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REVIEW

Managing migraine by patient profile: role of frovatriptan

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Abstract: For the last quarter of a century, triptans have been available for acute treatment of migraine but with little guidance on which of the different triptan products to use for which patient or which attack of migraine. In this article, we propose a structured approach to analysis of individual migraine attacks and patient characteristics as a means of defining and optimizing acute intervention. Assessment of patient and attack profiles includes the "5-Ps": pattern, phenotype, patient, pharmacology, and precipitants. Attending to these five components of information can assist in developing an individualized behavioral, pharmacological, and nonpharmacological comprehensive treatment plan for most migraine patients. This clinical approach is then focused on frovatriptan because of its unique molecular signature and potential novel clinical applications. Frovatriptan like all triptans is indicated for acute treatment of migraine but its role has been explored in management of several unique migraine phenotypes. Frovatriptan has the longest half-life of any triptan and consequently is often promoted for acute treatment of migraine of longer duration. It has also been studied as a short-term preventive treatment in women with menstrual-related migraine. Given that 60% of female migraineurs suffer from menstrual-related migraine, this population is the obvious group for continued study. Small studies have also explored frovatriptan's use in treating migraine predicted by premonitory symptoms as a preventive for the headache phase of migraine. By identifying patient and attack profiles, clinicians may effectively determine the viability of frovatriptan as an effective pharmacological intervention for migraine.

Keywords: frovatriptan, acute treatment, preventive therapy, early intervention

Introduction

The cornerstone of treatment for migraine is acute pharmacology and virtually all people living with migraine take some form of medication during acute attacks of migraine.[1] When attack frequency increases, patients often are prescribed preventive treatments.

Numerous medications are currently available as acute treatment for migraine. The most commonly utilized acute therapies for migraine are over-the-counter (OTC) analgesics, nonsteroidal anti-inflammatories (NSAIDs), triptans, and prescription analgesics. Triptans are considered the gold standard for acute treatment and subcutaneous sumatriptan is the most efficacious acute treatment available.[2] There are six oral triptans and one combination product containing sumatriptan and naproxen.

There is little scientific evidence available to guide clinicians to which acute migraine medication is likely to be most effective for a specific attack of migraine or for a specific migraine patient. There is even less medical evidence available as to how to critically evaluate patients in order to decide on which of the available therapeutic interventions will be most beneficial. In this article, we explore patient and attack profiles as a viable

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method for selecting migraine therapeutics. Specifically this article will focus on the unique role of frovatriptan as both an acute and preventive treatment for migraine as it relates to individualized patient and attack profiles.

Profiles of patients with migraine

The migraine population is heterogeneous, collectively as well as individually. Over the lifetime of migraineurs, most will experience considerable variability in their migraine in terms of symptom expression and frequency of attacks.[3,4] Adding to its complexity, as migraine endures and becomes more chronic, it commonly becomes associated with other acute and chronic diseases. These add significantly to the lifetime disability of those living with the disease of migraine. Consequently, it is essential that health care providers (HCPs) become well versed in both the science of migraine as well as the broader health care needs of the migraine patient.

Many of the diseases comorbid with migraine occur at a frequency that is higher than would be predicated by chance, suggesting perhaps that migraine may be pathophysiologically reflective of a larger more pervasive disease process.[5,6] Systematically defining patients and their attacks of migraine is an essential step toward the successful delivery of long-term health care to this patient population.

Diary

The most important tool for assessing a patient with migraine over time is a headache diary. When properly utilized, it is a communication tool that tracks data important to the patient and the clinician, such as when a headache occurs, its severity, how it progresses over the attack, medications utilized, and treatment response. Once the basics have been determined, a diary may be expanded to plot functional status of the patient between attacks of migraine, sleep pattern, mood, behavioral interventions, and identifying triggers or risk factors.

Ideally the diary becomes the foundation for communication between patient and clinician and is a dynamic focal point for education and treatment modifications. A simple mnemonic to assist in gaining the information necessary to formulate the most effective intervention is called the "5-Ps": pattern, phenotype, patient, pharmacology, and precipitants.[7] Attending to these five components of information can assist in developing an individualized behavioral, pharmacological, and nonpharmacological comprehensive treatment plan for most migraine patients.

