# Ondansetron-Induced Dystonia, Hypoglycemia, and Seizures in a Child

Aneet Patel, Shweta Mittal, Samiksha Manchanda, and Jacob Mammen Puliyel

**OBJECTIVE:** To document ondansetron-induced dystonia, hypoglycemia, and seizures in a child.

**CASE SUMMARY:** A 4-year-old boy was admitted with dystonia following an intravenous dose of ondansetron 2 mg (0.13 mg/kg) that he had received for vomiting that day. In the emergency department, he developed generalized tonic-clonic seizures lasting for a few minutes. He was administered lorazepam 1.5 mg (0.1 mg/kg) to control the seizures. His blood glucose level was 10 mg/dL; the hypoglycemia responded promptly to intravenous dextrose 10% (7 mL/kg). Serum electrolytes, renal profile, capillary blood gas, and results of a computed tomography scan of the brain were normal. Subsequent blood glucose values were within normal range. On follow-up after 7 days, the child was healthy with no recurrences of the symptoms. A provisional diagnosis of ondansetron-induced acute dystonia with seizures and hypoglycemia was made.

**DISCUSSION:** Ondansetron is an antiemetic known for its safety profile. There have been a few case reports of extrapyramidal adverse effects and seizures from this drug but none of ondansetron-associated hypoglycemia. 5-Hydroxytryptamine (5-$HT_3$) receptors are involved in arginine vasopressin–mediated release of adrenocorticotropin hormone and cortisol in response to stress. Blunting of this stress response by ondansetron, a 5-$HT_3$ receptor antagonist, could have caused the hypoglycemia in this patient. According to the Naranjo scale, ondansetron was probably the cause of the dystonia and seizures, and possibly the cause of the hypoglycemia. Other potential explanations for hypoglycemia were considered but were thought to be less likely.

**CONCLUSIONS:** Dystonia and seizures have been associated with ondansetron in a few case reports. In addition, clinicians need to consider hypoglycemia as a possible adverse effect of ondansetron.

**KEY WORDS:** 5-hydroxytryptamine (5-$HT_3$) receptor, dystonia, hypoglycemia, ondansetron, seizures.

*Ann Pharmacother* 2011;45:xxxx.

Published Online, 28 Dec 2011, *theannals.com*, DOI 10.1345/aph.1P332

Ondansetron is a 5-hydroxytryptamine (5-$HT_3$) receptor antagonist with antiemetic properties used extensively in the treatment of nausea and vomiting, especially postoperatively and in patients receiving chemotherapy. It decreases vagal activity and inhibits the vomiting center in the medulla oblongata. It is also known to decrease activity of the chemoreceptor trigger zone by blocking the serotonin receptors in the brain. Ondansetron does not affect dopaminergic, histaminergic, adrenergic, or cholinergic receptor activity and it has few neurologic adverse effects.[1] It is used widely as an antiemetic in gastroenteritis in children.[2-9] Unlike other antiemetic drugs, it rarely produces extrapyramidal symptoms or seizures, although a few cases of extrapyramidal adverse effects[10-18] and isolated cases of seizures[19,20] have been reported. 5-$HT_3$ receptors have been found to mediate stress-induced secretion of arginine vasopressin.[21-32]

We describe a 4-year-old boy who developed dystonia, seizures, and hypoglycemia soon after receiving an intravenous dose of ondansetron. We speculate on the mechanism underlying these reactions.

## Case Report

A 4-year-old boy weighing 15 kg presented to our emergency department following an episode of dystonia. Earlier that day, he had pain in his abdomen and 2 episodes of non-bilious, non-projectile vomiting and an episode of passing loose stools for which a physician had administered ondansetron 2 mg (0.13 mg/kg) intravenously. Within half an hour, he developed dystonic posturing of both upper limbs and clenching of teeth while still at the physi-

Author information provided at end of text.

cian's office; for this reaction, he was referred to our institution. He was otherwise conscious and well oriented.

