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Review Article

A COMPARATIVE ANALYSIS OF CLASSICAL TRIPTANS FOR ACUTE MIGRAINE MANAGEMENT

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ABSTRACT

Migraine, a prevalent and debilitating neurological condition, necessitates effective acute treatment options. This study undertakes a comparison of the safety and effectiveness of triptans, 5-hydroxytryptamine1F (5-HT1F) receptor agonists, and calcitonin gene-related peptide (CGRP) antagonists using a network meta-analysis and systematic review agonists, and CGRP antagonists in managing acute migraine attacks. Triptans, known for their role in modulating nociception and cranial vasoconstriction, remain primary treatments. Among them, for quick symptom relief, subcutaneous sumatriptan 6 mg proved to be the most effective; eletriptan 80 mg and rizatriptan 10 mg both shown to be more effective than sumatriptan 100 mg. 2.5 mg of naratriptan and 2.5 mg of frovatriptan. While generally well-tolerated, triptans' side effects and potential for medication overuse headaches limit their long-term utility, and their vasoconstrictive properties pose risks for individuals with cardiovascular conditions. Notably, only a minority of patients achieve complete pain relief within 2 h, and a significant proportion discontinue due to inadequate efficacy or adverse effects. The study highlights the promise of 5-HT1F receptor agonists and CGRP antagonists as viable alternatives, offering effective relief without vasoconstriction. Special populations, including children and pregnant or breastfeeding women, present unique considerations, with sumatriptan being unsuitable for the former and beneficial for the latter. Cost-effectiveness analysis reveals significant regional price variations. In conclusion, while triptans are effective for acute migraine management, their limitations necessitate exploring alternative therapies such as CGRP antagonists and 5-HT1F receptor agonists to improve patient outcomes. To test these alternatives and create all-encompassing treatment plans, more study is needed.

Keywords: Migraine, Triptans, 5-HT1F receptor agonists, Calcitonin gene-related peptide antagonists, Systematic review, Network meta-analysis, Efficacy, Safety.

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INTRODUCTION TO MIGRAINE AND TRIPTANS

Migraine is a neurological disease with a considerable economic and societal burden that may negatively impact the life of patients. Once thought to be a common treatment for acute migraines, ergot preparations have been linked to a number of serious side effects (adverse effects [AEs]) and few advantages. Triptans, which are selective agonists of the 5-hydroxytryptamine1B/1D (5-HT1B/1D) receptor, have thus become the recommended option for treating acute migraines. However, just a small percentage of patients have pain relief 2 h after starting triptans, and over half of them stop their medication for a variety of reasons, including insufficient effectiveness. In addition, using triptans frequently might cause headaches from overusing medications, which emphasizes the necessity for alternate therapy. In addition, people who are at risk of cardiovascular illness may not benefit from triptans due to their vasoconstrictive effects, which are mediated via the 5-HT1B receptor.

Through a systematic review and network meta-analysis, the effectiveness of triptans, 5-hydroxytryptamine1F (5-HT1F) receptor agonists, and calcitonin gene-related peptide (CGRP) antagonists in the treatment of acute migraine attacks are to be compared in this article.

Migraine, a prevalent chronic neurological condition, affects more of the women than the men. It imposes an economic burden on society and is one of the common neurological disorders. Migraine attacks, characterized by severe headaches lasting 4–72 h and accompanied by symptoms such as phonophobia, photophobia, vomiting, and nausea, significantly impair quality of life and healthcare resource utilization.

Treatment strategies for migraines aim to prevent or alleviate attacks. Pharmacological interventions, including analgesics, anticonvulsants, corticosteroids, antiemetics, and triptans, are commonly used, along with complementary therapies.

Triptans, more specifically serotonin 5-HT1B/1D receptor agonists, are the primary pharmacological treatment recommended for migraines. Their mechanisms of action include modulation of nociception processing, suppression of trigeminal nerve transmission, and cranial vasoconstriction.

Despite the availability of several triptans on the market, limited direct comparative randomized clinical trials hinder the determination of their relative efficacy [1].

