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Pharmacology Matters

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HISTAMINE, NEUROKININ, AND OPIOID RECEPTOR ANTAGONISM FOR NAUSEA AND VOMITING

"The causes of nausea and vomiting (N&V) are many, but in general, are gastrointestinal, blood borne, or vestibular in origin. Gastrointestinal causes of N&V include: gastro-paresis, gastric distension, and constipation. Blood borne causes include: drugs and toxins. Vestibular N&V is caused by disruption of the inner ear often initiated by motion. All of these causes trigger a part of the brain called the area postrema (AP) located in the brain stem" (Welliver, 2013 p. 378). The chemoreceptor trigger zone (CTZ) located within the AP of the medulla oblongata has innervations connecting the vestibular apparatus, gut, and other areas of the body. It is this close association of multiple nauseagenic and emetogenic origins that may require a multifaceted drug approach to treatment.

The primary drug treatments for N&V include the serotonin ($5HT_3$ receptor) and dopamine (D_2 receptor) antagonists. When these are ineffective or specific causes are known, other receptors may be targeted to relieve symptoms. These targets may include acetylcholine–discussed in previous columns–histamine (H1), neurokinins (NK-1), or opioid receptors. Both histamine and neurokinin receptors are found in the gastrointestinal tract. Opioid receptors are found in the CTZ. Neurokinin receptors specifically are found in the vomiting center located in the AP. A review of the close interplay and nuances of each neurotransmitter and its related receptor discloses the mechanisms and actions of specific drugs that target N&V.

Vestibular Location

Histamine Receptor Antagonists

Histamine is a neurotransmitter released by mast cells located in tissues and basophil-type white blood cells. It also exists as a nonmast cell released neurotransmitter in the central nervous system. There are now four known subtypes of histamine receptors: H1, H2, H3, and H4. Histamine 2 (H2) receptors primarily respond to histamine in the gastrointestinal system. Histamine, like acetylcholine, is also a predominant neurotransmitter found in the vestibular system and, to a lesser extent, the CTZ (Soto & Vega,

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2010). Histamine can trigger N&V. Therefore, histamine antagonists may play a role in treating N&V (Gan et al., 2014). Commonly used histamine antagonists (antihistamines) used for treating N&V fall into several chemical classifications (see Table 1).

Histamine antagonists are not true antagonists, but rather inverse agonists, meaning that they stimulate the receptor to have a lower or opposite effect from that caused by agonists. Histamine inverse agonists stimulate a histamine receptor to produce a lowered effect from baseline. The drugs discussed here decrease histamine receptor activity by binding to and stimulating a receptor. True antagonists attach to and block all activity of a receptor. Inverse agonist drugs that lower histamine receptor activity are often referred to as histamine antagonists or histamine blockers because they have the effect of lessening the receptor's effect (Tables 2 and 3).

Neurokinin Receptor Antagonists

Neurokinins are peptide molecules bonded between the amine and the carboxyl group of amino acids (CO–NH) (Figure 1). Neurokinins are also called tachykinins as they can rapidly induce smooth muscle contraction including that of the gastrointestinal tract. This, in turn, may cause afferent impulses to the CTZ initiating the signaling process ending in N&V. The etymology of *tachykinin* is derived from the Greek words *tachy* meaning fast and *kinin* meaning movement. Neurokinin's role in N&V plays out in the emesis center (vomiting center) located in the medulla oblongata, which is in close communication with the CTZ. As its name implies, the emesis center, triggered by neurokinins, plays a primary role in the specific action of vomiting. Blocking neurokinin receptors has the effect of preventing or stopping vomiting. Neurokinin-blocking drugs (antagonists) have little effect on nausea.

Neurokinins can induce gastrointestinal spasm triggering vagal impulses to the brain causing N&V. A frequent culprit of N&V is the specific neurokinin known as substance P. Substance P is released by sensory nerves in response to tissue destruction, and in the brain in response to neuronal stimulation. Substance P also plays a significant role in pain transmission (DeVane, 2001). Our target for treatment of neurokinin-induced N&V is primarily the NK-1 receptor, one of the three types of neurokinin receptors (NK-1, NK-2, and NK-3).

Unique among the NK-1 antagonists is palonosetron (Aloxi Eisai Pharmaceutical Helsinn Healthcare SA, Switzerland). Palonosetron has a dual receptor action by blocking both NK-1 and serotonin $5HT_3$ receptors, making it an excellent drug treatment for N&V.

TABLE 1. Typical Antihistamine Drugs Used to Treat Nausea and Vomiting

Chemical Class	Drug Examples	Dose	Comments
Enthylamine	Diphenhydramine (Benadryl) Dimenhydrinate (Dramamine)	25–50 mg p.o. 1 mg/kg i.v.	Causes sedation Combination of diphenhydramine and chlorotheophylline
Piperazine	Hydroxyzine (Vistaril)	25–100 mg i.m.	Causes sedation
	Meclizine (Bonine)	50 mg p.o.	Causes sedation
	Cyclizine (Antivert)	50 mg p.o.	Causes sedation
Phenothiazine	Promethazine (Phenergan)	12.5–50 mg p.o., i.v.	Also has dopamine (D_2) and cholinergic (ACh) antagonism. Vessel irritation, necrosis if infiltrated

Note. Average doses for adults are listed. The table is not intended to guide patient administration. i.m. = intramuscular; i.v. = intravenous; p.o. = by mouth.