He had no past history of adverse reactions to medications nor was he receiving any herbal or indigenous drugs. In the emergency department, he developed generalized tonic-clonic seizures that were witnessed by the pediatric registrar. There was upward rolling of the eyeballs lasting for a short time (seconds to minutes), followed by drowsiness. On examination, there were no signs of dehydration and his pulse rate, respiration, blood pressure, and temperature were within normal limits. There were no meningeal signs (no neck rigidity, absent Kernig's and Brudzinski's sign) and no focal neurologic deficits. However, hypertonia was evident, deep tendon reflexes were brisk, and Babinski's sign was positive.

Blood glucose level checked using a glucometer was 10 mg/dL immediately following the seizures. He was administered intravenous lorazepam 1.5 mg (0.1 mg/kg) to control his seizures and dextrose 10% (7 mL/kg) for the hypoglycemia. A blood glucose level measured after half an hour was 96 mg/dL and subsequent tests at 6 and 12 hours were also within the normal range. The child regained consciousness within 5 minutes of receiving the dextrose bolus and was subsequently completely normal neurologically. Serum electrolytes, capillary blood gas, serum creatinine, and blood urea nitrogen were normal. A computed tomography scan of the brain done without contrast showed no abnormalities. On follow-up after 1 week, the child had had no recurrences of the symptoms and was healthy. A diagnosis of acute ondansetron-induced dystonia and seizures associated with hypoglycemia was made. According to the Naranjo scale, ondansetron was probably the cause of the dystonia and seizures, and possibly the cause of the hypoglycemia.[33]

## Discussion

Ondansetron is a powerful antiemetic with very few adverse effects. It is used on account of its safety profile, whereas other antiemetic drugs, such as metoclopramide and domperidone, are known to cause extrapyramidal adverse effects. The use of antiemetics in pediatric gastroenteritis is controversial and is not recommended by the American Academy of Pediatrics. However, there are proponents for their use. Ondansetron has been studied as an adjunct to oral rehydration therapy in the treatment of acute gastroenteritis with mild to moderate dehydration.[2-9] Although studies are limited, research suggests the medication is safe and effective in preventing vomiting, the need for intravenous fluids, and hospital admissions in children with gastroenteritis.[2-9] Cubeddu et al.[3] studied 36 children with acute gastroenteritis. The children received a standard dose of ondansetron, metoclopramide, or saline placebo (sterile NaCl 0.9%) in addition to oral rehydration therapy. The patients who received either of the antiemetic medications showed a statistically significant ($p < 0.05$) improvement in the number of emetic episodes, in the percentage of patients with no emetic episodes, and in the percentage of patients with treatment failures, compared with those who received saline placebo during the 24-hour study period. Reeves et al.[5] found that children who were given ondansetron and intravenous fluids were more likely to have complete cessation of vomiting symptoms compared with those who were given intravenous fluids and placebo (70% vs 51%; $p = 0.04$).

The first case of extrapyramidal symptoms associated with ondansetron was reported by Dobrow et al.[11] Since then, there have been other reports of extrapyramidal adverse effects.[10-18] It is postulated that ondansetron may inhibit or reduce mesolimbic dopaminergic activity and antagonize the locomotor activity caused by mesolimbic dopamine.[1] Very few cases of seizures have been reported with ondansetron. 5-$HT_3$ receptor antagonists are known to have a role in epileptogenesis and seizure propagation.[19,20]

Hypoglycemia associated with dystonia and seizures on receiving an intravenous dose of a 5-$HT_3$ receptor antagonist has not been reported previously. In various studies, 5-$HT_3$ receptors have been found to mediate stress-induced release of adrenocorticotropin hormone (ACTH) and cortisol.[21-27] It is postulated that in response to stress, arginine vasopressin (AVP) is secreted from the hypothalamus into the hypophysial pituitary portal system and it is through this that ACTH is stimulated. The stress of hypoglycemia and the resulting stimulation of AVP have been examined in various human and animal studies.[28-31] Plotsky et al.[31] reported that insulin-induced hypoglycemia in rats resulted in no change in hypophysial portal venous corticotropin-releasing factor levels, but caused significant increases in AVP levels. When hypoglycemia is moderate, corticotropin-releasing factor is the main factor responsible for the release of ACTH, which normalizes blood glucose. In severe hypoglycemia, AVP is dramatically increased and this regulates ACTH response.[31] 5-$HT_3$ receptors have also been studied in exercise-induced vasopressin secretion and it has been shown that ondansetron significantly reduced the AVP increase induced by physical exercise.[32]

Serotoninergic receptors act as afferent pathways that stimulate AVP-induced release of ACTH and cortisol in response to stress.[27] Ondansetron, a 5-$HT_3$ receptor antagonist, may lead to hypoglycemia by inhibiting the release of ACTH and cortisol.

