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Lasmiditan: A Novel Drug for the Acute Treatment of Migraine

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Introduction

Headaches are a universal experience that can affect individuals at any point in their lives [1]. It is painful and can disable a person to perform normal functions of their day today's life. Migraines can significantly impact productivity and daily functioning, affecting individuals across a wide age range. Headaches not only impact individuals but also create a financial strain on society due to healthcare expenses, lost workdays, and decreased productivity. 1.7-4% of the world's adult population suffer from prolonged headaches for 15 or more days a month [2]. One in ten patients seeks care from general practitioners [3], one in five requires emergency admissions [4], and one-third patient population is referred to neurology [5]. This underscores the importance of addressing migraine management comprehensively to improve patient outcomes. It's concerning to see such a substantial increase in the prevalence of migraine among children and adolescents over the years. A study done by WHO assessed the global prevalence of conditions and disability life years among children below 20 years of age from 1990 to 2019. Understanding these prevalence trends can help in developing targeted interventions and healthcare policies to improve the wellbeing of young populations [2].

Migraine is defined as an episodic headache associated with certain features, such as sensitivity to light, sound, or movement or "a recurring syndrome of headache associated with other symptoms of neurologic dysfunction in varying admixtures" [6]. The symptoms of migraine are recurrent severe headaches, often accompanied by nausea, vomiting, and sensitivity to light and sound. It affects millions of people worldwide, making it one of the most common and disabling conditions worldwide [7]. There are different phases, including a premonitory phase, transient neurological symptoms (i.e., migraine aura), an intense headache attack, and a postdrome phase [8].

Pathophysiology

The pathophysiology of migraine is still not well understood. Few of the proposed mechanisms surrounding the onset of migraine headaches are given below:

Genetic Studies

The genetic or the inherited component plays a very important role in the pathophysiology of Migraine. Studies have shown that individuals with a family history of migraines are more likely to experience migraines themselves, indicating a genetic predisposition to the disorder. Various genes and

genetic factors have been implicated in migraine susceptibility, including those related to neuronal excitability, neurotransmitter function, and vascular regulation [9]. There is an unexplained but epidemiologically well-established predisposition that relates to methyl tetrahydrofolate reductase gene mutation C677T that is certainly overrepresented in migraine with aura [10]. The presence of aura seems to be associated, in rarer inherited cases, such as CADASIL or autosomal-dominant retinal vasculopathy with cerebral leukodystrophy, with structural protein dysfunction [11]. and perhaps with an embryonic syndrome that includes patent foramen ovale [12].

Neuropeptide studies

Activation of the trigeminal nerve triggers the release of signaling molecules including calcitonin gene-relate d peptide (CGRP), resulting in secondary cerebral vasodilation, plasma protein extravasation and mast cell degranulation, all contributing to symptoms of migraine. Although, this theory does not explain the pathophysiology of migraine, CGRP can be considered as the initial trigger of trigeminal nerve stimulation causing migraine headaches [10]. It is also apparent that the dilatation of blood vessels is the result of neuronal inflammation, not the cause of migraine headaches. The roles of 5-HT and CGRP have been well documented. CGRP is a potent vasodilator that causes pooling of blood in the cerebral vasculature parallel to decreased levels of 5-HT [11, 12].

5-HT receptors, especially 5-HT1B, 5-HT1D and 5-HT1F receptors play a crucial role in migraine [13]. 5-HT1F receptors are expressed in the CNS, including major regions of migraine pathophysiology such as cortex, hypothalamus, the trigeminal ganglia, trigeminal nucleus caudalis (TNC) and in low concentrations on the cerebral blood vessels like the Middle Cerebral Artery without vasoconstrictive properties [14-16]. Additionally, 5-HT1B, 5-HT1D, but not 5-HT1F, receptors were found on cerebral microvascular smooth muscles and all three subtypes were expressed on astrocytes. These findings, along with pharmacological evidence that selective 5-HT1F receptor agonists lack vasoconstrictive effect, prompted Cohen et al. to hypothesis that the function of this receptor subtype may be related to blood-brain barrier physiology rather than vascular contractility [17]. Triptans have been the drug of choice for migraine over the last three decades. These 5-HT1B and 5-HT1D receptor agonists act on the blood vessels and nerve endings in the brain to inhibit the release of vasoactive neuropeptides (CGRP and Substance P) by trigeminal nerve innervating the intracranial vessels and dura mater [18, 19]. But triptans are not recommended for individuals with history of cardiac and cerebrovascular diseases and those who are at risk for developing such diseases because of their vasoconstrictive action [20]. Besides having limited efficacy, triptans are contraindicated in pregnancy and breastfeeding women [21-23].

Thus, there arose a need to develop more selective treatment for migraines that lack any cardiovascular and cerebrovascular side effects. Drugs targeting neurons (trigeminal pathway) were suggested and 5-HT1F receptors were considered as a contemplated victim for it.