SUMATRIPTAN VERSUS OTHER TRIPTANS

Although its exact analgesic impact is yet unknown, sumatriptan, a 5-HT receptor agonist, shows a particular affinity for the 5-HT1B/1D receptors. There are various pharmacological theories behind its effectiveness in treating acute migraines. Sumatriptan causes strong and targeted cerebral vasoconstriction by functioning as an agonist of the 5-HT1B receptor. Furthermore, it binds to the 5-HT1D receptor to prevent the production of vasoactive peptides such as substance P, neurokinin A, and CGRP. Strongly selective CGRP antagonists lend credence to the idea that CGRP inhibition is essential for stopping migraine attacks and might even be involved in rectifying the underlying pathological mechanisms. Moreover, it seems that sumatriptan raises the trigeminal neurons' sensory threshold.

While intact sumatriptan is unable to cross the blood–brain barrier, migraines may disrupt this barrier's integrity, allowing 5-HT receptors to reach the central nervous system.

Sumatriptan acts on the proximal section of trigeminal afferents to alleviate migraines. It suppresses neurotransmission to second-order neurons in the trigeminal nucleus caudalis when administered early in the migraine pathophysiological process, potentially preventing central neuron sensitization.

There are several different forms of sumatriptan on the market, such as rectal suppositories (20, 50, and 100 mg), nasal spray (20 and 5 mg), subcutaneous injection (4 and 6 mg), and tablet form.

While sumatriptan has a lower oral absorption rate compared to other triptans, newer fast-releasing tablet formulations aim to enhance absorption. Clinical trials have indicated its efficacy, with relief observed as early as 25 min for the 100 mg dose.

Different formulations of sumatriptan offer flexibility in delivery methods, allowing patients to tailor treatment based on preferences and attack characteristics. Combining with zolmitriptan formulations may maximize treatment efficacy, particularly for patients experiencing extreme nausea and vomiting [2].

ZOLMITRIPTAN

Zolmitriptan is rapidly absorbed into the bloodstream when administered as a single dose of 5 mg via nasal spray. Measurable plasma concentrations were observed within 2 min after administration. Ten minutes after a 2.5 mg intranasal dose, the plasma concentration of zolmitriptan reaches approximately one-third of its peak value.

Zolmitriptan medication has exhibited a plasma half-life of 3 h, exhibits higher lipophilicity compared to sumatriptan, and has an oral bioavailability of 40%. Zolmitriptan also demonstrates low plasma protein binding. The primary mechanisms responsible for zolmitriptan elimination are hepatic metabolism mediated by CYP1A2 and urinary excretion.

The main metabolites of zolmitriptan include the N-desmethyl derivative (183C91), which is a pharmacologically inactive 5HT1B/1D receptor agonist with at least twice the potency of zolmitriptan, along with the N-oxide and indoleacetic acid derivatives [3].

NARATRIPTAN

Naratriptan, a 5-HT1B/D agonist, decreases the frequency of cluster headaches and has the potential to be used as a migraine medication. Compared to other 5-HT agonists, naratriptan offers improved absorption and a longer half-life, making it a favorable option for the preventive treatment of cluster headaches. This study assessed the effectiveness of naratriptan as a preventive measure for cluster headaches.

In comparison to sumatriptan, naratriptan exhibits a longer t1/2β (6 h vs. 2 h) and the highest bioavailability among all oral triptans. Male peak plasma concentration (Cmax) is lower than that of females, showing dose proportionality.

The time to reach maximum concentration is <2.0 h under normal conditions and extends to 3.5 h during migraine attacks. This delayed time to reach maximum concentration (Tmax) during migraines is attributed to gastric stasis induced by the migraine condition. Subcutaneous injection of naratriptan results in a Tmax of 10 min, with a consistent t1/2 of 5 h. The faster onset of pain relief observed with subcutaneous naratriptan administration is likely due to its shorter Tmax. The subcutaneous injection reduces the risk of delayed absorption caused by gastric stasis during migraine attacks.

Naratriptan demonstrates a high affinity for 5-HT receptor subtypes 1B, 1D, and 1F, and its higher lipophilicity compared to sumatriptan facilitates easier absorption into the central nervous system. Naratriptan exhibits a 3-fold higher affinity for 5-HT1D receptors, along with a longer t1/2 and higher bioavailability when compared to sumatriptan [4].

RIZATRIPTAN

Oral rizatriptan is readily absorbed by the gastrointestinal system, with an absorption rate of about 90%. However, due to significant first-pass metabolism, its total bioavailability is only around 45%. The area under the plasma concentration-time curve (area under the curve [AUC]) and maximum plasma concentration (Cmax) increase approximately dose-proportionately up to 60 mg following a single dose. The tmax after a single dose of rizatriptan varies from 0.7 to 2.1 h.