Our patient had dystonia and seizures, as well as low blood glucose, in close proximity to an intravenous dose of ondansetron. Hypoglycemia per se can produce seizures. Symptomatic hypoglycemia in a child who was completely well before the episode seems unlikely to be due to a storage disorder. It is postulated that the glucose stores were low in this child who was vomiting and that on-

dansetron mediated both the dystonic reaction and blunted the steroid response to hypoglycemia through antagonism of serotoninergic receptors. This is, however, speculative and more studies are warranted to establish this association. According to the Naranjo scale, ondansetron was a possible cause of our patient's hypoglycemia.[33]

The dramatic onset of dystonia and seizures in our patient, an otherwise developmentally and neurologically healthy child, could be related to ondansetron. The associated hypoglycemia also seems to be related to the 5-$HT_3$ receptor antagonist ondansetron. The child recovered completely and has had no recurrence of dystonia or seizures and no neurologic sequelae subsequently. In conclusion, ondansetron is a relatively safe antiemetic but in rare instances it may result in adverse effects such as hypoglycemia, seizures, and dystonia.

**Aneet Patel**, MBBS Student, Department of Pediatrics, St. Stephen's Hospital, Tis Hazari, New Delhi, India
**Shweta Mittal** MD, Registrar, Department of Pediatrics, St. Stephen's Hospital
**Samiksha Manchanda** MBBS, House Officer, Department of Pediatrics, St. Stephen's Hospital
**Jacob Mammen Puliyel** MD MRCP M Phil, Head of Department, Department of Pediatrics, St. Stephen's Hospital
**Correspondence:** Dr. Mittal, dr_shveta07@rediffmail.com
**Reprints/Online Access:** www.theannals.com/cgi/reprint/aph.1P332
**Conflict of interest:** Authors reported none