The five "Ps"

Pattern

Inevitably as life and biology change, so too does the pattern of migraine. Routine assessments of a patient's migraine pattern can be accomplished by diary review or simply asking patients how their migraine has changed since the last visit or over a specified time period. Particular attention should be paid to attack frequency as well as to the duration and completeness of recovery between episodes of migraine. Failure to achieve full recovery between episodes of migraine may indicate impending migraine chronification or development of comorbid disease. Changes suggestive of new or different headache symptomatology should prompt diagnostic reevaluation.

Attention to the pattern of migraine can detect the need to improve acute treatment or add preventive treatment measures. It can also alert the clinician to dynamics that may be fueling a change in a previously stable migraine pattern.

Five key considerations clinicians can gain from understanding their patient's pattern of migraine:

1. Awareness of whether the patient is at risk for or has developed chronic migraine (CM).
2. Need for more effective acute treatment tools or initiation or altering of preventive therapies.
3. Potential medication misuse, underuse, or overuse.
4. Possibility of a new primary or secondary headache diagnosis.
5. Improvement or worsening of the existing treatment plan.

Phenotype

Phenotype refers to the characteristics of the headache and its associated features. It also may include pre- and post-headache symptoms such as premonitory symptoms (prodromes), auras, and postdromes. Frequently, patients report experiencing more than one type of headache (phenotype) and this leads to the belief that each headache presentation is unique and requires a unique treatment.[8,9] For example, a patient may have low impact headaches considered as a tension-type headache, yet that headache if left untreated or under the "right circumstance" has the potential to become a fully developed migraine. Likewise patients with nasal symptoms and frontal headache may think it is a "sinus" headache and develop another unique treatment strategy for this presentation of migraine. Often it is useful to help patients understand that multiple headache phenotypes are seen with migraine and are in fact all part of the spectrum of migraine.

Phenotype should not be simply a checklist used to make a diagnosis, but an in-depth patient-focused understanding of how the events and symptoms of migraine unfold over the duration of an attack and integrating this understanding into successful treatment.[10] For example, a migraine with an abrupt onset associated early nausea is likely to respond better to a parenteral therapy while an attack phenotype associated with recurrence may respond better to an acute intervention with a long half-life.

Asking for a description of a person's worst headaches leads to understanding the physiological potential of the nervous system to generate disabling primary headaches and to a better understanding of the impact of severe migraine. It is an interesting side-note that for many patients a severe migraine represents the worst pain they have ever experienced (author's personal experience).

Common migraine phenotypes described by patients are migraine with or without aura, "tension-type headache", "sinus migraine", "early morning migraine" (migraine causing awakening from sleep), "abrupt onset migraine", "long duration migraine", "frequent episodic migraine", "migraine associated with early onset of nausea", "thunderclap migraine", "chronic migraine", and "migraine associated with autonomic features". Awareness that different phenotypes occur even in the same patient allows the clinician to provide patients with the necessary range of therapeutic tools to successfully manage their attacks.

Five key points obtained from understanding a patient's headache phenotypes:

1. Diagnostic criteria to define primary headache disorders.
2. Assessment of the clinical spectrum of each primary headache diagnosis. For example, migraine can present with many levels of severity from a thunderclap headache to a slowly evolving headache over days to one associated with nasal autonomic symptoms to others with significant gastrointestinal (GI), sensory or musculoskeletal symptoms.
3. Comprehension of different therapeutic tools the patient requires for management of their migraine. For example, some attacks may need parenteral interventions while other will do better with a long half-life oral intervention.
4. Specific migraine presentations a patient must be prepared to manage.
5. Phenotypes a patient finds most challenging to treat so that modifications can be tailored to improve outcome and minimize disability.

