.3390/ijms21249532. PMID: 33333774; PMCID: PMC7765178. <https://doi.org/10.3390/ijms21249532> PMID:33333774 PMCID:PMC7765178

7) Stroup TS, Gray N. Management of common adverse effects of antipsychotic medications. *World Psychiatry.* 2018 Oct;17(3):341-356. doi: 10.1002/wps.20567. PMID: 30192094; PMCID: PMC6127750. <https://doi.org/10.1002/wps.20567> PMID:30192094 PMCID:PMC6127750

8) Kattalai Kailasam V, Chima V, Nnamdi U, Sharma K, Shah K. Risperidone-induced reversible neutropenia. *Neuropsychiatr Dis Treat.* 2017 Jul 25;13:1975-1977. doi: 10.2147/NDT.S141472. PMID: 28794632; PMCID: PMC5536090. <https://doi.org/10.2147/NDT.S141472> PMID:28794632 PMCID:PMC5536090

9) Semba J, Okui S. Risperidone-induced thrombocytopenia: a case report. *Gen Hosp Psychiatry.* 2009 Jan-Feb;31(1):97-8. doi: 10.1016/j.genhosppsy.2008.06.005. Epub 2008 Jul 30. PMID: 19134517. <https://doi.org/10.1016/j.genhosppsy.2008.06.005> PMID:19134517

10) Galbaud du Fort G: Hematologic toxicity of antidepressive agents. *Encephale* 1998; 14:307-318

11) Balon R, Berchou R: Hematologic side effects of psychotropic drugs. *Psychosomatics* 1986; 27:119-120 [https://doi.org/10.1016/S0033-3182\(86\)72722-9](https://doi.org/10.1016/S0033-3182(86)72722-9) PMID:2869545

12) Flanagan RJ, Dunk L. Haematological toxicity of drugs used in psychiatry. *Hum Psychopharmacol.* 2008 Jan;23 Suppl 1:27-41. doi:10.1002/hup.917. PMID:18098216. <https://doi.org/10.1002/hup.917> PMID:18098216

13) Chen ML, Tsai TC, Wang LK, et al. Risperidone modulates the cytokine and chemokine release of dendritic cells and induces TNF- α -directed cell apoptosis in neutrophils. *Int Immunopharmacol.* 2012;12(1):197-204. [PubMed] [Google Scholar] <https://doi.org/10.1016/j.intimp.2011.11.011> PMID:22154580

14) Etain B, Roubaud L, Le Heuzey MF, Mouren Simeoni MC. A case of leukopenia in treatment with risperidone in an adolescent. *L'encephale.* 2000 Sep-Oct;26(5):81-84. PMID: 11192809.

- 15) Alrahili NM. Risperidone induced pancytopenia: a case report. *Int J Basic Clin Pharmacol* 021;10:1016-8. <https://doi.org/10.18203/2319-2003.ijbcp20212932>
- 16) Finkel B, Lerner AG, Oyffe I, Sigal M. Risperidone-associated agranulocytosis. *Am J Psychiatry*. 1998 Jun;155(6):855-6. doi: 10.1176/ajp.155.6.855a. PMID: 9619165. <https://doi.org/10.1176/ajp.155.10.1460> PMID:9766785
- 17) Calarge CA, Ziegler EE, Del Castillo N, Aman M, McDougale CJ, Scahill L, et al. Iron homeostasis during risperidone treatment in children and adolescents. *J Clin Psychiatry*. 2015 Nov;76(11):1500-5. doi: 10.4088/JCP.14m09258. PMID: 26301448; PMCID: PMC6728911 <https://doi.org/10.4088/JCP.14m09258> PMID: 26301448 PMCID:PMC6728911
- 18) Jauhari AC, Bista D, Johorey AC, Saha S, Saha A. Thrombocytopenia after Ibuprofen: A Case Report. *Journal of Clinical and Diagnostic Research*. 2009;3(1):1329-33.DOI: <https://doi.org/10.7860/JCDR/2009/451>