Pharmacology

Lasmiditan is the first of a new group of headache medicines that are being called the “ditans.” Lasmiditan is unique as it is the only drug in its class which works specifically on the 5-HT_{1F} receptor as compared to triptans that primarily act via $5HT_{1B/1D}$ agonism. They do not cause vasoconstriction in contrast to triptans. It contains a pyridinoyl- piperidine scaffold instead of an indole group [24]. The mention of offsite interaction with the 5HT1F receptor suggests that there may be other mechanisms through which the triptans exert their therapeutic effects. The exact role of 5HT1F receptors in the context of migraines and triptan therapy is an area of ongoing research, and understanding these interactions may contribute to the development of more effective migraine treatments. It is important to note that while triptans can be effective for many people with migraines, they are not suitable for everyone, and their use should be discussed with a healthcare professional to ensure proper diagnosis and appropriate treatment [25]. The precise mechanism of action is not fully understood, but there are several proposed ways in which 5HT1F receptor activation may contribute to its activity in migraine treatment. Some of the effects associated with 5 HT 1F receptor agonist include decreased plasma protein extravasation, decreased c-fos expression, suppressed neuronal firing within the trigeminal nucleus caudalis, inhibition of CGRP release from perivascular fibres, direct anti nociceptive action.

While these proposed mechanisms provide insights into how Lasmiditan may work in treating migraines, it's important to note that the exact interplay of these effects and the overall mechanism of action are still subjects of ongoing research. As with any medication, individuals should consult with their healthcare providers for a thorough understanding of its benefits, potential side effects, and suitability for their specific condition [25, 26]. Lasmiditan is highly lipophilic and hence crosses the blood brain barrier which leads to central nervous system abnormalities [27].

Pharmacokinetics

Lasmiditan is administered orally with bioavailability of about 40 % [27]. Lasmiditan can be taken with or without food as the co-administration of drug and a high fat meal was not found to produce a clinically significant difference in exposure [28]. The median peak time to peak plasma concentration is 1.8 hours and the onset of action is 30 to 60 mins post ingestion [29]. The fact that Lasmiditan is primarily metabolized by non- CYP enzymes suggests that the influence of CYP inhibitors or inducers on its pharmacokinetics is unlikely. This can be advantageous in terms of drug interactions, as it reduces the risk of significant alterations in Lasmiditan levels when co-administered with medications that affect CYP enzymes. On the other hand, the "gepant" class of medications which includes Ubrogepant and Rimegepant, is metabolized by CYP3A4 enzymes. CYP3A4 is a major hepatic enzyme involved in the metabolism of various drugs, and its activity can be influenced by inhibitors or inducers. Therefore, when these "gepant" medications are used concurrently with strong CYP3A4 inhibitors or inducers, it can lead to significant changes in plasma concentrations, potentially affecting their efficacy and safety. In summary, the difference in the metabolic pathways of Lasmiditan and the "gepant" competitors contributes to variations in their susceptibility to drug interactions with CYP inhibitors or inducers. It is essential for health care professionals to be aware of these differences when prescribing or adjusting medication regimens to minimize the risk of adverse effects and ensure optimal therapeutic outcomes. Lasmiditan undergoes oxidation on the piperidine ring to form metabolites M7 and M18, as you mentioned, is a combination of M7 and M8 pathways. These metabolites are considered pharmacologically inactive, meaning they do not contribute significantly to the therapeutic effects of the drug. Regarding excretion, a small portion of the active drug of around 3% is excreted in the urine unchanged. This indicates that a minor fraction of the administered Lasmiditan is eliminated from the body without undergoing significant metabolism [30]. The majority of Lasmiditan is excreted in the urine as the metabolite S-M8, accounting approximately 66% of the total excretion. S-M8 is likely a metabolite formed through some specific metabolic pathway, and while it may be inactive, the elimination of the drug through this pathway contributes to its overall clearance from the body. Understanding the metabolism and excretion of the drug excretion of a drug is crucial for assessing its pharmacokinetic profile, potential drug interactions, and overall safety. It also provides insights into how the body processes and eliminates the drug, which can be important for dose adjustments and considerations in specific patient populations [30].

Adverse effects

Lasmiditan, being a CNS (central nervous system) depressant, can lead to significant adverse events when co-administered with other CNS depressants, such as alcohol. The potential for serious driving impairment is noted, and it's emphasized that patients should refrain from driving a motor vehicle for at least 8 hours after each dose of lasmiditan. This caution is crucial for patient safety, as impaired driving can pose risks to both the individuals taking the medication and others on road [31]. Alternative therapies such as rimegepant and ubrogepant are considered to have a high safety profile with relatively low adverse effects. Dizziness, a common adverse event reported in lasmiditan trials (16% to 18% of participants), is mentioned to occur at less than 2% for both ubrogepant and rimegepant. This suggests that these alternative medications may be associated with a lower incidence of dizziness, making them potentially more tolerable for some individuals [32]. Considering the potential for CNS adverse effects and driving impairment with Lasmiditan, healthcare providers may need to carefully assess individual patient profiles, consider alternative therapies, and provide appropriate guidance on driving restrictions and potential risks.

