Case Report

DOI: 10.7860/JCDR/2025/79244.21356

Internal Medicine Section

Serotonin Syndrome Triggered by Ondansetron in Organophosphorus Poisoning Presenting as a Dual Clinical Challenge: A Case Report

KARRA KEERTHI REDDY[1], MANNE LAKSHMI NARASIMHA SANDEEP[2], NALABOTHULA RAVI TEJA[3]

ABSTRACT

Organophosphorus compound poisoning continues to be a significant clinical concern in developing countries, presenting with diverse neurological and systemic complications. While cholinergic crisis and intermediate syndrome are well-recognised sequelae, serotonin syndrome remains a rare and underreported complication in such cases. We describe the case of a 48-year-old man who intentionally ingested a large amount of a chlorpyrifos-based pesticide (Killer 505) in an act of self-harm. Upon admission, he was drowsy but arousable, with a Glasgow Coma Scale (GCS) score of 14/15, and was initially managed with atropine and pralidoxime infusions. By the fourth day, he developed signs of intermediate syndrome and required mechanical ventilation. On day 7, he was started on ondansetron 8 mg intravenously every eight hours for persistent nausea. Within 24 hours, he developed fever, agitation, spontaneous clonus, and hyperreflexia. Clinical assessment, supported by Hunter's Criteria, led to a diagnosis of serotonin syndrome. His brain Magnetic Resonance Imaging (MRI) showed old infarcts but no new findings to explain the sudden change in his neurological status. After stopping ondansetron, his condition improved rapidly, confirming the diagnosis. He was later decannulated and discharged with a full recovery. This case illustrates that ondansetron, a 5-HT3 antagonist, can trigger serotonin syndrome in high-risk individuals, especially those already affected by neurotoxicity from organophosphorus compound poisoning. Early detection and withdrawal of the triggering drug are critical. Clinicians must remain vigilant for unusual symptoms and drug-induced effects in complex toxicology cases.

Keywords: Acetylcholinesterase inhibitors, Antiemetics, Drug-induced neurological disorders, Intermediate syndrome, Toxicology

CASE REPORT

A 48-year-old male with no history of medical or psychiatric conditions was brought to the Emergency Department in an unconscious and drowsy state after intentionally ingesting approximately 100-125 mL of Killer 505, a commercially available organophosphorus pesticide consisting of 50% chlorpyrifos and 5% permethrin. He was found in a decreased responsive state two hours post-ingestion by his brother and was initially taken to a government primary healthcare facility. There, he received gastric lavage and initial supportive management. The patient was subsequently referred to our tertiary care center for further evaluation and management. The incident was registered as a medicolegal case, and appropriate legal documentation was completed.

Upon admission to our hospital, the patient was drowsy but responsive to verbal stimuli. His initial vital signs were as follows: blood pressure of 130/80 mmHg, respiratory rate of 20 breaths per minute, pulse rate of 110 beats per minute, and Oxygen Saturation (SpO_2) of 98% on room air. His body temperature was 98°F. Neurological examination revealed a Glasgow Coma Scale (GCS) score of 14/15. There was no initial evidence of cholinergic symptoms such as miosis, salivation, lacrimation, diarrhoea, or fasciculations. The patient was diagnosed with deliberate self-harm due to organophosphorus compound poisoning. A day-wise progression of the patient's clinical status and corresponding interventions is summarised in [Table/Fig-1].

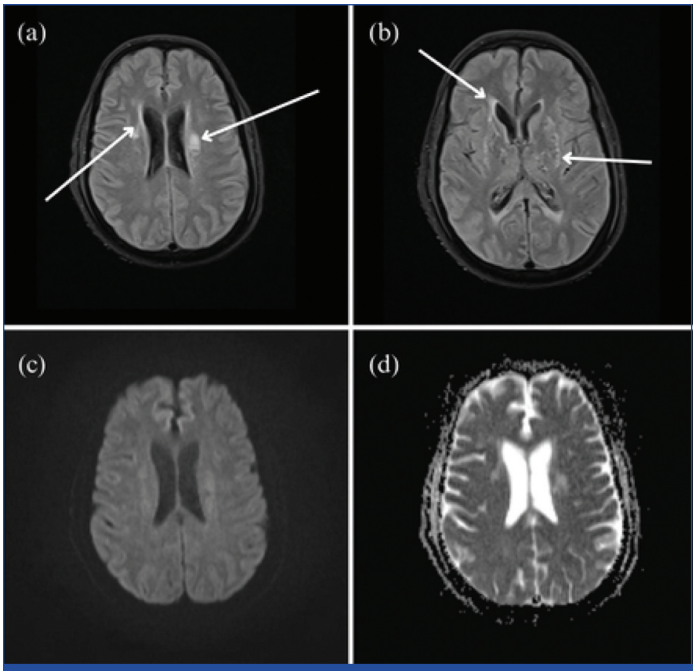
The patient was initially managed with intravenous atropine infusion at 2 mg/hour and pralidoxime 2 g intravenously twice daily, in accordance with standard treatment protocols for organophosphorus poisoning. Serum pseudocholinesterase levels were markedly reduced (252 U/L), supporting the diagnosis of organophosphorus poisoning. By day 4, the patient developed areflexia, hypotonia, and drowsiness, all indicative of intermediate syndrome. His GCS score dropped to 7 out of 15, and he required mechanical ventilation due to respiratory compromise.

