Ondansetron toxicity in an infant
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Introduction. Ondansetron, an increasingly prescribed 5-HT₃ antagonist used in the management of nausea and vomiting of various etiologies, has a well-established safety profile in therapeutic use. However, little is known about its effects in the setting of an overdose. We describe the first case of severe toxicity in an infant who unintentionally ingested a large quantity of ondansetron. Case report. A 12-month-old infant who ingested seven to eight tablets of his mother’s Zofran (ondansetron) ODT 8 mg rapidly developed obtundation and myoclonic movements. While treated by health care providers, he developed seizures, hepatotoxicity, QTc prolongation, and a serotonin syndrome that required endotracheal intubation and intensive care unit management. His clinical status improved over the course of 24 h with supportive care, and he was discharged to home with no sequelae. Discussion. With the increasing popularity of ondansetron among health care providers, particularly for the control of nausea in pregnant women, toddlers in the household may become inadvertently exposed to ondansetron toxicity. This case portrays that, despite the safety of this agent in therapeutic dosage, severe toxicity may be seen in excessive amounts, particularly in infants. Conclusion. Health care providers should recognize the risk for acute toxicity following ondansetron overdose, particularly in infants and toddlers.

Keywords Ondansetron; Toxicity; Acute poisoning; Adverse effects; Antiemetic

Introduction

Ondansetron hydrochloride is an antiemetic commonly used to treat nausea and vomiting in patients receiving chemotherapy, in post-operative patients, and in pregnancy. Recently, a number of pediatric studies have documented the drug’s efficacy in treating vomiting secondary to acute gastroenteritis, where it increases the success of oral hydration therapy and reduces the need for hospitalizations (1,2). Ondansetron has become the preferred antiemetic in children and adults because of its superior efficacy and low rate of adverse events. There have been few reports of serious toxicity after overdose of this drug.

We report the clinical course of a 12-month-old infant who ingested his mother’s ondansetron, developing deep sedation requiring endotracheal intubation for airway protection. To our knowledge, this is the first report of significant toxicity in an infant after ondansetron overdose. Given the increasing use of this drug in both inpatient and outpatient settings, this case illustrates the potential for major toxicity from this drug in young children.

Case report

A 12-month-old, healthy infant weighing 10 kg ingested seven to eight tablets of 8 mg ondansetron, an estimated 5.6–6.4 mg/kg (therapeutic dosage = 0.15 mg/kg), recently prescribed to his mother to treat pregnancy-related nausea and vomiting. She found the infant playing with the open bottle of the medication and estimated the number of tablets that were missing. No other medications were in proximity to the child.

Within 20 min of ingestion, the infant developed somnolence and intermittent “jerking” movements of his extremities. Emergency medical services were called and the infant was transported to a local emergency department. Upon arrival, his vital signs included a heart rate of 175 beats/min (age-specific normal range 89–151 beats/min), a respiratory rate of 35 breaths/min (age-specific normal range 23–39 breaths/min), a blood pressure of 123/74 mmHg (age-specific normal range <102/55), and an oxygen saturation of 98% on room air. He was noted to be responsive only to painful stimulus. His breathing was stridorous. He had horizontal nystagmus and persistent myoclonic movements of his extremities. Because of his depressed mental status, the decision was made to perform endotracheal intubation. Rapid sequence induction was accomplished using intravenous midazolam, morphine, and succinylcholine. After securing his airway, a dose of activated charcoal was administered via a nasogastric tube. His initial laboratory tests revealed a white blood cell count of
12.3 k/mm³ (age-specific normal range 6.0–17.0 k/mm³), a hematocrit of 36.2% (age-specific normal range 33–36%), and platelets of 376 k/mm³ (age-specific normal range 150–350 k/mm³). The electrolytes were within normal limits for his age. His hepatic function tests were notable for an aspartate aminotransferase (AST) of 93 U/L (age-specific normal range 20–65 U/L) and an alanine aminotransferase (ALT) of 127 U/L (age-specific normal range <54 U/L). Urine drugs of abuse and serum acetaminophen, ethanol, aspirin, and tricyclic antidepressant immunoassay toxicology screens were negative. No additional confirmatory tests were performed given the witnessed ingestion and absence of other agents in the household. After initial stabilization, the infant was transferred to a tertiary care center intensive care unit.

