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Lasmiditan: A new drug for acute migraine

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Abstract
In related to the increased risk of cardio vascular (CV) diseases associated with migraine, there is a interest in the development of a new drug in the treatment of acute migraine which selectively act on non-vascular targets. Existing treatments are limited due to contra indications, or patient avoidance of side effects. This analysis show that 5-HT_{1F} agonist have shown improved results in the treatment of migraine head ache. Also indicated the safety and efficacy of oral lasmiditan, a selective serotonin 5-hydroxytryptamine 1F receptor agonist in the migraine treatment. Research suggests that lasmiditan lacks vasoconstrictive properties and may be a safe and effective treatment in patient's refractory to the acute migraine medications compared to the currently used drugs for migraine.

Keywords: lasmiditan, 5HT-1F, migraine, headache, serotonin

Introduction
Migraine is a neurological condition that can cause multiple symptoms. Migraines are severe, recurring, and painful headaches. They can be preceded or accompanied by sensory warning signs and other symptoms. It's frequently characterized by intense, debilitating headaches. Symptoms may include nausea, vomiting, difficulty speaking, numbness or tingling, and sensitivity to light and sound. Migraines often run in families and affect all ages. The most common categories of migraine headache are those without aura (previously known as common migraines) and those with aura (previously known as classic migraines). Migraines can begin in childhood or may not occur until early adulthood. Women are more likely than men to have migraines. Family history is one of the most common risk factors for having migraines [2].

Symptoms
Symptoms during this stage can include:
- food cravings
- depression
- fatigue or low energy
- frequent yawning
- hyperactivity
- irritability
- neck stiffness

In migraine with aura, the aura occurs after the prodrome stage. During an aura, you may have problems with your vision, sensation, movement, and speech. Examples of these problems include:
- difficulty speaking clearly
- feeling a prickling or tingling sensation in your face, arms, or legs
- seeing shapes, light flashes, or bright spots
- temporarily losing your vision

The next phase is known as the attack phase.
This is the most acute or severe of the phases when the actual migraine pain occurs. In some people, this can overlap or occur during an aura. Attack phase symptoms can last anywhere from hours to days. Symptoms of a migraine can vary from person to person. Some symptoms may include:
- increased sensitivity to light and sound
- nausea
- dizziness or feeling faint
- pain on one side of your head, either on the left side, right side, front, or back, or in your temples
- pulsing and throbbing head pain
- Vomiting [3].

Causes
Doctors don't know the exact causes of migraine. It is suspected that they cause from the abnormal activity in the brain. However some reasons believed to cause migraine are:
Hormonal changes
Emotional conditions
Physical causes
Medications
Changes in the diet
Triggers in the environment [4].

Treatment
Migraine treatment is aimed at stopping symptoms and prevent future attacks.
Medication used to treat migraine are categorized into two groups:-
- Pain relieving medications: Also known as acute or abortive treatment, which is used to stop the symptoms.
- Preventive medications: These drugs are taken regularly, often daily to reduce the severity of the migraine.

Medications for Relief

Medication that can be used to treat migraine include:-

- Pain relievers**:** Aspirin, Ibuprofen
- Triptans**:** Sumatriptan, Rizatriptan
- Dihydroergotamines**:** D.H.E 45, Migranal
- Opioid medications**:** Codiene
- Anti-nausea drugs**:** Chlorpromazine**,** Metochlopramide [5].

Apart from all these drugs a new drug named Lasmiditan was approved by FDA for the treatment of acute migraine.

Lasmiditan

A new drug approved by FDA for the acute treatment of migraine is Lasmiditan. Lasmiditan is a 5-HT receptor agonist, which selectively binds to the 5-HT 1F receptor sub type. It is a neuraly acting anti-migraine agent. Developed by Eli Lilly and approved in United States in 2019. Lasmiditan was first discovered by Eli Lilly and company and relicensed to CoLucid Pharmaceuticals in 2006. The drug is protected by patents until 2031. Phase II clinical trials for dose finding purposes were completed in 2007 for intravenous form and in early 2010 for oral form. Eli Lilly submitted a new drug application to the FDA in November 2018. Three Phase III clinical trials were completed. SPARTAN evaluated three doses of lasmiditan (50, 100, and 200mg) were compared to placebo in the treatment of acute migraine. SAMURAI compared placebo with 100 and 200 mg doses of lasmiditan. GLADIATOR is an open-label study that compared 100 and 200 mg doses of lasmiditan in patients that received the drug as part of a prior trial. The FDA approved the drug on 11 October 2019.[6]

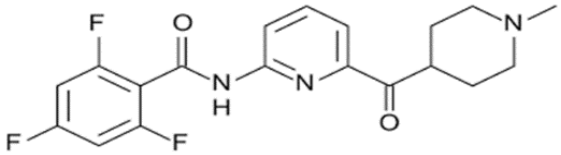

Fig 1: Molecular structure of Lasmiditan

IUPAC Name: (2, 4, 6-Trifluoro-*N*-[6-[(1-methyl-4-piperidinyl) carbonyl]-2-pyridinyl] benzamide)

