Review Article

Opioid-induced nausea and vomiting

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Abstract: Opioids are broad spectrum analgesics that are an integral part of the therapeutic armamentarium to combat pain in the palliative care population. Unfortunately, among the adverse effects of opioids that may be experienced along with analgesia is nausea, vomiting, and/or retching. Although it is conceivable that in the future; combination agents (opioids combined with agents which may nullify emetic effects) currently; nausea/vomiting remains a significant issue for certain patients. However, there exists potential current strategies that may be useful in efforts to diminish the frequency and/or intensity of opioid-induced nausea/vomiting.

Key Words: Nausea; vomiting, opioids; olanzapine; NK-1; antagonists; moxduo; tapentadol

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Introduction

Although it is not uncommon for patients being started on opioids to initially experience nausea and/or vomiting, generally tolerance to these effects tends to occur within days to weeks (1). However, it is also appreciated that OINV is not always a transient or short-term adverse effect. In 2007, Portenoy and colleagues reported the results of a 3-year U.S. registry study evaluated more than 200 patients in chronic treatment with controlled-release (CR) oxycodone (2). The mean daily dose of CR oxycodone was 52.5 mg, and this was associated with adverse effects; the most common being constipation and nausea (2).

Nausea is highly distressing symptom that may occur with or without vomiting and can affect overall outcome, medication (e.g., opioid therapy), compliance, enteral absorption, and quality of life. These symptoms occur in about one-third of those started on morphine, and the incidence severity is roughly in the same ballpark for all opioids (3). However, patients who have experienced these symptoms from a phenanthrene opioid with a hydroxyl group at position 6 (6-OH) (e.g., morphine), may be able to tolerate a "dehydroxylated" phenanthrene opioid (lacking a 6-OH) (e.g., hydromorphone) with less nausea (4). Approximately 60% of patients with advanced cancer report nausea and 30% report vomiting (5).

There may be significant interindividual variation in the incidence, intensity, or the development of tolerance of nausea and/or vomiting among various patients. Adverse effects as well as analgesia may depend on patient-specific factors influencing drug metabolism and drug interactions (6), as well as differences in the pharmacokinetics and/or pharmacodynamics of different opioids (7). Thus, careful titration of a selective trial and error approach (e.g., trying different opioid analgesics; opioid rotation) may reveal a particular beneficial opioid with maximal analgesia and minimal nausea/vomiting for an individual patient, whereas a different opioid analgesic may be similarly optimal for another patient.

Moore and McQuay performed a systematic review of oral opioids for chronic noncancer pain which revealed that 25% of patients developed dry mouth, 21% developed nausea, and 15% developed constipation (8). Furthermore, a significant proportion of patients on opioids withdrew due to adverse events (8). Kalso and colleagues also performed a systematic review of randomized controlled trials of opioids

for chronic noncancer pain that reported that roughly 80% of patients experienced at least one adverse event; 32% of patients developed nausea and 15% developed vomiting (9).

Pathophysiology of OINV

The experience of nausea/vomiting may involve multiple receptors (10). Opioid-induced nausea/vomiting (OINV) may be difficult to tease apart from chemotherapy-induced nausea/vomiting (CINV), radiation-induced emesis (RIE), or postoperative nausea/vomiting (PONV); thus "pure" OINV has not been extensively well studied alone. Although the precise mechanisms of opioid-induced nausea and vomiting are not entirely certain, multiple and complex mechanisms are likely involved, OINV may be due to multiple opioid effects, including (I) enhanced vestibular sensitivity (symptoms may include vertigo and worsening with motion), (II) direct effects on the chemoreceptor trigger zone, and (III) delayed gastric emptying (symptoms of early satiety and bloating, worsening postprandially).

Nausea and vomiting are well-known opioid-induced effects that may possess peripheral and central components. The mechanisms involved in nausea are extremely complex. Low doses of opioids activate mu opioid receptors in the chemoreceptor trigger zone (CTZ), thereby stimulating vomiting. Alternatively, higher dose opioid doses may suppress vomiting by acting at receptor sites deeper in the medulla. The CTZ is in the floor of the fourth ventricle, a location which is considered in the periphery due to its incomplete blood brain barrier.