Patient

Clinician needs to understand both the headache a patient has as well as the patient that has the headache. In episodic migraine physiological function should be restored between episodes of migraine. Failure to establish normal baseline function should be explored to determine if it results from poor treatment outcome, increasingly frequent migraine, or development of comorbid or coexisting disease. Patients with CM rarely return to normal physiological function between migraines and often have comorbidities or coexisting disease. Exploration of patient factors is critical to successful management of a migraine patient.

Several patient factors have been associated with diminished response to acute treatment to triptans including obesity, hypertension, and psychological comorbidity especially depression.[11,12] In addition, patient factors such as cardiovascular, cerebrovascular, renal, hepatic, and GI (to name a few) risk factors need to be assessed and reassessed over time.

Also development of obesity, metabolic syndrome or diabetes and their associated disease risk are commonly associated with some migraine preventives and medications used to treat migraine comorbidities. Additionally, understanding the psychological, behavioral, and physiological make-up of patients is essential in understanding their susceptibility to anticipatory behaviors, adherence, or likelihood of adverse events from medications. Further, a comprehension of a patient's attitude toward the disease of migraine and pharmacological interventions being prescribed is essential. Finally, an appreciation of past and current life traumas and the support systems available to a specific patient need to be investigated.

Queries about sleep, mood, and changes in general health can target the appropriate selection of preventive interventions and consultations with other medical specialists can incorporate the treatment needs of specific comorbid diseases into the headache treatment plan.[5,13,14] It is essential to effectively treat comorbid diseases rather than assume they will resolve as migraine improves. Many comorbidities left untreated become independent risk factors for poor treatment outcomes and progression of the disease of CM.[15] There are several simple screening questionnaires that can assist in this effort such as the Migraine Disability Assessment Screen, Headache Impact Test, Beck Anxiety and Depression inventories, Zung Depression Scale, or Patient Health Questionnaire 9, Epworth Sleepiness Scale, Opioid Risk Assessment tool, to name a few.

Five key points gained from understanding the patient include:

1. Detect comorbid or coexisting disease.
2. Psychological or behavioral issues affecting treatment.
3. Changes in health status over time.
4. Integrate nonmigraine disease diagnoses into treatment plans, for example, hypertension and obesity.
5. Define risk factors for other important diseases.

Pharmacology

It is critical to have a complete understanding and inventory of all medications a patient is using to treat migraine as well as their other medical and nonmedical conditions. Equally important is an understanding of how a patient uses medications. This is particularly relevant in migraine patients as they have access to many nonprescription medications. Remember patients ultimately decide if, with what, and when they treat migraine with medication. Realistically, their choices are frequently different from decisions discussed during their last office visit. It is essential to inform patients that OTCs are not free of medical risk. In all likelihood, OTC analgesics cause more renal disease, gastrointestinal disease, cardiac disease, and death than triptans.[16] In addition, migraineurs who take NSAIDs may suffer more GI bleeds or renal failure requiring dialysis than those who rely on triptans.[17]

While many acute treatment medications, whether migraine specific or symptomatic, are hypothesized to lead to medication overuse headache (MOH), simply discontinuing prescription acute medications is not a guarantee that the need or use for acute medication will decrease and in many instances the need for acute medication may increase as may the risk of serious systemic disease. In addition, understanding the dynamics of a patient's decision making around medication usage assesses potential barriers to optimal use of acute treatment. Frequently, patients develop complex schemes to determine the "treatment worthiness" of a specific headache and these dynamics may be important barriers to long-term successful treatment outcomes. Several common barriers to effective acute intervention are "waiting to see" if the headache becomes severe, "stockpiling", and having quantity limitations on acute treatment medication.[18] This assessment also identifies barriers for preventive therapy where patients may believe that because migraine is less frequent, they no longer have a need for daily medication.

Five key points gained from understanding the pharmacology used by a patient:

1. The effectiveness of acute and preventive therapies.
2. Potential and experienced changes in health risk factors acquired over time.
3. Medication interactions.
4. Strategies patients use in treating their migraine.
5. Barriers to effective treatment experienced by the patient.