Clinical Data

Trade name: Reyvow
Other name: COL-144
Routes of administration: oral, intravenous

Chemical and Physical Data

Molecular formula: $C_{19}H_{18}F_3N_3O_2$
Molar mass: 377.36 g/mol.[6]

Mechanism of Action

Lasmiditan is a 5-HT receptor agonist, which selectively binds to the 5-HT 1F receptor sub type. A number of triptans are present in the Subtype, but only after their affinity for 5-HT 1B and 5-HT ID has been made responsible for their anti-migraine activity. The compound consist of a new class of drugs, “ditans”. Mainly possess an indole like structure and ditans present in the structure replace this indole group with a pyridine-piperidine scaffold. Triptans non-specifically bind to the 5-HT1B and 5-HT1D receptors and causing direct vascular vasoconstriction. 6

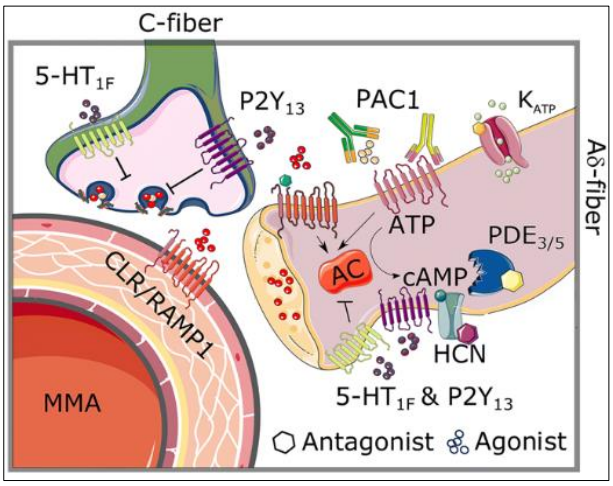

Fig 2: Mechanism of Action

Pharmacokinetics

During Phase I clinical trials, peak drug concentration(C max) and time at peak concentration (T max) were measured. The C max and T max of 200mg of lasmiditan was found to be 394.7ng/ml. In double-blind, larger multicenter, placebo controlled parallel group and dose ranging study fastly disintegrating lasmiditan were used for the treatment of acute migraine pain.

The onset of action was very fast. This show the oral bio availability, linear pharmacokinetics and rapid absorption of the drug. It also proves that lasmiditan reduces the severity of migraine as early as possible [7].

Side Effects

The most common side effect in the 200-mg drug were:

- Dizziness (16.3%-18.0%)
- Paresthesia (6.6%-7.9%)
- Somnolence (5.4%-6.5%)
- Fatigue (3.1%-4.8%)
- Nausea (2.6%-5.3%) [8].

Contraindications

Due to vasoconstriction associated with the 5-hydroxytryptamine receptor 1B (5-HT_{1B}) activity, lasmiditan are contra indicated in patients with:

- Ischemic coronary artery disease (CAD).
- Coronary artery vasospasm.
- Wolff-Parkinson-White syndrome.
- Peripheral vascular disease.
- Ischemic bowel disease [8].

Route of Administration

- Oral: may take with or without food.
- Intravenous

Fig 3: Lasmiditan tablet

Doses

- 50 mg
- 100 mg
- 200 mg

Each of the lasmiditan tablets (50 mg, 100 mg and 200 mg) are match with the Placebo tablets. For the acute treatment of migraine one dose is required.

For rescue or recurrence of migraine second dose is allowed between 2 and 24 hours.

In case of geriatric patients, the dose ranging is 50 mg, 100 mg, or 200 mg PO PRN; initiate at lower end of dosage range.

Not to exceed more than 1 dose/24 hr.

For pediatrics, safety and efficacy was not established [8].

Drug Interactions

- Lasmiditan inhibits P-gp and breast cancer-resistant protein (BCRP) so avoid co administration.
- When combined with alcohol or other CNS depressants, sedation, driving impairment, neuropsychiatric adverse reactions may occur.
- Co administration of lasmiditan with drugs like SSRIs, SNRIs, TCAs, MAO inhibitors may increase the level of serotonin which leads to serotonin syndrome.
- When combine with propranolol, it decreases heart rate [8].

Storage

Store at 20-25ºC (68-77ºF) in excursions, permitted to 15-30ºC (59-86ºF) [8].

Conclusion

In the new era, triptans are found to be the most effective dose of drug for the treatment of acute migraine pain. Unfortunately, there are large number of patients who are not respond to triptans, or contra indicated to tripatans. With the detailed clinical studies, lasmiditan appears to have the minimum side effects. Phase III studies are not yet reported. But the other reports state that lasmiditan is more effective than placebo in the treatment of acute migraine. With Eli Lilly & Co. having announced plans to apply for US FDA approval in early 2018, lasmiditan may soon be a new addition to the expanding headache medicines [9].

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