Opioids can directly stimulate the vestibular apparatus, although the mechanism of action is still unknown. It has been postulated that morphine and synthetic opioids increase vestibular sensitivity, perhaps by opioids activating MORs on the vestibular epithelium (11). The rate inner ear possesses DORs and KORs (12), however, the role of these receptors in humans remains uncertain. The vestibular apparatus provides direct input into the vomiting center by way of Histamine H1 and cholinergic (AchM) pathways (13). Due to the permeability of the blood-brain barrier at the chemoreceptor trigger zone, it is considered "peripheral' and the neurons in the chemoreceptor trigger zone may be exposed to the effects of various drugs, metabolites, and toxins. Endogenous opioids appear to be involved in the mechanisms of opioid-induced vomiting, likely via stimulating mu opioid receptors and delta opioid receptor in the chemoreceptor trigger zone of the vomiting center (14). Opioid-induced emesis appears to occur via pathways from the brainstem chemoreceptor trigger zone, tolerance at the central opioid receptor level may at different rates versus receptors outside the central nervous system (15). If the interaction between opioid agonists and opioid receptors in the chemoreceptor trigger zone for a particular opioid is relatively long compared with its peripheral actions, tolerance to the emetic actions of opioids could occur earlier or may be more intense (16).

Chronic opioid use may lead to long-term repeated activation of mu opioid receptors in the myenteric and submucosal plexi with subsequent uncoordinated bowel activity, and resultant opioid-induced bowel dysfunction (17). Opioids reduce peristalsis via decreasing gastrointestinal secretions and relaxing longitudinal muscle in the colon as well as simultaneously/increasing contractions of the circular muscles (15). Stool may dry and harden due to the absence of longitudinal propulsion and increased circular muscle activity enhance the tone of the bowel with resultant impaired gastrointestinal motility, bowel distention and cramping (18) that may be associated with nausea and/or vomiting.

Although the precise mechanisms of opioid-induced nausea are incompletely understood, it is likely that a predominant mechanism involves opioid-induced stimulation of the mu-opioid receptor (MOR), since it can be successfully treated by opioid receptor antagonists [e.g., naloxone (Naloxone is an antagonist at mu, kappa, and delta opioid receptors, but it is most active at the mu opioid receptor)] [this, however, does not rule out a role for other opioid receptors such as the kappa-opioid receptor (KOR) or delta-opioid receptor (DOR) in contributing to or modulating OINV].

The emetic effects of some opioids seem most likely to occur secondary to activation of the δ opioid receptor (DOR). In clinical settings, multiple receptors may play a role in contributing to nausea/vomiting. Some of the "emetogenic" receptors that have been proposed are dopamine-2 (D_2), histamine-1 (H_1), DOR, 5-hydroxytryptamine (serotonin) (5-HT_3), acetylcholine (ACh), neurokinin-1 (NK-1), and cannabinoid receptor-1 (CB_1). Antimemetics that antagonize these receptors include the following:

- D_2—haloperidol
- H_1—promethazine
- DOR—naloxone
- 5-HT_3—ondansetron, tropisetron, dolasetron, granisetron
- ACh—scopolamine

- NK-1—aprepitant
- CB_1—dronabinol

Pharmacogentic issues in OINV

A wide variety of genes may play a role in contributing to the risk of developing nausea and/or vomiting as well as modifying the intensity of the nausea and/or vomiting (19). Inter-individual variations in nausea and vomiting among cancer patients receiving opioids may be related to polymorphisms within the genes encoding proteins involved in multiple processes (20) including: transport of opioids across membranes at the blood-brain barrier, opioid receptor binding and downstream signaling of opioid effects, as well as modifying systems of opioid effects [e.g., catechol-O-methytransferase gene (COMT), and cannabinoid receptor 1 gene (CNRI)]. Multiple genes are also involved in the neural pathways converging in the vomiting center (vestibular, chemoreceptor trigger zone, peripheral gastrointestinal pathways, as well as the vomiting center itself [e.g., cholinergic receptor muscarinic 3 gene (CHRM3), cholinergic receptor muscarinic 5 gene (CHRM5), and histamine type 1 receptor gene (HRH1)] (15).

Panchal and colleagues reported on over 100 patients that received general anesthesia for abdominal surgery and screened for mu opioid receptor polymorphisms A118G (Asn 40 Asp) and COMT G1947A (Val 158 Met) polymorphisms (21). The heterozygous patients with A118G and G1947 mutations consumed significantly less morphine in the first 48 post-operative hours and also experienced a significant lower incidence of nausea (21).

Treatment

The classic "direct" treatment of traditional OINV due to potent mu opioid receptor agonists are opioid antagonists (e.g., continuous naloxone infusion, naltrexone, nalmefene). Peripheral acting mu opioid receptor antagonists reduced nausea and vomiting in a few trials that were not designed to specifically look at this effect. Weese and colleagues performed a meta-analysis of phase 3 clinical trials evaluating the use of alvimopan in patients with postoperative ileus and found a significant reduction in nausea and vomiting from alvimopan as well (22).