Precipitants

Assessments of factors that act to protect the person from an attack of migraine and factors that provoke or trigger migraine should be addressed on a regular basis. This communicates to patients that often an attack of migraine is predictable and understandable and once risk factors are identified and avoided or modified, an attack can be averted. Another treatment strategy is to treat early when the headache is mild or in highly selected patients even earlier when the nervous system is or will be vulnerable to migraine. Well identified triggers can in many instances be integrated into treatment, such as, when an individual is planning a trip to the mountains (high altitude) and has documented from past experiences that this triggers migraine. Treating early or even preemptively has been shown to prevent certain attacks and/or minimize impact and disability.[19] Diaries over time can pinpoint many risk and protective behaviors associated with episodes of migraine and thus allow important risk and protective factors to be incorporated into a comprehensive treatment plan.[20–23]

An important education point for patients is the awareness that as migraine frequency increases, so too does a patient's susceptibility to most risk factors. Patients with very frequent migraine find that virtually anything can provoke their next migraine making identification of "triggers" more challenging. It is often valuable to pursue the concept of risk factors generating an environment likely to provoke migraine rather than define an individual trigger responsible for each migraine attack. One method to assist patients' understanding of this distinction is the concept of the migraine threshold, where multiple factors impact the genetic vulnerability of a migraineur to an attack.

Migraine threshold

The migraine threshold is the physiological point at which the nervous system can no longer sustain its integrity and an attack of migraine is initiated. The migraine threshold is likely determined by genetic and epigenetic factors and the interrelationship of multiple risk and protective factors impacting the nervous system at any point in time. This concept is worthy of discussion with most migraineurs. By suggesting self-nurturing activities that support and strengthen the migraine threshold, patients can engage in activities that compensate for

their vulnerability to migraine. This empowers patients with a better understanding of migraine and a sense of control over individual migraine attacks. Ultimately, this transforms the migraineur's perception of the world from being hostile and unpredictable into being understandable and controllable. The idea that a migraineur can raise the migraine threshold to reduce the frequency of attacks is empowering and presents patients with the opportunity to become better decision makers.

Five key points in assessing precipitants and protective factors with a patient:

1. Define potential triggering factors for episodic migraine.
2. Develop risk management strategies when migraine is frequent.
3. Assess protective factors and positive health changes that support the migraine threshold.
4. Understand patient level of involvement in self-management of migraine.
5. Enhance understanding of the genetic/epigenetic hyperexcitable nervous system and the environment that provokes or prevents migraine.

Patient profiles and patient care

Both attack and patients' characteristics are used to make clinical decisions that develop a successful, dynamic, and sustainable treatment plan. Specific patient profiles often lead clinicians to choose specific preventive medications while attack characteristics assist clinicians in deciding issues around acute treatment formulation or specific attribute of an acute or preventative medication that would be most appropriate in a given attack associated need. Also anticipatory anxiety and other medication issues leading to misuse of acute medication can be screened by an understanding of the patient's psychological profile.

Other issues may be specific to physician behaviors and this too needs to be understood and integrated into a cogent treatment plan. Several of these behaviors are discussed later.

Five key points in using patient profiles to direct patient care:

1. Acute medication should not be overused

Overuse of acute medications for migraine are associated with chronification of the underlying migraine pattern and the development of MOH.[24] The threshold quantities for defining medication overuse varies depending on the pharmacological class of medication. Triptan, ergotamine, opioid, and butalbital overuse is defined as 10 days (not doses) a month for a period of 3 months. OTCs and NSAIDs require 15 days per month of sustained use. The International Headache Society also warns that copharmacy with different acute medications does not reduce the risk of MOH.[24] The limits defined for MOH are largely consensus-based, but do provide a guideline for limitations of acute medication usage.

Clinicians often approach MOH by controlling prescribed acute medications and fail to recognize that patients will do "something" when in the throes of a severe migraine. HCPs need to provide options for this eventuality.

2. Acute medications should be initiated early in a migraine attack

Multiple studies of triptans demonstrate that intervention when the headache is mild improves pain-free efficacy.[25–27] Early intervention is associated with less recurrence of migraine, fewer triptan-related adverse events, and a reduction of the time of migraine-related disability. This is also likely to be the case for nontriptan acute medications as well.

