CASE REPORT

Refractory nausea and vomiting in the setting of well-controlled idiopathic intracranial hypertension

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SUMMARY

A 27-year-old woman with a history of recurrent nausea and vomiting in the setting of idiopathic intracranial hypertension (IIH) was admitted for control of unremitting nausea and vomiting. Initial antiemetic therapy included optimisation of IIH therapy by titrating acetazolamide, in addition to using ondansetron and metoclopramide as needed, with minimal relief. She was ultimately treated with palonosetron with complete resolution of her acute nausea. Nausea, often treated with 5-hydroxytryptamine (5-HT₃) receptor antagonists, approved for perioperative and chemotherapy-induced nausea, are used off-label to treat nausea and vomiting outside of those settings. The efficacy of different regimens has been compared in the literature and continues to remain controversial. When choosing from different 5-HT₃ antagonists there are other considerations, in addition to efficacy to consider: dosing schedule, half-life, time of onset, duration and cost-to-benefit ratio, and although one 5-HT₃ antagonist may not have been effective, another one may be. In our case palonosetron, with a significantly longer half-life than other 5-HT₃ antagonists, was effective in resolving nausea when compared with the more commonly used ondansetron.

BACKGROUND

Often plaguing inpatient medical treatment and idiopathic intracranial hypertension (IIH) is nausea and vomiting, which has been extensively studied but still remains, at times, difficult to resolve. Treatment revolves around antagonising specific receptors such as serotonin, muscarinic, dopamine, histamine, neurokinin and addressing the underlying aetiology. Treatment options may be limited due to the availability of medications, the patient's comorbidities and physician experience placing limitations on the vast amount of alternative treatments available. As many studies have been performed to compare the efficacy of different agents, even in specific situations, these studies have not been well distributed amongst off-label prescribers and consequently alternative agents may be underprescribed. This case demonstrates how although many commonly prescribed medications had been unsuccessful, reviewing the literature and ultimately prescribing palonosetron, that is, switching medications within the same class resulted in the resolution of symptoms. While working within the scope of one's practice and what is available on formulary using other approved agents, even within the same class,

may prove to be effective and beneficial for the patient.

CASE PRESENTATION

A 27-year-old gravida 7 para 4 woman with a history of difficult to control IIH was admitted for control of unremitting nausea and vomiting as well as symptoms of bilateral flank pain and dysuria. As a result of the nausea and vomiting, she had been unable to take her acetazolamide, which ultimately resulted in increased transient visual obscurations (TVO), as well as headache and tinnitus.

Her medical history had been significant for IIH, which had been treated with an optic nerve sheath fenestration, a sigmoid sinus stent, acetazolamide and multiple lumbar punctures. Regarding her surgeries, she had a herniorrhaphy, tubal ligation, tonsillectomy and cholecystectomy. Her family history had been unremarkable and she had denied the use of any tobacco, ethanol or illicit drug use. Other than the aforementioned, her review of systems was significant for a single febrile episode and diarrhoea.

On presentation her vitals had a temperature of 97.1°F, a heart rate of 85 beats per minute, a respiratory rate of 14 breaths per minute and blood pressure of 115/61 mmHg, with a pain rating of 5 on a 10-point scale. Optic examination had been pertinent for minimally elevated optic discs bilaterally with an anomalous vascular pattern, without an apparent obscuration of the nerve fibre layer. Her visual fields were to full confrontation without fixed visual field defects. Also with the use of an automated perimeter, her visual fields were examined and demonstrated mild patchy depressions (oculus dexter 6.84 and oculus sinister 10.43 Mallett distance units). She had an unchanged gait from baseline, without other focal neurological deficits.

INVESTIGATIONS

As nausea, headache and tinnitus are known symptoms of uncontrolled IIH, the initial work up was aimed at evaluation of the extent of the current disease. It included a CT of the head, which failed to demonstrate abnormalities, and an abdominal series, which demonstrated a non-obstructive bowel gas pattern.

In order to assess the dysuria and bilateral flank pain, a CT of the kidney, ureter and bladder was performed and was without evidence of nephrolithiasis or ureterolithiasis. Urinalysis was assessed and was negative for signs suggestive of an infection.

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Laboratory work up consisted of a normal basic metabolic panel and a negative β -human chorionic gonadotropin. Cerebrospinal fluid (CSF) examination showed normal protein, glucose, cell count and white cell count differential. Gram stain and culture were negative for infectious organisms.

Furthermore, for evaluation of her IIH, the lumbar puncture demonstrated an opening pressure of 18 cm H₂O, approximately 24 h after 1500 mg intravenous acetazolamide was administered. She underwent a full visual field examination which demonstrated new visual field constrictions above baseline.

Finally an esophagogastroduodenoscopy was performed and demonstrated mild gastritis, likely secondary to retching and determined not to be responsible for her nausea and emesis.

DIFFERENTIAL DIAGNOSIS

- ▶ Nausea and vomiting secondary to IIH
- ▶ Idiopathic nausea
- ▶ Cyclic vomiting syndrome
- ▶ Drug-induced nausea and vomiting
- ▶ Gastro-oesophageal reflux syndrome
- ▶ Functional nausea and vomiting
- ▶ Rumination syndrome

TREATMENT

As nausea and vomiting initially resulted in her non-adherence with acetazolamide, she was dosed 1500 mg of intravenous acetazolamide per day, which resulted in subsequent normal opening pressure during her lumbar puncture.

Then as her IIH appeared to be under adequate control, based on CSF pressure, escalating doses of ondansetron and metoclopramide were used, followed by scopolamine, with minimal success. All the while during her treatment, her QT_C was monitored with serial ECG. Next, as needed, metoclopramide was switched for promethazine, with continued failure of resolution of her nausea and vomiting.