Methylnaltrexone (MNTX) was shown to markedly reduce the nausea associated with parenteral morphine administration (22); and also appeared to produce a decrease in vomiting in patients who received methylnatrexone for reversal of opioid-induced urinary effects (22). This decrease in vomiting may have occurred from an action of MNTX at the CTZ receptors and/or a modulation of afferent impulses from the enteric nervous system to the brain (23).

Although, 6β-naltrexol is not yet FDA approved in the U.S. and has not been well studied for the treatment of OINV, it is conceivable that 6β-naltrexol may have some beneficial effects for OINV. 6β-Naltrexol is the main human metabolite of naltrexone, accounting for up to 43% of the dose (24-26). Ranking among a class of analogs shown to be neutral antagonists, 6β-naltrexol inhibits activation of opioid receptors, but unlike inverse agonists such as naloxone and naltrexone, does not suppress basal receptor signalling (27-32). In animal models, 6β-naltrexol precipitates a less severe withdrawal compared with the inverse agonists naloxone and naltrexone (26,27). Therefore, neutral opioid antagonists may be optimally effective in treatment of unwanted opioid side effects (e.g., opioid induced bowel dysfunction), while avoiding aversion and severe withdrawal (33).

Of interest, out of the subjects given 10 mg of intravenous morphine sulfate and 0.0 mg 6β-naltrexol, 4 subjects developed significant nausea and 2 subjects developed significant emesis, however, out of the same number of subjects given 10 mg of intravenous morphine sulfate and 10 mg of 6β-naltrexol, only 1 subject developed nausea and no subjects had emesis.

Other pharmacologic treatments for OINV are similar to the general use of antiemetics as in postoperative nausea/vomiting (PONV) or chemotherapy-induced nausea/vomiting (CINV); although some antiemetic agents may be particularly useful for the treatment of OINV.

Dopamine D2 receptor antagonists may be utilized to treat OINV although their prophylactic use does not appear to be effective. One agent that may be especially useful is olanzapine. Ishihara and colleagues conducted a multi-institutional retrospective study, in which 619 eligible hospitalized patients receiving oral opioid analgesics for cancer pain were enrolled from 35 medical institutions (34). The primary endpoint was the incidence of opioid-induced side effects in patients receiving prophylactic medication. The results of the meta-analysis revealed that prophylactic laxatives significantly reduced the incidence of constipation (overall odds ratio=0.469, 95% confidence interval =0.231-0.955, P=0.037), whereas dopamine D2 blockers were not effective in preventing opioid-induced nausea or vomiting (34).

Olanzapine is an atypical antipsychotic agent of the thienobenzodiazepine class. Olanzapine blocks multiple neurotransmitter receptors, including dopaminergic (D_1, D_2, D_3, and D_4), serotonergic [5-hydroxytryptamine 2A ($5\text{-}HT_{2A}$), $5\text{-}HT_{2C}$, $5\text{-}HT_3$, and $5\text{-}HT_6$], adrenergic (α_1), histaminergic (H_1), and muscarinic (M_1, M_2, M_3, and M_4) receptors. Olanzapine has a high affinity for the $5HT_{2A}$ receptor, which is up to 5 times greater than the dopamine receptor, resulting in less propensity to the development of extrapyramidal side effects. Adverse effects of olanzapine include somnolence, postural hypotension, constipation, dizziness, restlessness, and weight gain (35).

Torigoe and colleagues performed animal studies that involved evaluating olazapine administration for animals with morphine-induced emetic-type behaviors and post-sciatic nerve ligation neuropathic pain behaviors and sleep disturbances (36). Olanzapine showed high affinity for muscarinic M1 receptor in brain tissue. Olanzapine decreased morphine-induced nausea and vomiting in a dose-dependent manner. Olanzapine at a dose that had an antiemetic effect (0.03 mg/kg) did not induce catalepsy or hyperglycemia, and had no effect on the morphine-induced release of dopamine or inhibition of gastrointestinal transit. Olanzapine also inhibited thermal hyperalgesia and completely alleviated sleep disturbances, suggesting that olanzapine may be useful for the treatment of morphine-induced emesis (36).

The substituted benzamide metoclopramide (at high doses) blocks both dopamine and $5\text{-}HT_3$ receptors and also increases lower esophageal sphincter tone; it exhibits prokinetic activity (facilitating gastric emptying) but may lead to extrapyramidal side effects (37) and can, like other D_2 antagonists, have a negative impact on "hedonic tone" (38).