Rizatriptan is absorbed more quickly than oral sumatriptan. The tmax of rizatriptan was shorter compared to sumatriptan 100 mg. Following treatment, rizatriptan's bioavailability and Cmax are similar in tablet and wafer forms, although the wafer formulation has a slightly longer tmax ranging from 1.6 to 2.5 h. Rizatriptan exhibits a minimum binding of 14% to plasma proteins [5].

ALMOTRIPTAN

Almotriptan exhibits the highest bioavailability among all triptans and is extensively distributed throughout the body following oral administration. Almotriptan is a strong and specific 5-HT1B/1D receptor agonist, with its antimigraine mechanisms involving vasoconstriction, suppression of trigeminocervical complex neurotransmission, and inhibition of vasoactive peptide release from trigeminal nerve endings. Other triptans like rizatriptan 10 mg and eletriptan 80 mg, have demonstrated the most consistent effectiveness in treating migraines. Like other triptans, almotriptan induces vasoconstriction and blocks nociceptive transmission by activating 5-HT1D receptors in trigeminal nerves, affecting both central brainstem trigeminal nuclei and peripheral dural vasculature. Although almotriptan exhibits lower potency and binding affinity to 5-HT1D receptors compared to other triptans, its impact on nociceptive transmission contributes to its efficacy in pain relief and alleviation of associated symptoms such as nausea, vomiting, phonophobia, and photophobia.

Almotriptan is bioavailable and exhibits wide tissue distribution, low protein binding, and a short elimination half-life of approximately 3.5 h. Almotriptan reaches peak plasma concentrations between 1.4 and 3.8 h post-administration, with food having minimal effect on its absorption. Metabolism primarily occurs through monoamine oxidase-A, cytochrome P450 enzymes, and flavin monooxygenase-3. About 50% of the dose is excreted unchanged in the urine.

Clinically significant drug interactions with triptans are unlikely, and age or gender-based dosage adjustments are unnecessary. However, patients with severe renal impairment should not exceed the dose of almotriptan 12.5 mg/day, and those with liver issues are advised to take similar precautions [6].

FROVATRIPTAN

Frovatriptan, also known as three-methylamino-6-carboxamino-1,2,3,4-tetra hydrocarbazole, is a novel selective serotonin receptor agonist. It undergoes metabolism, yielding four metabolites, including an active N-demethylated metabolite. Among serotonin receptor subtypes, frovatriptan exhibits the highest affinity for 5HT 1B and comparable affinity for 5HT 1D, with moderate affinity for 5HT 1F, 5HT 1A, and 5HT 7. It shows minimal affinity for other serotonin receptors, and no affinity for dopamine, histamine, or adrenergic receptors. Frovatriptan is indicated for acute treatment of migraine of longer duration and short-term treatment in women with menstrual migraine.

Frovatriptan's potency in narrowing the human basilary artery is 8.5 times greater than sumatriptan. Notably, it induces cerebral vasoconstriction but uniquely relaxes coronary arteries, with a bell-shaped concentration curve at high concentrations.

When administered orally, frovatriptan exhibits bioavailability <30% and minor protein binding. Peak plasma concentration is observed within 2–4 h post-dose, with males showing a lower Cmax than females. However, the half-life of a single 2.5 mg dose is about 26 h, unaffected by gender or dose.

Frovatriptan's pharmacokinetics remains consistent across individuals with migraines and healthy volunteers. While plasma concentrations increase with age over 65, pharmacokinetics remains similar across migraine users aged 12–65 years. Metabolism occurs primarily in the liver and kidneys, with CYP1A2 involved in hepatic metabolism.

Frovatriptan is not metabolized by monoamine oxidase or CYP3A4, reducing the risk of drug interactions. Renal insufficiency does not affect its metabolism. Oral contraceptive use increases frovatriptan Cmax and AUC values, while concurrent administration of propranolol enhances its bioavailability in both genders [7].