During his interfacility transport, the infant developed a brief generalized tonic–clonic seizure associated with significant oxygen desaturation. The seizure resolved with the administration of lorazepam. Also while in the ambulance, the patient developed a diffuse erythematous rash that was more pronounced in the extremities. Upon arrival to the pediatric intensive care unit, his physical exam was notable for facial flushing, dilated and poorly reactive pupils, diaphoresis, and hyperreflexia with three to four beats of clonus in his lower extremities. His electrocardiogram revealed a sinus tachycardia with a manually calculated QTc interval of 461 ms (age-specific normal value ≤440 ms).

The infant was successfully extubated 20 h post-ingestion. His heart rate normalized to 110 beats/min and his repeat electrocardiogram revealed a QTc at 390 ms. He was monitored in the intensive care unit for a period of 24 h after his ingestion. During the initial hospital course, his maximum temperature recorded was 38.4°C. He was discharged after a 48-h hospitalization. At the time of discharge, physical exam and electrocardiogram were normal. His AST and ALT improved to 52 and 78 U/L, respectively. Although we cannot exclude the presence of pre-existing abnormal hepatic tests, due to the absence of baseline testing, the rapid clinical and biochemical improvement precluded the need for further diagnostic evaluation.

Discussion

Ondansetron is a commonly used antiemetic with a favorable safety profile. It has been shown to be effective in treating chemotherapy-induced nausea and vomiting when compared with older antiemetics. Given the drug’s efficacy, clinicians are increasingly using ondansetron to treat a range of illnesses, including acute gastroenteritis and nausea and vomiting during pregnancy (1–3). Consequently, this medication is being found with greater frequency in households with young children.

Ondansetron is available both in intravenous formulation as well as in 4- and 8-mg tablets for oral administration. For the prevention of nausea and vomiting during chemotherapy, adults and children over the age of 12 years receive an initial oral dose of 8 mg; children aged 4–11 years receive a 4 mg dose. The mechanism of action of ondansetron is antagonism of the serotonin sub-type 3 (5-HT₃) receptor where it overcomes the emetogenic effects of serotonin at the chemoreceptor trigger zone (CTZ) in the central nervous system. In addition, ondansetron is thought to have peripheral effects at 5-HT₃ receptors in the gastrointestinal tract, leading to decreased gastrointestinal motility. Ondansetron is rapidly absorbed after oral administration but has low systemic bioavailability (less than 10%). The cytochrome P-450 enzymes responsible for ondansetron metabolism are CYP1A1, CYP1A2, CYP2D6, and CYP3A4 (4–7). The drug’s major metabolites are 7- and 8-hydroxyl and N-desmethyl derivatives (7); its mean elimination half-life in normal adult volunteers ranges from 3.5–5.5 h. Children less than 18 years of age tend to have higher ondansetron clearance rates compared to adults leading to a shorter half-life in the range of 2.8–4.9 h (4,6). In contrast, very young infants (age 1–4 months) have decreased rates of clearance as evidenced by an elimination half-life of 6.7 h (4,5). Ondansetron does not appear to induce or inhibit the cytochrome P-450 drug metabolizing enzyme system of the liver. Drugs such as phenytoin, carbamazepine, and rifampicin, which are potent inducers of CYP3A4, could potentially accelerate the clearance of ondansetron (4,6). Renal clearance of the drug is low, indicating that the major route of systemic clearance is via hepatic metabolism.