Palonosetron may possess several unique characteristics, including allosteric binding to $5\text{-}HT_3$ receptors with subsequent receptor internalization, negative cooperativity with neurokinin-1 receptors, and a long half-life of 40 h (39,40). The incidence of PONV in two pivotal studies was 74% in the placebo group and 57% in the 0.075 mg palonosetron group in one trial (41), and 64% and 44% in the other trial (42). This translates to relative risk reductions of 29% (¼1-0.57/0.74) and 31% (¼1-0.44/0.64), which is very similar to the relative risk reductions of about 30% observed with other 5-HT3 receptor antagonists (43).

Park and colleagues compared 8 mg ondansetron with 0.075 mg palonosetron for the prevention of PONV reported a 67% incidence of PONV in the ondansetron group and 42% in the palonosetron group (44). It is uncertain whether palonosetron's edge was due to its considerably longer half-life (40 h) compared with ondansetron (3-4 h) or whether palonosetron would still be more effective at equipotent doses. Moon and colleagues (45) have compared the incidence of PONV in a group who received an 8 mg i.v. bolus of ondansetron plus 16 mg ondansetron added to a fentanyl patient-controlled analgesia (PCA) pump with that in a group who received just a single 0.075 mg i.v. bolus of palonosetron without any addition to the PCA pump.

Apfel (46) has argued that the Park *et al.* study (44) looked more at opioid-induced nausea and vomiting (OINV) than at PONV, since postoperative opioids are one of the primary drivers of PONV, especially delayed PONV (47-49).

OINV affects about 30% of surgical patients, with no difference between morphine and piritramide (20) (or between morphine and hydromorphone (50). Although PCA is commonly used for controlling postoperative pain, patients have reported a lower postoperative quality of life with PCA than with an epidural, perhaps because of a higher incidence of OINV with PCA (51). Tramer and colleagues performed a systemic review and meta-analysis suggesting that not only the dopamine antagonist droperidol but also other antiemetics such as $5\text{-}HT_3$ receptor antagonists are effective in preventing OINV (52). Bonnet *et al.* conducted a relatively large study that demonstrated that both 8 and 16 mg ondansetron were effective for treating established OINV (53).

The study performed by Moon and colleagues (45), it was even more impressive to see that the incidence of PONV (or OINV) was significantly lower with 42% in the palonosetron group compared with 62% in the ondansetron group.

Droperidol and ondansetron have now received a US FDA black box warning after reports of prolonged QTc interval and severe cardiac complications have been associated with its use. Although the vast majority of anesthesia providers believe that both drugs are sufficiently safe (54).

Based largely on data from perioperative studies, transdermal scopolamine appears to help ameliorate OINV (55-59). Although aprepitant has not been studied for alleviating "pure" OINV, it seems, intuitively, that it could be a promising agent for this purpose. The acute administration of morphine may cause an increase in central nervous system (CNS) expression of substance P (60). Furthermore, morphine upregulates functional expression of the NK-1 receptor (NK-1R) in cortical neurons (as evidenced by mRNA levels, as well as immunofluorescence and Western blot assays using specific antibody to NK-

1R protein), possibly via MOR-induced changes in cyclic adenosine monophosphate, leading to activation of the p38 MAPK signaling pathway (via phosphorylation) and activation of the NK-1R promoter (61). Therefore, it does not seem unreasonable to study aprepitant—an NK-1R antagonist used for the treatment of PONV and CINV—for its efficacy in treating OINV.

Other opioid or opioid-like products that may produce less nausea/vomiting than traditional opioid agents

Tapentadol

Tapentadol is a centrally acting analgesic with two mechanisms of action: mu-opioid receptor agonism and norepinephrine reuptake inhibition in a single molecule (62,63). The combination of these two mechanisms of action may contribute to both the analgesic effect of tapentadol and the reduction in the occurrence of the side effects associated with mu-opioid agonists (63).

Tapentadol immediate-release is available as 50, 75, and 100 mg tablets and provides 4-6 hours of analgesia. Tapentadol immediate-release was shown to provide analgesia comparable with that of 10-15 mg of immediate-release oxycodone (64,65) in patients recovering from dental extraction pain (66) and pain following bunionectomy. It was also as effective as oxycodone in patients presenting with chronic osteoarthritis pain and chronic low back pain (67,68), however, in a bunionectomy trial (69), the composite incidence of nausea and vomiting in patients treated with tapentadol 50 mg every 6 hours was significantly lower than in patients treated with oxycodone 10 mg.

