

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

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Ondansetron is a 5-hydroxytryptamine (5-HT₃) 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 effects¹⁰⁻¹⁸ and isolated cases of seizures^{19,20} have been reported. 5-HT₃ 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.

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-HT₃) 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-HT₃ 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-HT₃) receptor, dystonia, hypoglycemia, ondansetron, seizures.

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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-

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-HT₃ 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-HT₃ receptor antagonist has not been reported previously. In various studies, 5-HT₃ 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-HT₃ 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

Serotonergic receptors act as afferent pathways that stimulate AVP-induced release of ACTH and cortisol in response to stress.²⁷ Ondansetron, a 5-HT₃ 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 serotonergic 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-HT₃ 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.

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