Migraine Headache and Its Association with Emesis and Gastric Motility: A Brief Review

Migraine headache is a chronic and debilitating disorder that affects approximately 17% of all adult women and 5% of all men. The duration of an attack may be between 4 and 72 hours, but typically lasts one whole day. Migraines are frequently associated with nausea and vomiting in the majority of sufferers, as well as other symptoms such as sensitivity to light and sound. In this review, we separately discuss the pathophysiology of both migraine headaches and emesis, as well as the effect of migraines on gastric motility. We attempt to decipher the complex interplay between the central nervous system and the peripheral nervous system within the context of delayed gastric emptying and migraine-associated emesis.

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(2) It is frequently associated with nausea (87%) and/or vomiting (56%), and other symptoms such as photophobia and phonophobia are also quite common (3). As reported in a review in The New England Journal of Medicine on the pathophysiology and treatment of migraine headaches (4), fifteen percent of migraine sufferers will experience transient focal neurological symptoms that typically precede their headaches. This phenomenon is known as "migraine with aura," and the neurological symptoms are usually manifested as visual disturbances. However, some studies show that up to 31% of patients report the presence of aura with their migraines at one time or another (5). It is the (continued on page 68)
17.6% of all adult women, and 5.6% of adult men, are affected by migraines (3). The median frequency of an attack is approximately 1.5 times per month, and the median duration is 24 hours (7). Five percent of the general population has at least 18 days of migraine headaches per year (4). This translates into countless hours of absence from work and school, as well as millions of visits to the offices of primary care physicians each year.

**PATHOPHYSIOLOGY OF MIGRAINE**

The pathophysiology of migraine headaches has long been debated and incompletely understood. It is essentially regarded as a primary brain disease involving the cranial blood vessels, but other neurogenic factors are thought to play an important role as well. Inappropriate activation of the trigeminal nerve fibers cause the release of local sensory neuropeptides which, in turn, promote vasodilation, perivascular edema, and the recruitment of certain inflammatory cells (8). The inflammation proximal to the meninges (Figure 1) is thought to cause the severe pain experienced during a migraine. It is unclear as to what factors are responsible for the initial stimulation of the trigeminovascular system that leads to the cascade of events producing the headache. Imbalances in the release of the neurotransmitter serotonin, however, have been implicated because of its ability to mediate vasoconstriction and trigeminal nerve activation (9). It is for this reason that the current abortive therapies for an acute migraine attack are all serotonin (5-HT) receptor subtype agonists.
Trigeminal nerve stimulation and intracranial vasodilation, however, are not sufficient to explain all the features associated with a migraine headache—especially the aura (10). The aura of a migraine is felt to be due to a wave of oligemia (4) that originates in the occipital lobe of the cerebral cortex and progresses anteriorly towards the frontal pole. It is this spreading oligemia that produces the distinct focal and transient neurological symptoms seen in migraine with aura. This phenomenon is thought to be due to primary disturbances in cortical metabolism and function (10); a mechanism of action that is separate from stimulation of the trigeminovascular system.

PATHOPHYSIOLOGY OF EMESIS

Emesis is associated with several conditions other than migraine headaches. Nausea and vomiting are seen with head trauma, chemotherapy, the extremes of emotion, drug withdrawal, disturbances in the eighth cranial nerve, and several primary gastrointestinal diseases (11). The pathophysiology of vomiting involves a complex interplay between the central and the peripheral nervous systems. Within the CNS exists the “vomiting center” of the brain located in the lateral reticular formation of the medulla (12). The vomiting center is comprised of two major groups of brainstem nuclei known as the nucleus tractus solitarius (NTS) and the dorsal motor nucleus of the vagus (DMNV). They are responsible for receiving information promoting emesis from several different areas within the CNS and PNS (Figure 2). For example, the gastric mucosa—via vagal and splanchnic afferents—communicates directly with the vomiting center of the brainstem. Other areas of the nervous system that influence the vomiting center include the chemoreceptor trigger zone, located in the area postrema below the fourth ventricle; the vestibular system; and higher cortical areas in charge of sight, smell, pain, etc. (11,13). All of these areas send information to the vomiting center, which subsequently stimulates its gastrointestinal motor correlates to cause emesis.

Vomiting is ultimately achieved by relaxation of gastric tone in preparation for a large retrograde contraction that begins in the proximal small intestine and propagates orally to the gastric antrum (11). While the lower esophageal sphincter is completely relaxed, undigested food is pushed up through the esophagus. This action is facilitated by contraction of the

Figure 2. NTS = nucleus tractus solitarius, DMNV = dorsal motor nucleus of the vagus. Adapted from DePonti, F: Pharmacology of emesis and gastrointestinal motility: implications for migraine. Functional Neurology 2000; 15, suppl 3.
diaphragm and abdominal muscles against a closed pyloric sphincter (14).