Day	Event	Management/Findings
1	OP ingestion	Gastric lavage; atropine and pralidoxime started
4	Intermediate syndrome	GCS dip; Intubation
6	Ondansetron initiated	8 mg i.v. TID
7	Neuromuscular symptoms	Suspected Serotonin Syndrome (SS), atropine and pralidoxime were stopped
9	Ondansetron stopped	GCS improved, symptoms regressed
13	Tracheostomy	Due to prolonged ventilation
30	Neurological recovery	Full consciousness regained
32	Discharge	Stable condition

[Table/Fig-1]: Timeline of clinical events and management.
OP: Organophosphate

On day 7, the patient began to exhibit agitation, persistent jerky movements, spontaneous clonus, and developed a fever of 102°F. Neurological examination revealed bilateral lower limb hyperreflexia, inducible ankle clonus, and upper limb rigidity. There were no signs of meningism or seizure activity.

Magnetic Resonance Imaging (MRI) of the brain revealed chronic lacunar infarcts in the bilateral corona radiata, periventricular white matter, thalamus, and gangliocapsular region. No acute pathology or restricted diffusion was noted on Diffusion-Weighted Imaging (DWI), and Apparent Diffusion Coefficient (ADC) mapping confirming



[Table/Fig-2]: Magnetic Resonance Imaging (MRI) brain of the patient. FLAIR images show hyperintensities in the bilateral corona radiata and periventricular white matter (white arrows in a); with additional involvement of thalamus and gangliocapsular region (white arrows in b); Diffusion Weighted Imaging (DWI) shows no diffusion restriction suggestive of chronic infarcts (c); and Apparent Diffusion Coefficient (ADC) mapping confirms chronic infarcts in bilateral corona radiata (d).

the chronic nature of these infarcts [Table/Fig-2a-d]. Atropine and pralidoxime were discontinued on day 7 following adequate atropinisation, evidenced by clear lung fields, heart rate ≥80 bpm, mydriasis, dry skin, and systolic blood pressure >90 mmHg.

The patient was suspected to have developed Serotonin Syndrome (SS) based on signs and symptoms fulfilling Hunter's criteria [1]. After reviewing his list of medications, it was noted that he had been receiving Inj. Ondansetron 8 mg i.v. three times a day since day 6 to manage persistent nausea. Ondansetron was considered the likely offending agent and was promptly discontinued. The correlation of clinical features with diagnostic criteria is detailed in [Table/Fig-3]. On day 9, ondansetron was discontinued. Within 48 hours of cessation, the patient's GCS improved to 9/15, and neuromuscular symptoms started regressing. A tracheostomy was performed on day 13 due to prolonged ventilator dependency. Over the subsequent days, the patient continued to improve neurologically. He was weaned off ventilator support and eventually decannulated. On day 32, the patient was discharged in stable condition with full neurological recovery.

Feature	Observed	Hunter's criteria met?
Spontaneous clonus	Yes	Yes
Agitation	Yes	Yes
Inducible clonus	Yes	Yes
Hyperreflexia	Yes	Yes
Fever	Yes (102°F)	Yes

[Table/Fig-3]: Hunter's criteria correlation.

DISCUSSION

We present a case of acute organophosphorus poisoning in a 48-year-old male who consumed a lethal dose of pesticide and subsequently developed intermediate syndrome and SS, likely triggered by the use of a serotonergic agent, ondansetron, in the context of altered neurological vulnerability induced by Organophosphate (OP) toxicity [2].