ELETRIPTAN

Eletriptan has a high tolerability profile and consistent clinical effectiveness in the treatment of migraine. Oral eletriptan is available in tablet form, with dosages of 20 mg and 40 mg, not exceeding maximum daily limit of 80 mg. Eletriptan's higher lipophilicity (+0.5 log D at pH 7.4) allows it to display improved absorption, central nervous system penetration, and volume of distribution when compared to other triptans. During an acute migraine attack, it reaches peak plasma concentration (Cmax) within 2 h after oral ingestion, with rapid absorption from the gastrointestinal tract. The half-life of eletriptan is relatively long, and its protein binding capacity is around 85%, with 50% bioavailability.

However, eletriptan's ability to penetrate the blood-brain barrier efflux process, which is mediated by P-glycoprotein (P-gp) and eliminates lipophilic medications from the central nervous system, limits the size of the brain. This necessitates higher oral dosages to overcome P-gp efflux, as it reduces brain exposure to eletriptan by approximately 40 times. The pharmacokinetic parameters of eletriptan remain consistent across various demographic factors, such as age, sex, ethnicity, and menstrual cycle timing.

The majority of eletriptan clearance occurs non-renally through hepatic metabolism, primarily through the CYP3A4 enzyme, more especially, the cytochrome P-450 pathway. N-desmethyl eletriptan, the sole known active metabolite of etriptan, makes up roughly 10–20% of the N-desmethyl eletriptan, comprises about 10–20% of the original drug's plasma concentration. When coadministered with medications that affect CYP3A4 function, eletriptan plasma levels may be altered, leading to an increased risk of AEs or reduced treatment efficacy.

However, eletriptan itself does not significantly interact with other drugs by activating or inhibiting CYP enzymes. Moreover, prostaglandin G/H synthase 1, also known as cyclooxygenase-1, metabolizes eletriptan, presenting no risk of interactions with drugs that affect frovatriptan or eletriptan metabolism [8].

META ANALYSIS

A meta-analysis was conducted on seven oral triptans (e.g., eletriptan, almotriptan, naratriptan, rizatriptan, zolmitriptan, and frovatriptan), as well as subcutaneous, intranasal, and rectal forms of sumatriptan to assess their effectiveness in alleviating headaches and menstrual migraine.

Sumatriptan 100 mg was shown to be less efficacious than eletriptan 80 mg and subcutaneous sumatriptan 6 mg. When compared to sumatriptan 100 mg, the mean therapeutic effectiveness of rovatriptan 5 mg and naratriptan 2.5 mg was lower. For the treatment of headaches, subcutaneous sumatriptan 6 mg was found to be more effective than sumatriptan 100 mg tablets. In comparison to sumatriptan, rizatriptan 10 mg was more efficacious; naratriptan 2.5 mg was less effective. After 2 h, subcutaneous rizatriptan (10 mg) and sumatriptan (6 mg) both worked better for pain alleviation than sumatriptan 100 mg. In conclusion, the most successful triptan was found to be subcutaneous sumatriptan 6 mg. Eletriptan 80 mg and rizatriptan 10 mg showed superiority over sumatriptan 100 mg, while naratriptan 2.5 mg and frovatriptan 2.5 mg were less effective [9].

Subcutaneous Sumatriptan 6 mg has the highest efficacy for rapid relief of migraine symptoms, outperforming other triptans. Eletriptan 80 mg and Rizatriptan 10 mg have superior efficacy compared to sumatriptan 100 mg. Naratriptan 2.5 mg and frovatriptan 2.5 mg have less efficacy compared to other triptans. The findings underscore the efficacy of triptans, particularly subcutaneous sumatriptan, in providing rapid relief from migraine symptoms. However, the limitations of triptans, such as potential side effects, medication overuse headaches, and cardiovascular risks, highlight the need for alternative treatments. 5-HT1F receptor agonists and CGRP antagonists have the potential to be safer and more effective treatments for acute migraines. These alternatives do not cause vasoconstriction, making them suitable for a broader range of patients, including those with cardiovascular conditions.

The migraine-related health-related quality of life (HRQoL), disability, and job productivity were assessed. The migraine attacks had a negative impact on the HRQoL, disability, and work productivity of people with migraine. Therefore, there is insufficient efficacy with acute triptans treatment and there is a need for effective treatment of acute migraine [10].

SPECIAL POPULATIONS

The inclusion of oral sumatriptan in the essential medicines list for children is not recommended due to a lack of randomized controlled trials and its unlicensed status for children under 12 years old. Although sumatriptan has shown superiority over placebo in adolescents aged 12–17 with episodic migraine, the oral form did not significantly outperform placebo in achieving pain relief within 2 h.