The literature regarding adverse drug reactions of ondansetron remains limited to case reports of iatrogenic medication errors and data from post-marketing spontaneous drug reports. When compared to antiemetics from other classes, ondansetron has been found to be remarkably safe with few severe adverse events reported. According to the manufacturer’s drug monograph, the most common adverse events are headache, constipation, dizziness, sedation, diarrhea, and transient elevation of liver enzymes (—two to three times the upper limit of normal) (4,5). Of those, headache is the most commonly reported symptom. Other rare reported adverse events include QTc prolongation, tachycardia, chest pain, dystonic reactions, seizures, and transient blindness (4,5).

In our patient, the initial presentation consisted of somnolence, myoclonic movements, rash, airway obstruction, possible seizures, clonus, elevated liver enzymes, and a prolonged QTc interval. Among the initial symptoms, the rash and stridorous breathing could be attributed to a hypersensitivity reaction, one of the reported potential adverse drug reactions associated with therapeutic use of ondansetron (5).

A few cases reporting seizures with the therapeutic use of ondansetron have been documented. However, the scientific basis for this complication remains speculative (7–9). An in vivo study of rodent hypothalamus cells suggests that ondansetron’s role in suppressing GABA-activated current may be the molecular basis of convulsions. In terms of hepatotoxicity, an increase in hepatic transaminases has been reported in up to 2% of patients treated with ondansetron for the prevention of chemotherapy-induced nausea and vomiting. Our patient had peak levels of ALT and AST of 127 and 93
U/L, respectively, which normalized within 48 h of ingestion. The mechanism of ondansetron hepatotoxicity is also unclear.

Other antiemetics belonging to the 5-HT3 antagonist class have QTc prolonging effects reported, for example, dolasetron (Anzemet®), another 5-HT3 antagonist (10–12). Boike et al. investigated the cardiovascular effects of ondansetron in 13 healthy adults and found that the mean post-dose QTc interval was longer after ondansetron compared to that in patients receiving placebo (12).

It is also notable that our patient’s symptom complex was consistent with the serotonin surge that defines the serotonin syndrome. The syndrome is characterized by a triad of altered mental status, neuromuscular abnormalities, and autonomic dysfunction. Its symptoms are quite variable and include hyperthermia, hypomania, myoclonus, hyperreflexia, seizures, diarrhea, nausea, and changes in blood pressure. Our patient developed tachycardia, facial flushing, mydriasis, myoclonic movements, temperature and blood pressure instability, and lower extremity hyperreflexia, all of which are components of the serotonin syndrome. The application of the recently proposed Hunter Serotonin Toxicity Criteria supports this diagnosis in this patient (15). There are case reports of patients taking proserotonergic drugs who develop the syndrome after administration of ondansetron. The authors reporting this phenomenon have speculated that the antagonism at the 5-HT3 receptor subtype increases the synaptic levels of serotonin, particularly in the central nervous system, leading to features of serotonin excess (16,17).

Treatment of ondansetron-induced toxicity is primarily supportive. Activated charcoal could be beneficial if administered within 1 h of ingestion. However, because ondansetron may slow gastrointestinal motility, the presence of bowel sounds should be confirmed prior to charcoal administration to avoid its potential complications in the setting of an ileus. Furthermore, the ingestion of oral dissolvable tablets likely eliminates all advantages related to the early use of charcoal because of the extremely rapid absorption of the drug. Airway protection should be initiated if there is evidence of alteration of consciousness, excessive drooling, or stridor. Laboratory assessment should include serial measurement of transaminases and an electrocardiogram to evaluate for QTc prolongation. Furthermore, medications known to prolong the QTc interval should be withheld. Based on published references, including Poisindex, and our own experience, we would recommend a brief period of observation (up to 2 h) in asymptomatic children. Those children can be safely discharged to home if they remain symptom-free for that interval. The importance of educating caregivers about the value of childproofing both prescription and nonprescription medications can never be overemphasized, having the goal of preventing potentially life-threatening events secondary to unintentional drug exposures in the pediatric population.

This case describes the potential toxicity that may be seen after accidental overdose with ondansetron in a healthy infant. Given the increasing use of this medication in outpatient settings, health care professionals and caregivers should recognize this risk and be reminded of the importance of safeguarding medications in households with young children.

References