Palonosetron-induced migraine-type headache

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To the Editor,

I read with great interest the case written by Singh *et al.*¹ regarding ondansetron-induced migraine-type headache. I recently encountered a case of severe migraine-type headache triggered in a young female following the administration of palonosetron for postoperative nausea and vomiting (PONV) prophylaxis prior to two different anesthetic exposures. The patient provided her consent to publish details about this case.

A 25-yr-old female with primary infertility was scheduled to undergo diagnostic laparoscopy. Her medical history included occasional migraines and anxiety for which she was taking oral propranolol 80 mg once a day. Physical examination and investigations were unremarkable. The patient fasted overnight, and she was premedicated with diazepam 5 mg *po* and ranitidine 150 mg *po* the night before and the morning of surgery. She was also given propranolol 80 mg *po* the morning of surgery.

After applying routine anesthesia monitors in the operating room, an 18G venous access was secured in the patient's right upper limb. Subsequently, palonosetron 0.075 mg *iv* was administered over ten seconds for the prophylaxis of PONV. After approximately ten minutes and before induction of anesthesia, the patient complained of a severe throbbing headache that was reported as predominantly unilateral and frontal in location. The patient described the headache as similar to her previous migraine

attacks. The symptoms lasted for 25 min and responded to treatment with a bolus of propofol 20 mg *iv* followed by a propofol infusion at the rate of 150 mg·hr⁻¹. Additionally, paracetamol 1 g *iv* was given over 20 min. After discussion with the patient and the surgeon, anesthesia was induced intravenously with fentanyl 100 µg and propofol 80 mg. The airway was secured with a 7.5-mm internal diameter endotracheal tube after adequate neuromuscular blockade with intravenous vecuronium. The procedure lasted about 45 min, and the patient's trachea was extubated after she awoke following reversal of neuromuscular blockade with neostigmine and glycopyrrolate. There was no headache on recovery, and the patient was transferred to the postanesthesia care unit.

The patient was rescheduled for tubal reconstruction one week later. After an 18G epidural catheter was secured at the L1-L2 interspace for intraoperative and postoperative pain management, a pre-emptive dose of palonosetron was administered as PONV prophylaxis. Once again, the patient developed a similar migraine-like headache after five minutes, which was treated effectively with propofol sedation. With the patient's agreement, anesthesia was induced with propofol and fentanyl. Anesthetic maintenance and recovery were uneventful. On the first postoperative day, intravenous paracetamol 1 g was given every six hours to prevent repeated attacks of migraine, and epidural analgesia with a continuous infusion of a dilute solution of local anesthetic was provided for 48 hr. The patient remained asymptomatic except for dull migraine following discharge to the ward.

Palonosetron is the latest 5-hydroxytryptamine-3 (5-HT₃) antagonist, which is being described as the first of a "second generation" of 5-HT₃ antagonists.² Following successful Phase III clinical trials, the Food and Drug Administration approved its use for prevention of PONV in

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March 2008. Compared with other 5-HT₃ antagonists, palonosetron has a far higher receptor affinity and a much longer half-life, conferring a prolonged duration of action. Palonosetron presents high receptor affinity and high selectivity for certain receptors and demonstrates low affinity for various other receptors, including 5-HT_{1A}, 1D, 2A, 2C.³ This feature makes it unlikely that palonosetron will produce unwanted effects at other receptor sites.² However, the non-serious and short duration headache remains palonosetron's most common side effect (9%).^A The exact mechanism of this palonosetron-induced headache is unknown. The severe headaches in our patient, a known migraine sufferer, may possibly have been precipitated by a weak 5-HT₁ antagonistic effect of palonosetron in association with 5-HT₇ receptor-mediated dilatation of the carotid artery.⁴ The subanesthetic doses of propofol (cumulative dose $\approx$ 90–100 mg) were highly effective in managing these migraine attacks on both occasions. This outcome has been attributed to the gamma aminobutyric acid A receptor agonist and cerebral vasoconstriction effects of propofol.⁵

It is not known if the incidence of migraine-type headache with palonosetron differs from that with other 5-HT₃ antagonists. As Singh *et al.* indicated, “Ondansetron should be used as a second- or third-line agent for treatment of

PONV and not as a routine drug for PONV prophylaxis in patients with a history of migraine or debilitating headache”.¹ This case suggests that caution should be exercised with all 5-HT₃ antagonists, including palonosetron, in patients susceptible to headache.

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