Oxycodone IR, 15 mg, provided equivalent analgesia to tapentadol IR, 100 mg, but the latter had a significantly lower incidence of nausea and/or vomiting (53% *vs.* 70%, respectively; nominal P=0.007) (69). Vorsanger and colleagues performed a post hoc analyses of data from a 90-day clinical trial evaluating the tolerability and efficacy of tapentadol immediate release and oxycodone immediate release for the relief of moderate to severe pain in elderly and nonelderly patients (70). They concluded that tapentadol IR was safe and effective for the relief of lower back pain and osteoarthritis pain in elderly patients, and was associated with a better gastrointestinal tolerability profile than oxycodone IR (70). However, if doses of over 75 mg of tapentadol IR t.d.s. are compared to low doses oxycodone IR, 5 mg t.d.s., they both similary significant delayed gastric emptying $t_{1/2}$, small bowel transit, and increased nausea compared to placebo (71). Tapentadol extended release (100 to 250 mg, bid) was associated with better gastrointestinal tolerability than oxycodone HCl controlled release (20 to 50 md bid) and provided similar analgesia for the management of moderate to severe chronic pain from osteoarthritis (72) or low back pain (73) and which appears to be sustainable for at least a year (74). The incidences of specific gastrointestinal treatment-emergent adverse events (TEAEs) were statistically significantly lower in the tapentadol extended release group compared with the oxycodone controlled release group, including the incidences of constipation [16.9% (166/981) *vs.* 33.0% (330/1001); P<0.001], nausea [20.7% (203/981) *vs.* 36.2% (362/1001); P<0.001], vomiting [8.2% (80/981) *vs.* 21.0% (210/1001); P<0.001], and the composite of nausea and vomiting [23.3% (229/981) *vs.* 42.7% (427/1001); P<0.001] (75).

Risk of nausea, vomiting, and constipation significantly increased with exposure to tapentadol, oxycodone, or oxymorphone versus placebo. However, elevated risk per drug exposure of AEs for tapentadol was ~3-4 times lower than that of oxycodone, while elevated AE risk per drug exposure of oxycodone was ~60 times lower than that for oxymorphone, consistent with reported *in vitro* receptor binding affinities for these compounds. Simulations show that AE incidence following administration of tapentadol IR is lower than that following oxycodone IR intake within the investigated range of analgesic noninferiority dose ratios. This PK/PD analysis supports the clinical findings of reduced nausea, vomiting and constipation reported by patients treated with tapentadol, compared to patients treated with oxycodone (76).

Moxduo®

Moxduo® (morphine/oxycodone 3/2) is a dual-opioid combination of morphine and oxycodone used to treat acute pain but not yet FDA approved in the U.S. Controlled trials with morphine/oxycodone 3/2 have enrolled approximately 1,500 subjects with moderate to severe post-surgical pain who received multiple doses of morphine/oxycodone 3/2 or single-entity opioids for a maximum of 23 days, revealed analgesic efficacy that is at least comparable to the individual components and a 50-75% reduction in moderate to severe AEs, especially nausea and vomiting (77).

Although the use of drug combinations for OINV has not been studied, it is not uncommon for clinicians to empirically combine multiple antiemetic agents in

attempts to optimize outcomes. Corticosteroids, despite their uncertain mechanism of action, have been utilized as "antiemetic adjuvants" in combination with other antiemetic agents (78).

It is also conceivable that in the future; combination agents (opioids combined with agents which may nullify their emetic effects while maintain or enhancing their analgesic effects (79). Preliminary preclinical data suggest that LNS5662 (Flavonol-PgP Modulator)—a flavonol thought to activate PgP efflux of pump ligands at the blood–brain barrier—may ameliorate opioid adverse effects in OINV, thereby improving tolerability without interfering with analgesic efficacy. This agent may therefore deserve further study (80).

In 2010, Davis and Hallerberg published that neither ondansetron nor metoclopramide (two commonly employed agents utilized to treat OINV) improved opioid-induced emesis, based on a randomized controlled trial (81). In the future, it is hoped that further research on OINV is conducted, as there remains a relative dearth of robust evidence surrounding "pure" OINV.

Summary

Nausea and vomiting are among the most distressing of all symptoms for many patients. Opiids as well as many other drugs may lead to nausea and/or vomiting. Nausea tends to occur roughly one-fifth to one-third of the time with vomiting occurring about half of that. Although the precise mechanisms of opioid-induced nausea and vomiting are not entirely certain, it appears that opioid stimulation of the vestibular apparatus chemoreceptor trigger zone, and receptors in the gastrointestinal tract are three major areas involved. Targeting specific areas and/or receptors/receptor-subtypes that opioids may directly or indirectly stimulate may lead to improved patient outcomes for patients with OINV who require opioids for medically necessary treatment.

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