OP poisoning continues to be a significant concern in medicine and public health, particularly in countries like India, where farming is widespread and pesticides are easily accessible. Chlorpyrifos, a widely used chemical, irreversibly inhibits the enzyme acetylcholinesterase. This enzyme usually breaks down acetylcholine, a neurotransmitter at the Neuromuscular Junction (NMJ). When the enzyme is blocked, acetylcholine accumulates at the NMJ and muscle joints, throwing the whole system off balance and causing serious effects [3]. This results in overstimulation of muscarinic and nicotinic receptors, manifesting as the classic cholinergic toxidrome: miosis, salivation, bronchorrhoea, bradycardia, fasciculations, and potentially seizures or coma [4].

Few patients develop intermediate syndrome within one to four days after organophosphorus compound ingestion. This syndrome is characterised by weakness in the proximal muscles, areflexia, and palsy, often leading to the need for respiratory support. While it is well known that OPs affect the nervous system, how they might affect serotonin levels in the brain is something researchers are just beginning to investigate more closely [5].

In our patient, SS was triggered after the initiation of ondansetron therapy, a selective 5-HT3 antagonist primarily used for nausea and vomiting. Although ondansetron is not classically considered a serotonergic agent, recent literature has suggested that it may increase serotonergic toxicity indirectly, especially in the presence of other contributing factors such as blood-brain barrier disruption or critical illness [6].

SS is a potentially life-threatening condition resulting from overstimulation of central and peripheral 5-HT receptors. Classical features include a triad of mental status changes (agitation, confusion), autonomic hyperactivity (fever, tachycardia, hypertension), and neuromuscular abnormalities (hyperreflexia, clonus, rigidity). Diagnosis is clinical, often guided by the Hunter serotonin toxicity criteria, which our patient fulfilled entirely [7].

Many case reports and reviews have highlighted ondansetron's potential role in triggering SS. For example, Ibarra A and Meng L detailed a patient who had undergone surgery and developed SS following the combined use of remifentanil and ondansetron alongside chronic SSRI therapy [8]. Similarly, Wiseman D et al., reported a case during pregnancy where SS developed after the administration of ondansetron and prochlorperazine [9].

Exactly how ondansetron plays a role in SS is not fully clear yet. Some researchers propose that by blocking 5-HT3 receptors on nerve endings, ondansetron may contribute to SS through a less direct but biologically plausible mechanism. By blocking presynaptic 5-HT3 receptors, which typically provide inhibitory feedback on serotonin release, the drug may unintentionally enhance central serotonergic activity. This reduction in inhibitory control may result in elevated serotonin levels within the synaptic cleft, potentially raising the likelihood of serotonin toxicity in individuals with underlying vulnerability [10]. This effect may be amplified in individuals with existing disruptions to central neurotransmitter regulation, such as those suffering from OP-induced encephalopathy or intermediate syndrome.

A study in the Intensive Care Unit (ICU) by Prakash S et al., found that ondansetron was the most common drug linked to SS, appearing in over 58% of the cases they reviewed. What stood out was that none of these cases were identified by the medical teams caring for the patients. This highlights the need for improved awareness among healthcare providers regarding the signs of serotonin toxicity [4].

A turning point in our diagnostic path came from the dechallenge response—a rapid and sustained improvement in the GCS and neuromuscular symptoms within 48 hours of discontinuing ondansetron. This temporal association significantly strengthens the causal link between ondansetron and the patient's clinical presentation. To further support this, the Naranjo algorithm was applied, yielding a score of 6, indicating a "probable" adverse drug reaction. Such structured tools are essential in pharmacovigilance, and their validity in assessing causality has been reinforced

in comparative studies like that of Acharya TA et al., which demonstrated strong concordance between the Naranjo algorithm and World Health Organisation - Uppsala Monitoring Centre (WHO-UMC) causality criteria [11].

Ondansetron's link to SS brings attention to the layered and sometimes unpredictable nature of how it works in the body. Though ondansetron is mainly used as a 5-HT3 blocker to help relieve nausea during chemotherapy or surgery, research suggests it might also influence serotonin activity in the brain in more indirect ways. This matters even more in critically ill patients, who are often on several drugs at once and may have a weakened blood-brain barrier, making them more likely to experience toxic effects on the nervous system [12].

Health regulatory agencies have also issued warnings regarding ondansetron's serotonergic risks. For example, Health Canada updated ondansetron's safety profile to include the risk of SS following reports of agitation, hyperreflexia, and fever in patients who had received the drug either alone or in combination with other agents [13].

Moreover, in animal models, the combined administration of ondansetron with Selective Serotonin Reuptake Inhibitors (SSRIs) significantly worsened serotonergic neurotoxicity, as evidenced by hippocampal inflammation and neurotransmitter imbalance [14]. This synergistic toxicity may be relevant even in the absence of other serotonergic drugs, particularly in neurologically compromised individuals, such as those with OP-induced encephalopathy.