## References

1. Wilde MI, Markham A. Ondansetron. A review of its pharmacology and preliminary clinical findings in novel applications. Drugs 1996;52:773-94.
2. Manteuffel J. Use of antiemetics in children with acute gastroenteritis: are they safe and effective? J Emerg Trauma Shock 2009;2:3-5.
3. Cubeddu LX, Trujillo LM, Talmaciu I, et al. Antiemetic activity of ondansetron in acute gastroenteritis. Aliment Pharmacol Ther 1997;11:185-91.
4. Freedman SB, Adler M, Seshadri R, Powell EC. Oral ondansetron for gastroenteritis in a pediatric emergency department. N Engl J Med 2006; 354:1698-705.
5. Reeves JJ, Shannon MW, Fleisher GR. Ondansetron decreases vomiting associated with acute gastroenteritis: a randomized, controlled trial. Pediatrics 2002;109:e62.
6. Ramsook C, Sahagun-Carreon I, Kozinetz CA, Moro-Sutherland D. A randomized clinical trial comparing oral ondansetron with placebo in children with vomiting from acute gastroenteritis. Ann Emerg Med 2002;39:397-403.
7. Roslund G, Hepps TS, McQuillen KK. The role of oral ondansetron in children with vomiting as a result of acute gastritis/gastroenteritis who have failed oral rehydration therapy: a randomized controlled trial. Ann Emerg Med 2008;52:22-9.e6.
8. Spirko BA. Antiemetic use for gastroenteritis in children. Ann Emerg Med 2003;41:585-6.
9. Leman P. Utility of ondansetron in children with vomiting. Ann Emerg Med 2002;40:366-7.
10. Garcia-del-Muro X, Cardenal F, Ferrer P. Extrapyramidal reaction associated with ondansetron. Eur J Cancer 1993;29A:288.
11. Dobrow R, Coppock M, Hosenpud J. Extrapyramidal reaction caused by ondansetron. J Clin Oncol 1991;9:1921.
12. Extrapyramidal side-effects during ondansetron therapy. Geneesmiddelen Bull 1993;27:7.
13. Tolan M, Fuhrman T, Tsueda K, Lippmann SB. Perioperative extrapyramidal reactions associated with ondansetron. Anesthesiology 1999;90:340-1.
14. Duncan M, Nikolov N, O'Kelly B. Acute chorea due to ondansetron in an obstetric patient. Int J Obstetr Anesth 2001;10:309-11.
15. Ritter MJ, Goodman BP, Sprung J, Wijdicks EF. Ondansetron-induced multifocal encephalopathy. Mayo Clin Proc 2003;78:1150-2.
16. Sprung J, Choudhry FM, Hall BA. Extrapyramidal reactions to ondansetron: cross-reactivity between ondansetron and prochlorperazine? Anesth Analg 2003;96:1374-6.
17. Lee CY, Ratnapalan S, Thompson M, et al. Unusual reactions to 5-$HT_3$ receptor antagonists in a child with rhabdomyosarcoma. Can J Clin Pharmacol 2010;17:e1-4.
18. Turner SR, Pinsk M. Ondansetron associated hypokalemia in a 2-year-old with pre-B-cell ALL. J Pediatr Hematol Oncol 2008;30:58-60.
19. Sharma A, Raina V. Generalized seizures following ondansetron. Ann Oncol 2001;12:131-2.
20. Singh NN, Rai A, Selhorst JB, Acharya JN. Ondansetron and seizures. Epilepsia 2009;50:2663-6.
21. Iovino M, Steardo L. Effect of substances influencing brain serotonergic transmission on plasma vasopressin levels in the rat. Eur J Pharmacol 1985;113:99-103.
22. Van de Kar LD. Neuroendocrine pharmacology of serotonergic neurons. Annu Rev Pharmacol Toxicol 1991;31:289-320.
23. Udelsman R, Chrousos GP. Hormonal responses to surgical stress. Adv Exp Med Biol 1988;245:265-72.
24. Van de Kar LD, Richardson-Morton KD, Rittenhouse PA. Stress: neuroendocrine and pharmacological mechanisms. Methods Achiev Exp Pathol 1991;14:133-73.
25. Hashimoto K, Murakami K, Takao T, Makino S, Sugawara M, Ota Z. Effect of acute ether or restraint stress on plasma corticotropin-releasing hormone, vasopressin and oxytocin levels in the rat. Acta Medicina Okayama 1989;43:161-7.
26. Fyhrquist F, Tikkanen I, Linkola J. Plasma vasopressin concentration and renin in the rat: effect of hydration and hemorrhage. Acta Physiol Scand 1981;113:507-10.
27. Jørgensen H, Knigge U, Kjaer A, Warberg J. Serotonergic involvement in stress-induced vasopressin and oxytocin secretion. Eur J Endocrinol 2002;147:815-24.
28. Volpi R, Chiodera P, Giuliani N, et al. 5-$HT_3$ serotoninergic receptor mediation of hypoglycemia induced arginine vasopressin but not oxytocin secretion in normal men. J Endocrinol Invest 1998;2:7-11.
29. Caraty A, Grino M, Locatelli A, et al. Insulin induced hypoglycemia stimulates corticotrophin-releasing factor and arginine vasopressin secretion into hypophysial portal blood of conscious, unrestrained rams. J Clin Invest 1990;85:1716-21.
30. Baylis PH, Robertson GL. Rat vasopressin response to insulin-induced hypoglycemia. Endocrinology 1980;107:1975-9.
31. Plotsky PM, Bruhn TO, Vale W. Hypophysiotropic regulation of adrenocorticotropin secretion in response to insulin-induced hypoglycemia. Endocrinology 1985;117:323-9.
32. Coiro V, Maffei ML, Volta E, et al. Effect of serotonergic system on AVP secretion induced by physical exercise. Neuropeptides 2010;44:53-6.
33. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45.