UNUSUAL REACTIONS TO 5-HT_3 RECEPTOR ANTAGONISTS IN A CHILD WITH RHABDOMYOSARCOMA

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ABSTRACT

A case of unusual reactions consisting of involuntary abnormal facial movements in a child following exposure to the 5-HT_3 receptor antagonists for prophylaxis against chemotherapy-induced vomiting is presented. Potential mechanisms for these reactions are discussed.

Key words: *5-HT_3 receptor antagonists, child*

Case Report

A 7-year-old boy with a history of prostatic rhabdomyosarcoma and lung and bone metastases developed abnormal facial movements while receiving ondansetron 4 mg p.o. q8h (5 mg/m^2/dose) for anti-emetic prophylaxis. These movements consisted of involuntary blinking of the eyes, pursing of the lips, forward thrusting of the jaw and protrusion of the tongue. The patient had no loss of consciousness and had no previous history of movement disorders or seizures. Over the course of 3 days, the frequency of these movements increased from 1 to 2 times a day to 2 to 3 times per hour, prompting the patient's mother to bring the patient to a local emergency department. His past medical history was significant for asthma and prostatic rhabdomyosarcoma. Concomitant medications at that time included hydromorphone, hydroxyzine, dimenhydrinate, lorazepam, ranitidine, bisacodyl, and docusate. There was no herbal product use. The patient had a previous history of adverse reactions to sulfonamides (hives), morphine (pruritis), vancomycin (red man syndrome), and dexamethasone (mood changes). His blood tests showed normal electrolytes, hepatic and renal function. Magnetic resonance imaging was performed and was reported to be normal. The patient was evaluated by a paediatrician with expertise in neurological disorders and a diagnosis of ondansetron-induced movement disorder was made. These movements decreased when the dose of ondansetron was reduced and resolved with its discontinuation.

On admission for a subsequent cycle of chemotherapy with ifosfamide and etoposide, the patient was treated with granisetron 480 µg iv. q12h (20 µg/kg/dose) for anti-emetic prophylaxis. (The patient previously had tolerated these chemotherapeutic drugs and 5-HT_3 receptor antagonists, ondansetron or granisetron, for anti-emetic prophylaxis.) Other medications included hydromorphone (controlled release) 9 mg p.o. q12h, hydromorphone (conventional release) 2 mg p.o. q4h p.r.n. for pain, ranitidine 75 mg p.o. b.i.d., bisacodyl 5 mg p.o. q.h.s. p.r.n., docusate 100 mg p.o. o.d., lorazepam 0.5 mg iv./p.o./sl. q6h p.r.n., dimenhydrinate 20 mg iv. q6h, hydroxyzine 25 mg p.o. b.i.d., and cefuroxime 1 g iv. q8h (the latter was started during his hospitalization for empiric treatment of possible chest infection). His physical examination on admission was unremarkable.

On day 3, the patient developed repeated forward thrusting of the jaw and simultaneous blinking of the eyes, which were self-limiting (each episode lasting for seconds, followed by minutes of resolution and recurrent episodes over 90 minutes) and less severe than those associated with ondansetron use. The temporal relation between granisetron infusion (over 15 minutes) and the onset of these abnormal movements was approximately 5 hours. As vomiting was effectively prevented, granisetron was continued until completion of therapy, despite recurrence of similar abnormal movements on the following day. The patient was discharged from the hospital. With subsequent cycles of chemotherapy, the patient was able to tolerate granisetron. Verbal consent for this case report was provided by the patient's mother.