Although a dechallenge response has already been described, it is important to contextualise our findings within a broader pharmacovigilance framework. The potential role of ondansetron in precipitating SS has been documented in several other reports. For instance, a case by Guo MH et al., describes SS exacerbated by ondansetron in a patient already on serotonergic agents [6]. Similarly, Ibarra AJ and Meng L, reported a patient developing serotonin syndrome in the post-anesthesia care unit after receiving ondansetron and remifentanil in the context of SSRI use [8]. A third case by Choudhry M involved a patient with fatal overlapping syndromes, including serotonin syndrome and hyponatremia, where ondansetron was implicated alongside SSRIs and opioids [15]. Additionally, Gerardi D et al., described diagnostic challenges in a paediatric case where ondansetron contributed to a misdiagnosed serotonergic-anticholinergic toxidrome. These cases collectively support a plausible link between ondansetron and serotonin toxicity, particularly when used in vulnerable individuals or alongside other serotonergic agents [16].

From a mechanistic standpoint, it is important to distinguish the non-classical serotonergic pathways. While ondansetron does not inhibit serotonin reuptake or monoamine oxidase directly, it can amplify serotonergic tone through disinhibition in the brainstem or spinal cord pathways [17].

Chronic microvascular infarcts, like the ones seen on our patient's MRI, may cause serotonin receptors to become unusually sensitive. In such situations, even a small change in serotonin levels can be enough to bring on symptoms. This increased sensitivity could help explain why some patients develop SS after taking ondansetron alone—particularly when there's already some disruption in how the brain manages blood flow and nerve signalling [18].

Healthcare providers should be aware of SS, even if the only serotonergic drug given is a 5-HT3 blocker like ondansetron. This is particularly important in patients with prior neurological conditions, such as those who have had a stroke or are dealing with OP poisoning, as they may be more vulnerable to serotonergic effects. Since ondansetron is commonly given in ICUs, emergency rooms, and cancer treatment centres, this is not just a theoretical concern; it could make a real difference in saving lives [9].

Lastly, the Hunter Criteria remains the most sensitive and specific tool for diagnosis and should be systematically applied when serotonin syndrome is suspected [1]. In our case, the presence of spontaneous clonus, agitation, hyperreflexia, and fever satisfied this diagnostic tool. When combined with a positive dechallenge test and the absence of other plausible etiologies, the diagnosis was confirmed with high certainty.

CONCLUSION(S)

SS is an uncommon and sometimes missed consequence of organophosphorus poisoning, especially when caused by antiemetic drugs such as ondansetron. Early detection using tools like the Hunter Criteria, along with a strong sense of clinical suspicion, is key. This case shows just how important it is to take a close look at every medication a patient is on—even those that aren't usually linked to serotonin-related side effects. Prompt removal of the offending substance resulted in complete neurological recovery. Clinicians treating OP poisoning should be on the lookout for unusual medication responses to minimise unnecessary complications and decrease morbidity in critical care settings.

REFERENCES

[1] Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med. 2005;352:1112-20. Available from: https://doi.org/10.1056/NEJMra041867.

[2] Rojas-Fernandez CH. Can 5-HT3 antagonists really contribute to serotonin toxicity? A call for clarity and pharmacological law and order. Drugs- Real World Outcomes. 2014;1:03-05. Available from: https://doi.org/10.1007/s40801-014-0004-3.

[3] Pawar KS. Management of organophosphorus pesticide poisoning: Common questions and answers: Ultimate Guide for Primary Health Centers, Hospitals and Intensive Care Units. Notion Press; 2021.

[4] Prakash S, Rathore C, Rana K. The prevalence of serotonin syndrome in an intensive care unit: A prospective observational study. J Crit Care. 2020;63:92-97. Available from: https://doi.org/10.1016/j.jcrc.2020.12.014.

[5] Goncharov NV, Belinskaia DA, Avdonin PV. Organophospate-induced pathology: Mechanisms of development, principles of therapy and features of experimental studies. J Evol Biochem Phys. 2023;59:1756-96. Available from: https://doi.org/10.1134/S002209302305023X.

[6] Guo MH, Monir R, Wright A, Holland NP. Case of serotonin syndrome initially presenting as diffuse body pain. Am J Case Rep. 2018;19:1227-31. Available from: https://doi.org/10.12659/AJCR.911204.