MIGRAINE HEADACHES AND GASTRIC MOTILITY
What exactly causes vomiting during a migraine headache, and why do some patients have it worse than others? For many years neuroscientists have debated whether the central nervous system or the peripheral nervous system is responsible for the initiation of emesis during a migraine. In other words, is it mainly a central mechanism of action with stimulation of the trigemino-vascular system that somehow activates the vomiting center of the brain; or is it initially a peripheral mechanism with alterations in gastric motility that ultimately sends signals to the vomiting center via its vagal and splanchnic afferents.

Since the 1970’s researchers have studied the effects of migraine headaches on gastric motility. Previous studies have shown that there is a delay in drug absorption during an acute migraine (15–18), and it has been postulated that this slowed absorption is caused by a delay in gastric emptying. These initial studies essentially measured blood levels of certain compounds such as paracetamol and tolfenamic acid both at baseline and during an acute migraine attack. Drug levels were significantly reduced in patients during their migraine headaches. In one particular study that utilized epigastric impedance recordings to detect changes in gastric emptying, researchers found that the severity of a headache correlated with the degree of delay in gastric emptying (17). Other studies looked at prokinetic agents such as metacloperamide and its effect on drug absorption during an acute attack. Blood levels of both effervescent aspirin and tolfenamic acid were improved during migraine headaches when metacloperamide was given just prior to the attack (16,19). This suggests that the prokinetic effect of metacloperamide is indirectly responsible for the improved absorption, and thus a disturbance in gastric motility does exist during an acute migraine.

To the best of our knowledge, there have not been any published studies utilizing radionuclide as a measure of gastric motility in patients during an acute migraine headache. Nonetheless, with the information from studies that are currently available, there is enough evidence to suggest that there is a delay in gastric emptying during a migraine. It is thought that this alteration in motility then produces gastric distention, which stimulates central receptors in the brainstem to subsequently cause vomiting. For those patients who do not experience vomiting with their migraine headaches, one theory postulates that these patients may have a reduced perception to gastric distention; thus, the vomiting center of the brainstem is not stimulated sufficiently to produce emesis. Altogether, it seems as though vomiting during a migraine may be the direct result of changes in gastric motility; yet those alterations in motility appear to be initially motivated by a central stimulus from the migraine itself.

MIGRAINE THERAPY AND GASTRIC MOTILITY
The treatment of migraine headaches raises another important point concerning gastric emptying. Over the last decade, the class of drugs known as "the triptans" have risen to the forefront as the major anti-migraine therapy for an acute attack. The leader in this group of medications is sumatriptan, a 5-HT1B/D agonist that crosses the blood-brain barrier. There are several theories as to how it relieves migraines, and most of them are focused on 5-HT receptor-mediated vasoconstriction and inhibition of trigeminal nerve firing (20,21). The most intriguing aspect of sumatriptan, however, is its effect on gastric motility in dosages similar to those used in migraine patients. Sumatriptan has been shown to cause a delay in gastric emptying of both liquids and solids (22–24). In a recent article by Cipolla, et al the author thoroughly reviews the current data on the gastric motor effects of sumatriptan in both humans and animals (8). Within this review, he discusses prior studies that have demonstrated a delay in gastric emptying with this medication. Furthermore, he also notes a more recent study in which sumatriptan was shown to relax the gastric fundus and allow for larger intragastric volumes before thresholds for pain and discomfort were reached (25).

By delaying gastric emptying, it is difficult to imagine how a medication such as sumatriptan would not cause further symptoms of nausea and vomiting. Some studies, however, report a significant improve-
ment in nausea with both sumatriptan and the newer second generation triptans. On the other hand, these same studies report nausea as the principle side effect of these medications (26,27). As Cipolla, et al points out, no study has specifically differentiated between disease-associated nausea and nausea as a side effect of the medication (8). 

One theory as to why sumatriptan improves symptoms of nausea is because of its ability to relax the gastric fundus and allow for greater distention without perception of discomfort (25). Increased gastric distention should typically induce nausea, and eventually vomiting. Sumatriptan, however, may be interfering with the ability of the PNS to communicate with the appropriate central receptors; thus it masks the central response to gastric distention. 

The exact mechanism as to how sumatriptan causes proximal stomach relaxation and a reduced perception of discomfort remains to be discovered. This finding, however, suggests that it may be beneficial for patients with functional dyspepsia who suffer from symptoms of frequent bloating and early satiety. Further studies with specific 5-HT1B and 5-HT1D agonists/antagonists will help to elucidate this issue. Investigating more specific serotonin receptor subtype agents will not only aid in the progression of research for migraine therapy, but it may also help to uncover additional agents used to relieve symptoms of functional dyspepsia. ■

References