DISCUSSION

Ondansetron and granisetron are 5-HT_3 receptor antagonists that are commonly used for the prevention of chemotherapy-induced nausea and vomiting.[1] Individual 5-HT_3 receptor antagonists differ in their chemical structures, affinities for the 5-HT_3 receptor, and pharmacokinetics.[1] Ondansetron, the prototypical drug, is a carbazole derivative that is absorbed in the gastrointestinal tract and metabolized in the liver by multiple cytochrome P450 (CYP) isozymes, including CYP1A1, CYP1A2, CYP2D6, and the CYP3A subfamily (with none of the CYP enzymes dominating the metabolism),[2] followed by glucuronide or sulphate conjugation.[1] For ondansetron, the time to reach peak plasma concentration (t_{max}) following oral and intravenous administration was 60-90 min and 20-30 min, respectively (reviewed in[3]). The mean elimination half-life of ondansetron in normal adult volunteers ranged from 3.5 to 5.5 hours and that in adult cancer patients was 4.0 hours.[4] In paediatric cancer patients (< 15 years of age), the plasma half-life of ondansetron was 2.4 hours.[4] It is excreted primarily in the urine, but also in the feces.[5-6] Ondansetron is a substrate of P-glycoprotein in the blood-brain barrier.[7] Following oral administration of ondansetron in volunteers, its concentrations in the cerebrospinal fluid were <15% of plasma concentrations.[8]

Granisetron is an indazole which undergoes primarily hepatic metabolism.[1] CYP3A is known to be involved, although a recent study reports that CYP1A1 is a more important CYP isozyme for both the main 7-hydroxylation pathway and an alternative 9'-demethylation pathway).[9] The t_{max} following oral and intravenous administration was 60-90 min and 30 min, respectively.[3] The mean terminal-phase plasma half-life of granisetron in adult volunteers was 4.91 hours and that in adult cancer patients was 8.95 hours.[10] Approximately 12% of the administered dose in normal volunteers was eliminated unchanged in the urine, with the remainder being excreted as metabolites (49% in the urine and 34% in the feces).[10] The pharmacokinetics of granisetron in adults and children is similar when total clearance and volume of distribution are adjusted by body weight.[10] Like other members of its class, granisetron is well tolerated.[1,11-15]

The most common side effects of 5-HT_3 receptor antagonists are constipation or diarrhea, headaches, and light-headedness.[1] Extrapyramidal reactions[16-25] to ondansetron have been described in adults, with an estimated frequency of <1%.[26] In the paediatric population, tremor, twitching, ataxia and rare acute dystonic reactions to ondansetron have been documented.[27] Recently, a case of neonatal extrapyramidal movements[28] that were attributed to withdrawal following maternal exposure to citalopram and ondansetron during pregnancy was reported.[29] In multiple clinical studies of granisetron, involving both adults and children,[11,30-39] extrapyramidal side effects were not observed.

In this case report, we described involuntary abnormal facial movements in a child following exposure to ondansetron and granisetron. The exact mechanism for these reactions remains elusive. In particular, it is unclear why this patient developed these abnormal facial movements, despite having had a history of uneventful exposures to these 5-HT_3 receptor antagonists (including their use with the same chemotherapeutic drugs) in the past. In estimating the probability of adverse reactions to 5-HT_3 receptor antagonists, we applied the Naranjo adverse drug reaction probability scale[40] – a tool which is commonly used to estimate the probability of adverse drug reactions and to improve reproducibility of assessments.[40-41]

Applying this scale to our patient, a score of 7 was obtained for ondansetron and a score of 3 for granisetron, consistent with probable and possible adverse drug reactions, respectively.

With regard to potential mechanisms, interaction between dopaminergic and serotonergic systems has been proposed as a possible explanation for dystonic reactions to ondansetron in adults.[20] Potential drug-drug interactions, including interactions with chemotherapeutic agents,[42] remain a possibility, although no specific interaction could be identified in this patient. In addition, inter-individual differences in drug metabolism cannot be excluded.[43]

In summary, this paper reports a case of unusual reactions consisting of involuntary abnormal facial movements in a child following exposure to the 5-HT$_3$ receptor antagonists for prophylaxis against chemotherapy-induced vomiting. Health professionals need to be aware of these possible, albeit rare, reactions to 5-HT$_3$ receptor antagonists in paediatric oncology patients.

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