Acetazolamide, for the treatment of IIH, was titrated to maximum tolerated doses, without improvement in symptoms. This was then followed by a trial-off of acetazolamide, which is known to induce nausea, without substantial impact on the patient's symptoms. Ultimately, the patient's antiemetic regimen was broadened and palonosetron was substituted for ondansetron with improvement of symptoms within 1 h and complete resolution of nausea within 3 h.

OUTCOME AND FOLLOW-UP

After treatment with 0.25 mg of palonosetron emesis had completely resolved, with significant improvement in nausea symptoms. Twenty-four hours after administration of palonosetron she was discharged home with esomeprazole for gastritis, continued acetazolamide for her IIH and as needed, ondansetron and scopolamine for nausea, as palonosetron is only offered intravenously.

On follow-up for nausea as an outpatient, she was noted to use ondansetron or metoclopramide on an as-needed basis. Ultimately, for symptoms of continued headaches and TVOs, after in-depth testing that included a 48 h continuous intracranial pressure (ICP) monitor, a ventriculoperitoneal shunt was placed, with improvement in TVOs and overall headache control.

DISCUSSION

Nausea is often due to an imbalance of neurotransmitter stimulation at the area postrema or other intrinsic aetiologies, and antiemetic selection is based on the likely aetiology.

5-Hydroxytryptamine (5-HT₃) receptor antagonists, which are approved for perioperative and chemotherapy-induced nausea, are often the first-choice therapy. In our case, multiple different traditional and non-traditional regimens were attempted during the treatment of this patient with IIH.

However, nausea in patients with IIH has been speculated to be the result of increased pressure on the vestibulocochlear nerve due to increased ICP.¹ This, in part, stems from the constellation of symptoms such as tinnitus, headache, dizziness and nausea which is found in IIH and often improved with lowering of ICP. This is by no means conclusive in suggesting that this is the only means of nausea in these patients, as having IIH and other known causes of nausea are not mutually exclusive. Thus in this patient only after control of the most likely aetiology, uncontrolled IIH secondary to non-adherence, were other aetiologies and treatments investigated. This included the previously effective ondansetron, promethazine and metoclopramide, all used off-label, prior to drug switching within the 5-HT₃ antagonist class with resolution of the acute symptoms.

Palonosetron, a 5-HT₃ antagonist with a half-life of 40 h and improved side-effect profile compared with others in its class, has been demonstrated to be superior to ondansetron, ramosetron and placebo for postoperative nausea prevention.²⁻³ Highlighting the complexity of treating refractory nausea, this case describes palonosetron being successfully used for nausea and vomiting, as well as class switching and switching therapy within classes. During a prospective, randomised, double-blinded, head-to-head trial, Kim *et al*² demonstrated that palonosetron was superior to ondansetron and ramosetron in the following postsurgical outcomes when used prophylactically: total number of patients nausea free, retching, vomiting and those who needed rescue antiemetics.

While the mechanism of palonosetron's increased effectiveness over ondansetron continues to be debated, it appears to stem from the pharmacokinetics of the medication, which includes a slowed disassociation from the receptor, internalisation of the receptor, inhibition of substance P-mediated responses and allosteric binding, all the while giving it a 40 h half-life.⁴⁻⁵ Also the medication is known to prevent calcium influx on the serotonin receptor, which gives this medication another unique property over others in its class, which is of undefined clinical significance at this time.⁴

As there have been several studies which have compared the efficacy of palonosetron with other 5-HT₃ antagonists, Chun *et al*³ have also studied the efficacy of palonosetron for the prevention of postoperative nausea and emesis. They found no difference in outcomes in the first 24 h but did record a significant improvement in the incidence of nausea and vomiting over 72 h.³

Although palonosetron has been demonstrated to be effective and superior in the aforementioned platforms, there still remains a lack of studies on the off-label populations that are seen in the typical inpatient wards. These include those with infectious gastroenteritis, drug-induced nausea, idiopathic and so forth, for in these populations the more commonly used agents may be superior. Also in comparison to ramosetron and ondansetron, palonosetron is only available for intravenous administration. In addition to other reasons to use alternate antiemetics are the options on one's formulary and the cost-to-benefit ratio.

In summary, refractory nausea and emesis can be difficult to treat. The first priority should be medically managing contributing conditions maximally, in our case, IIH. If standard antiemetic therapy is insufficient to control symptoms and no other aetiologies are discovered, consideration should be given to the alternative drugs in the same class, as there are differences, and

even class switching as well. For our patient, the key was identifying palonosetron as an option, given a long half-life and equivalent, if not improved, safety profile in comparison to other 5-HT₃ antagonists. Finally, while this case report demonstrated efficacy in our patient with IIH, this is not to say it will be effective in all patients with IIH. Here, only further research and investigation will provide those much needed answers.

Learning points

- ▶ Palonosetron is an effective and safe alternative to ondansetron for the treatment of nausea and emesis.
- ▶ Palonosetron has a long half-life and might prove more effective for refractory nausea and emesis than traditional 5-HT₃ antagonists.
- ▶ Providers should not discount other drugs in the same class as ineffective, given the potential for slightly different pharmacokinetics and pharmacodynamics.

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Contributors DLB was the primary author and organiser for the project. JRD was directly involved with the care of the patient, as well as research for treatment aetiologies and RAR was the admitting, as well as primary care physician of the patient, who also aided in integrating all aspects of care, as well as confirming historical aspects or previous care of the patient.

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