[7] Kulikowski J, Parthasarathi U. Special syndromes: Serotonin syndrome, neuroleptic malignant syndrome, and catatonia. In: Fenn HH, Hategan A, Bourgeois JA, editors. Inpatient Geriatric Psychiatry: Optimum Care, Emerging Limitations, and Realistic Goals, Cham: Springer International Publishing; 2019, p. 277-92. Available from: https://doi.org/10.1007/978-3-030-10401-6_15.

[8] Ibarra AJ, Meng L. Serotonin syndrome in the post-anesthesia care unit after remifentanil infusion and ondansetron: A case report and literature review. J Anest & Inten Care Med. 2018;5(3):01-03. Available from: https://doi.org/10.19080/JAICM.2018.05.555663.

[9] Wiseman D, Samoukovic G, Durcan L, Malhamé I. Serotonin syndrome after treatment of nausea and vomiting in pregnancy. Obstet Gynecol. 2022;140(4):696-99. Available from: https://doi.org/10.1097/AOG.0000000000004941.

[10] Okada M, Okubo R, Fukuyama K. Vortioxetine subchronically activates serotonergic transmission via desensitization of serotonin 5-HT1A receptor with 5-HT3 receptor inhibition in rats. Int J Mol Sci. 2019;20(24):6235. Available from: https://doi.org/10.3390/ijms20246235.

[11] Acharya TA, Trivedi D, Joshi K, Chhaiya SB, Mehta D. A study of agreement between WHO-UMC causality assessment system and the naranjo algorithm for causality assessment of adverse drug reactions observed in medical ICU of a tertiary care teaching hospital. Biomed Pharmacol J. 2020;13(1):79-83. Available from: https://doi.org/10.13005/BPJ/1863.

[12] Cubeddu L, Hoffmann I, Fuenmayor N, Finn A. Efficacy of ondansetron (GR 38032F) and the role of serotonin in cisplatin-induced nausea and vomiting. N Engl J Med. 1990;322(12):810-16. Available from: https://doi.org/10.1056/NEJM199003223221204.

[13] Risk of serotonin syndrome with serotonin-blocking anti-emetics. React Wkly. 2014;1503:2. Available from: https://doi.org/10.1007/s40278-014-1033-0.

[14] Babaker MA, Alazabi NI, Haredy SA, Algohary AM, Anwar MM, Yousef EM, et al. Mitigative and neuroprotective effects of Lavandula angustifolia essential oil on serotonin syndrome-induced neurotoxicity in male albino rats. Drug Chem Toxicol. 2025:01-19. Available from: https://doi.org/10.1080/01480545.2025.2458618.

[15] Choudhry M. Serotonin syndrome and acute hyponatremia, complex overlapping syndromes, a case report and review. Case Rep Clin Med. 2014;3(2):92-96. Available from: https://doi.org/10.4236/CRCM.2014.32023.

[16] Gerardi D, Murphy T, Toufexis M, Hanks CE. Serotonergic or anticholinergic toxidrome: Case report of a 9-year-old girl. Pediatr Emerg Care. 2015;31(12):846-50. Available from: https://doi.org/10.1097/PEC.0000000000000515.

[17] The GK, Bleijenberg G, Buitelaar J, Meer JVD van der. The effect of ondansetron, a 5-HT3 receptor antagonist, in chronic fatigue syndrome: A randomized controlled trial. J Clin Psychiatry. 2010;71(5):528-33. Available from: https://doi.org/10.4088/JCP.08m04719whi.

[18] Simon LV, Torrico TJ, Keenaghan M. Serotonin Syndrome. StatPearls, Treasure Island (FL): StatPearls Publishing; 2025.

PARTICULARS OF CONTRIBUTORS:
1. Third Year Junior Resident, Department of General Medicine, SRM Medical College Hospital and Research Centre, Chennai, Tamil Nadu, India.
2. Third Year Junior Resident, Department of General Medicine, SRM Medical College Hospital and Research Centre, Chennai, Tamil Nadu, India.
3. Third Year Junior Resident, Department of General Medicine, SRM Medical College Hospital and Research Centre, Chennai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Nalabothula Ravi Teja,
House No. 5, 2nd Floor, Dravidian Street, Potheri, Chennai-603203, Tamil Nadu, India.
E-mail: raviat8@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Mar 26, 2025
- Manual Googling: Jun 12, 2025
- iThenticate Software: Jun 14, 2025 (7%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Mar 09, 2025**
Date of Peer Review: **Apr 30, 2025**
Date of Acceptance: **Jun 16, 2025**
Date of Publishing: **Aug 01, 2025**