TABLE 2. Neurokinin Antagonist Drugs Used to Treat Nausea and Vomiting That Tend to Work Best for Treating Vomiting as Opposed to Nausea

Drug Examples	Dose	Comments
Aprepitant (Emend)	125 mg p.o.	Works well for vomiting but not nausea
Fosaprepitant (Emend for injection)	150 mg i.v.	Works well for vomiting but not nausea
Casopitant (Rezonic)	150 mg p.o.	
Palonosetron (Aloxi)		Highly effective for N&V due to serotonin (5HT3) and NK-1 affinity

Note. Average doses for adults are listed. The table is not intended to guide patient administration. i.m. = intramuscular; i.v. = intravenous; p.o. = by mouth.

TABLE 3. Typical Drugs to Block Opioid Receptors

Classification	Drug Example	Dose	Comments
Peripheral antagonist	Alvimopan (Entereg)	6–12 mg	Limited to 15 doses. Intended to treat postoperative ileus and not N&V. Study reflects lower incidence of N&V (Weese et al., 2007; Wolf et al., 2004).
Inverse agonist	Naloxone (Narcan) infusion	0.4–2 mg	Short acting. Initial low dose may be repeated until desired effect.
Inverse agonist	Nalmefene	Incremental 0.25 μg/kg to max dose of 1 μg/kg	Longer acting than naloxone
Inverse agonist	Naltrexone	50 mg p.o. daily. 380 mg i.m. q 4 weeks	Long acting. Primarily used for opioid and alcohol dependence treatment

Note. The table is not intended to guide patient administration. i.m. = intramuscular; p.o. = by mouth.

Because palonosetron is so effective in treating N&V, it will be covered more fully in subsequent columns.

CTZ Location

Opioid Receptor Antagonists

Opioid-induced N&V is an unwanted side effect of narcotic pain medications. Although opioid (mu) receptors reside within the central nervous system, including the CTZ and vestibular apparatus, it is likely that opioid-induced N&V is multifactorial involving peripheral mechanisms such as delayed gastric emptying ileus (Smith, Smith, & Seidner, 2012). Opioid receptor antagonists are classified as inverse agonists or neutral antagonists. These drugs may effectively treat opioid-induced N&V, but may limit or interfere with pain management. Antagonizing opioid receptors may lower the analgesic effects and may precipitate withdrawal symptoms. Use of opioid receptor antagonists are never a first line drug for treatment of N&V but are discussed here as an informative review. Drugs that antagonize opioid receptors include alvimopan, naloxone infusion, naltrexone, and nalmefene.

The most unwanted peripheral effects of opioids are often gastrointestinal. Postoperative ileus is exacerbated by opioids and antagonism of these receptors may offer benefit to lower or prevent N&V. Recent studies of alvimopan (Entereg) have shown benefit in lowering the incidence of postoperative ileus. Although patient recovery times were faster in these studies, the incidences of N&V were not found to be statistically different (Delaney et al., 2005; Lee et al., 2014; Ludwig et al., 2008; Viscusi et al., 2006; Weese, Du, & Techner, 2007, Wolf et al., 2004). This can be explained by its peripheral action that improves peristalsis but has no effect centrally where N&V is triggered. This lack of central effect also allows analgesia to be maintained while improving bowel function postoperatively.

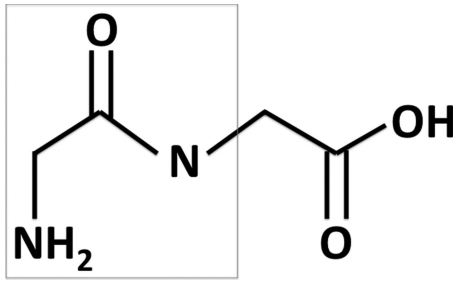

FIGURE 1. Peptide bond of a neurokinin. Amine group within boxed area. Carboxyl group lies to the right.

Naloxone, nalmefene, and naltrexone all work systemically and can treat μ-receptor-induced N&V as well as ileus. As these opioid antagonists reverse all effects of opioids, they are primarily used as a treatment for overdose. It is not desirable to treat N&V caused by μ-receptor stimulation while concurrently reestablishing pain perception. Treatment of respiratory depression is, therefore, sometimes accomplished by incremental low doses of these medications, particularly naloxone.

Conclusion

One needs to consider other receptors responsible for N&V when conventional treatments fail. Despite being highly effective, serotonin and dopamine antagonists sometimes do not work well even in higher doses. This is when other receptor causes of N&V should be considered. Acetylcholine receptors discussed in previous columns offer an appropriate target, as do histamine, neurokinin, and opioid receptors discussed here. This column offers several significant receptor targets to consider. The drugs that antagonize these receptors offer additional options to consider when N&V is refractory to initial treatment other drugs. As first introduced and discussed in the opening subject column on this subject, *Nausea and Vomiting: Mechanisms and Treatment Overview* (Welliver, 2013), the receptors most often responsible for N&V have been covered individually. Our following column will explore the renewed interest in cannabinoid receptors as targets for N&V treatment.

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