European Journal of Pharmacology 722 (2014) 67–78

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Review

Opioid induced nausea and vomiting

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ARTICLE INFO

Article history:
Accepted 30 September 2013
Available online 21 October 2013

Keywords:
Nausea
Vomiting
Opioids
Olanzapine
NK-1
Antagonists
Moxduo
Tapentadol

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, using 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 (OINV).

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1. 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

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0014-2999/$ - see front matter Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.ejphar.2013.09.074

(Coluzzi and Pappagallo, 2005). 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 US registry study evaluated more than 200 patients in chronic treatment with controlled-release (CR) oxycodone (Portenoy et al., 2007). 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 (Portenoy et al., 2007).

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. Opioids possess well known proemetic effects that appear to be related largely to the total opioid dose administered and the degree to which that dose is "acute" vs. "chronic" for a particular patient. 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 (Lehmann, 1997). 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 (Wirz et al., 2008). Approximately 60% of patients with advanced cancer report nausea and 30% report vomiting (Davis, 2005).

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 (Smith, 2008a), as well as differences in the pharmacokinetics and/or pharmacodynamics of different opioids (Smith, 2009). 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 (Moore and McQuay, 2005). Furthermore, a significant proportion of patients on opioids withdrew due to adverse events (Moore and McQuay, 2005). 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 (Kalso et al., 2004).

2. Pathophysiology of OINV

The experience of nausea/vomiting may involve multiple receptors (Smith, 2005). 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 (a) enhanced vestibular sensitivity (symptoms may include vertigo and worsening with motion), (b) direct effects on the chemoreceptor trigger zone, and (c) 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 mu opioid receptors on the vestibular epithelium (Yates et al., 1998). The rate inner ear possesses delta opioid receptors delta and kappa opioid receptors (Otto et al., 2006), 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 (Popper et al., 2004). 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 (Jongkamonwiwat et al., 2003). In addition to mu opioid receptor agonist effect morphine may causes a subunit-dependent inhibition of human 5-HT_3 receptors (Baptista-Hon and Deeb, 2012)

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 vs. receptors outside the central nervous system (Coluzzi et al., 2012). 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 (Herndon et al., 2002).

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 (Thomas, 2008). Opioids reduce peristalsis via decreasing gastrointestinal secretions and relaxing longitudinal muscle in the colon as well as simultaneously/increasing contractions of the circular muscles (Coluzzi et al., 2012). 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 (Iasnetsov et al., 1987) that may be associated with nausea and/or vomiting.

It is conceivable that opioid-induced effects on the esophagus and esophageal motility may partly contribute to OINV. Kraichely and colleagues retrospectively reviewed 15 patients with dysphagia referred for esophageal manometry while on chronic opioids (Kraichely et al., 2010). All patients demonstrated motility abnormalities. Incomplete lower esophageal sphincter (LES) relaxation (11.5 ± 1.6 mmHg) was seen in most cases. Ten patients demonstrated nonperistaltic contractions in $>$ or $=3$ of 10 swallows. Additional abnormalities included high amplitude contractions, triple peaked contractions, and increased velocity. The average resting lower esophageal sphincter (LES) met criteria for hypertensive LES in three patients. These features were suggestive of spasm or achalasia. Repeat manometry off opiates was performed in three cases. LOS relaxation was noted to be complete upon repeat manometry in these cases, and demonstrated complete improved peristalsis, and a return to normal velocity (Kraichely et al., 2010). Opioids may also at least in part also contribute to OINV by adversely affecting gastric motility and delaying gastric emptying and may in some cases possibly contribute to frank severe gastroparesis (Jakobovits et al., 2007).