Sumatriptan is available in oral tablets, subcutaneous injections, and intranasal sprays. However, the need for patient education with injection and nasal spray methods may affect their efficacy in real-world settings where such education may not be feasible. The intranasal sumatriptan is more expensive compared to the oral form, making oral sumatriptan the primary focus.

The 50 mg dose is recommended in clinical practice because to its equivalent efficacy to the 100 mg dose and decreased risk of AEs. There are two oral dosage forms available: 50 mg and 100 mg. Major scientific societies and agencies worldwide suggest sumatriptan as first-line treatment for acute migraines with or without aura. It is approved for this purpose. Adults have undergone thorough testing to determine its safety and effectiveness, and results have been positive up to a dosage of 100 mg. When it comes to minimizing the need for rescue medication, relieving pain after 2 h, and reducing symptoms of migraines such as nausea, light sensitivity, and functional impairment, oral sumatriptan 50 mg has proven to be much more effective than a placebo. However, studies comparing sumatriptan to other analgesics have yielded conflicting results. Sumatriptan has shown greater efficacy compared to other oral triptans and is considered safe for use in pregnant and breastfeeding women.

Given that Non-steroidal Anti-inflammatory Drugs like American Society of Anesthesiologists (ASA) are associated with medication overuse headaches and are not recommended during pregnancy, sumatriptan presents a valuable therapeutic option, especially for women of reproductive age who constitute a significant portion of migraine sufferers.

While sumatriptan is available as a cost-effective generic medication, its cost-effectiveness compared to other options like ASA and

paracetamol may vary depending on local pricing and long-term safety considerations.

In situations where existing analgesics are contraindicated or ineffective, sumatriptan offers a potentially beneficial and easy-to-administer treatment option, particularly for migraine sufferers who are pregnant or breastfeeding. Overall, considering its evidence-based recommendation and potential benefits for vulnerable populations, sumatriptan should be accessible to most migraine patients to alleviate unnecessary suffering.

There is a need for personalized treatment strategies considering patient-specific factors such as age, comorbidities, and pregnancy status. The efficacy and safety profiles of newer migraine treatments need clinical evidence. The high cost of triptans could limit their accessibility in regions with lower healthcare budgets. Therefore, economic considerations should also be factored into treatment decisions to ensure equitable access to effective migraine therapies [11].

ADVERSE EVENTS AND TOLERABILITY

Distinguishing between tolerability and safety is crucial. Tolerability refers to AEs like nausea and dizziness that, while bothersome, are not typically considered clinically significant. Safety, on the other hand, ensures the absence of clinically important adverse events such as liver toxicity, stroke, or myocardial infarction. Triptans, as a group, are well tolerated, with less than half of patients experiencing side effects, which are brief and mild. However, different triptans have varying tolerability profiles, and there is not a single safest option.

In triptan clinical trials, adherence to the International Headache Society Guidelines for controlled medication trials in migraine is observed. These guidelines cover various aspects including patient selection, inclusion/exclusion criteria, outcomes, statistical analysis, and data interpretation. Adverse events during treatment are to be contemporaneously recorded in the study diary, and spontaneous reporting should be reinforced with open-ended inquiries, categorizing adverse events as mild, moderate, or severe. However, there is a lack of description in randomized clinical trials regarding the procedures for evaluating tolerability. Methodological variations exist, with some trials employing an unprompted approach to collecting side effects, while others do not specify the procedures used. Patients may record side events in a headache diary or communicate with the study coordinator, depending on the trial. The formulations of triptans consisted of tablets, nasal sprays, and injections. The major side effects of triptans are reported to be palpitation, sleep disturbances, sweating, and difficulty in concentration.

Certain investigations focus on the incidence and nature of all serious adverse events, both before and after administration of the treatment. However, the data collection strategy impacts the outcome when evaluating triptan-related adverse occurrences. The approach used to collect data can affect the rates of side effects such as palpitations, chest discomfort, or tightness in the chest [3].

OVERALL CONCLUSION

While triptans are effective for acute migraine treatment, their limitations and side effects underscore the need for alternative therapies. 5-HT1F receptor agonists and CGRP antagonists represent promising alternatives that could offer effective migraine relief without the associated risks of triptans. Further research and clinical trials are necessary to validate these alternatives and optimize migraine treatment strategies.

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