Abuse Potential

Lasmiditan is a schedule V controlled substance. This classification is determined based on its potential for abuse and the perceived risks associated with its use. In abuse potential studies, lasmiditan was compared with alprazolam, a Schedule IV controlled substance. The "drug liking" scores for lasmiditan were higher than placebo but lower than alprazolam, indicating a lower abuse potential compared to alprazolam. As a result, lasmiditan was classified as a Schedule V controlled substance, while alprazolam remained in the higher Schedule IV category. It's worth noting that the classification of a drug as a controlled substance is influenced by various factors, including its pharmacological properties, abuse potential, and safety profile. The Schedule V classification suggests a lower potential for abuse relative to substances in higher schedules. Drugs like, rimegepant and ubrogepant, are not controlled substances. This difference in regulatory classification may be attributed to variations in their pharmacological profiles and abuse potential.

Understanding the controlled substance status of medications is important for healthcare providers, as it affects prescribing practices, dispensing regulations, and patient education on the responsible use of these substances to mitigate potential risks associated with abuse or misuse [33].

Dosage and Administration

Lasmiditan is available in 50 mg and 100 mg tablets, and the recommended dosing is 50 mg, 100 mg, or 200 mg taken orally as needed for the acute treatment of migraine attacks. It's important to note that a second dose of lasmiditan has not been shown to be effective in clinical studies [34].

Comparison of Ditans with Triptans

Triptans, act primarily on 5HT1B receptor, exert their effects through vasoconstriction. However, their use is contradicted in patients with cardiovascular or cerebrovascular diseases due to this mechanism. Triptans' efficacy varies, and approximately 40% of migraine attacks do not respond to them adequately. It is uncertain if there is significant CNS component to their efficacy, and the ability of some triptans to penetrate the blood brain barrier is limited. Lasmiditan provides a different mechanism of action compared to triptans.

It is highly lipophilic and capable of crossing the BBB, potentially acting in the central nervous system. This property distinguishes Lasmiditan from triptans and may contribute to its efficacy in migraine treatment. It's important to note that while the CNS effects of lasmiditan are observed, they don't necessarily prove that its efficacy against migraines is solely mediated in the CNS. There is preclinical and ex vivo evidence suggesting that lasmiditan may inhibit both PNS and CNS pain pathways, including the trigeminal nerve, through the modulation of neuropeptides and neurotransmitters such as CGRP and glutamate. The distinct pharmacokinetic and mechanistic features of lasmiditan make it an intriguing alternative for migraine treatment, especially in cases where triptans may not be suitable or effective. The ability to penetrate the BBB and potentially modulate both PNS and CNS pathways adds to the understanding of how lasmiditan may provide relief for migraine sufferers [35].

Drug Interactions

Lasmiditan administration is associated with mean decreases in heart rate, ranging from 5 to 10 beats per minute, which is higher than the decreases observed with a placebo (2 to 5 beats per minute). This indicates a cardiovascular impact of Lasmiditan [36]. Participants in phase III trials who reported taking concomitant heart rate-lowering medications, such as β-blockers, did not experience adverse reactions compared to other treatment participants. This suggests that, in clinical studies, the use of lasmiditan in combination with heart rate-lowering medications was generally well-tolerated [37]. Given its classification as a CNS depressant, caution is advised when using lasmiditan in conjunction with alcohol or other CNS depressant medications, including antiepileptic medications like valproic acid and topiramate used for migraine prophylaxis [38]. As with all drugs interacting with serotonin, there is a theoretical risk of serotonin syndrome with lasmiditan. Caution is recommended when using lasmiditan concomitantly with serotonergic drugs. A medical review of data from phase III studies assessed the risk of serotonin syndrome, and while five possible cases were identi-

fied, none were severe or serious, and they did not meet the Hunter Serotonin Toxicity Criteria. The risk of serotonin syndrome with lasmiditan is considered somewhat theoretical, and warnings are included out of caution. It's noted that alternative therapies, such as rimegepant and ubrogepant, do not carry the serotonergic risk associated with lasmiditan. The mechanism of action for rimegepant and ubrogepant involves CGRP signaling rather than serotonin agonism.

Understanding the cardiovascular effects and potential risks associated with lasmiditan is crucial for healthcare providers when making treatment decisions and counseling patients. Individual patient characteristics, medical history, and concurrent medications should be carefully considered to ensure the safe and effective use of lasmiditan for migraine treatment [30].

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