DEBATE: DO WE NEED A NEW MECHANISM OF ACTION FOR ACUTE MIGRAINE TREATMENT? *NO*

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Migraine is one of the complex diseases and the associated symptoms such as nausea, photophobia and photophobia are troublesome as well as the throbbing headache aggravated by motion. Neurobiology of migraine and mechanisms mediating headache have been clearly demonstrated over the last several decades. Based on these scientific achievements triptans have been developed as a specific treatment. Currently available pharmacological treatment mechanisms of an acute migraine attack includes inhibition of arachidonic acid-cyclooxygenase pathway and agonistic activation of serotonin receptors in the trigeminovascular system.

The trigeminovascular system plays a fundamental role in headache in regard to peripheral sensitization and neurogenic inflammation in the meninges and is also a predominant site of action for pharmaceutical agents such as triptans, ergots, neuropeptide antagonists, and non-steroidal anti-inflammatory drugs (NSAIDs). The initial sensitization and or activation of nociceptors and peripheral pain pathways lead to sensitization of central pain pathways. Though central sensitization depends on input from peripheral pathways at the beginning, it can be maintained independently of peripheral input in later stages. With prolonged nociceptive stimulation, glial cells in the central pathways become activated and release inflammatory mediators, including prostaglandins. The prostaglandins by amplify the pain signals, cause neurons to fire in a sustained manner which is characteristic of the central sensitization. Central sensitization and wind up phenomenon develops through the co-release of substance P & glutamate from trigeminal nerve endings in the dorsal horn of the spinal cord and NMDA receptor activation mediates subsequent events. The inhibition of peripheral trigeminal nociceptive activity at the onset of a migraine attack (mild, throbbing headache) could also abort central sensitization and a full-blown migraine attack. Triptans hyperpolarize trigeminal nerve endings and inhibit release of CGRP, SP and glutamate and thereby terminate both peripheral and central activity. As demonstrated by clinical and preclinical studies, triptans can alter initial peripheral sensitization but cannot substantially affect central sensitization in later stages; on the contrary, NSAIDs can terminate central sensitization. We do not have evidence that CGRP receptor antagonists affect central sensitization.

NSAIDs are the most commonly used drugs worldwide for mild and moderate pain, including headache. Treatment guidelines for migraine advise the institution of acetaminophen, prostaglandin inhibitors, like ASA and other nonsteroidal anti-inflammatory agents (NSAIDs) in the early treatment of mild migraine attacks. Nonspecific drugs are cheap, accessible without any prescription and simply administrated.

The triptans are fundamental in acute migraine treatment. Triptans target serotoninergic receptors within the trigeminal nerve fibers surrounding cephalic blood vessels. They display high affinity for 5-HT-1D and 1B receptors, and some of them are also agonists at the 5-HT1F receptor. The 5-HT1D and 5-HT1F receptors are located prejunctionally on the peripheral and central ends of sensory trigeminal neurons and hyperpolarize nerve terminals and thereby inhibit trigeminal activation. Triptans inhibit the release of CGRP, as well as other neuropeptides from perivascular nerve endings. Therefore triptans act upstream to CGRP receptor antagonisms and are superior since the CGRP is not the only player in migraine pathophysiology. Supporting that view, initial efficacy of telcagepant is low compared to triptans, as rizatriptan 10 mg (41%), almotriptan (35%) and sumatriptan (33%) seem superior to telcagepant (26%) for pain free at 2 hours. The development processes of new pharmaceuticals are very expensive and any new agent could have serious side effects such as liver toxicity reported for CGRP receptor antagonists. Parentally administered sumatriptan has an efficacy of 80% in acute migraine attacks, whereas tablets have only 50–60% efficacy. Hence, there is a drive to develop parenteral delivery of acute migraine drugs such as an iontophoretic patch to administer sumatriptan across the skin which delivers sumatriptan more consistently than oral tablets or a nasal preparation.

Multiple pathogenic mechanisms are involved in generation of migraine headache; therefore therapy targeting more than one mechanism could display advantages over individual monotherapy. For example, combination of sumatriptan and naproxen provides better management of pain and other associated symptoms than sumatriptan or naproxen sodium alone. Presence of gastroparesis reduces the absorption of medications from the GI tract during migraine attack and additional antiemetic agents such as metoclopramide can be combined in abortive medication. The highly selective 5-HT1F receptor agonist lasmiditan has recently shown positive results.

In conclusion, triptans and NSAIDS have been using many years and their efficacy, limitations, side effects and indications are very well known. We just need to develop rationale use of available drugs for each patient, to improve delivery of specific drugs to the system and to combine agents with different mechanisms in the abortive medications.