Despite these attributes, this clinical paradigm is not necessarily easy to implement in clinical practice. In a study by Foley et al,[28] 50% of migraineurs reported delaying treatment of migraine. The most common reasons were the desire to "wait and see" if the headache was going to be a migraine and wanting to treat migraine with medication only if it were severe. In other words, patients want to use medication only if the headache is deemed "worthy" of treatment. Helping patients to understand the spectrum of migraine they experience and consequence of delayed intervention may be useful in assisting a patient's decision making as to how to use acute therapy. Ironically "wait and see" can actually result in increasing the need for acute medication as the decreased efficacy often translates into more doses of acute medication being needed per attack. On the other hand, taking acute medication in anticipation of migraine that would resolve without medication can lead to excessive medication use. These issues highlight the critical role of the HCP's education for the migraine patient.

3. Sub-optimized acute treatment is a risk factor for CM

A recent study by Lipton et al[29] demonstrated that the risk of developing CM in a given year was significantly greater for patients who did not have an optimized acute treatment. Utilizing the Treatment Optimization Score, this study demonstrated that patients with the lowest treatment optimization scores had a twofold greater risk of CM than those with the highest optimization scores. Thus it appears that the use of acute medication is a door that swings both ways. Too much

medication leads to MOH while acute medication not utilized optimally may potentiate CM. Although definitive evidence is lacking, common sense dictates the value of considering effective acute treatment as the cornerstone of migraine prevention.

4. Migraine is not a benign headache disorder

Perhaps the most destructive migraine myth is that it is a benign medical condition. Migraine as seen in medical practice needs to be understood as a chronic medical condition with the potential to worsen over time and become one of the leading causes of worldwide disability. Migraine needs to be identified early, treated responsibly, and followed closely for decades of time. While the most common neurological disease encountered in medical practice, migraine is also the most treatable.

5. Failed treatment plans indicate a need for reassessment

Almost all treatment plans require modification over time. As the pattern of migraine changes, medications may require adjustment or discontinuation. Patients need to be active participants in monitoring their migraine over time. With maturity, migraine may become less severe but may not necessarily resolve.

Frovatriptan: the molecule

From a molecular perspective, frovatriptan is arguably an unique triptan. Also, but perhaps less arguably, it is the most under-utilized and misunderstood triptan. Like all triptans, it is a potent selective serotonin 5-HT-1B/D agonist and like all other triptans,[30] it is approved only for acute treatment of migraine with or without aura.

A differentiating pharmacokinetic feature of frovatriptan is a 26-hour half-life, which is over four times longer than any other triptan.[31] Undoubtedly, this accounts for the low recurrence rates associated with frovatriptan.[32,33] Savi et al[34] reported on a double-blind efficacy and pharmacokinetic study comparing frovatriptan to rizatriptan in acute treatment of migraine. They concluded that both triptans had similar initial efficacy, but frovatriptan had a longer duration of action that correlated with its PK profile. Numerous studies support lower recurrence rates with frovatriptan.[35,36] A second unique feature of frovatriptan is that it is eliminated by both renal and hepatic mechanisms.[37,38] This has obvious advantages in patients with mild-to-moderate renal or hepatic impairment and might be particularly relevant in patients requiring frequent use of NSAIDs for migraine or other medical conditions.

In addition, frovatriptan has no known medication interactions and unlike many other triptans, it is not metabolized by the monoamine oxidase system or the P450 3A4 enzyme.[38]

In terms of a dose response effect on coronary arteries, frovatriptan at lower doses is similar to other triptans, but in animal and cadaver studies, there is a reversal of coronary constriction that occurs at higher doses. In vitro experiments actually demonstrate coronary artery dilatation at higher doses, which is an effect not observed for other triptans or serotonin.[39] In addition, in dogs with experimentally induced myocardial infarction, frovatriptan had no negative effect on coronary blood flow.[40]

Another distinguishing feature of frovatriptan relative to other members of the triptan class, is its flat dose response curve with doses ranging from 2.5 to 40 mg. Below doses of 10 mg, there is essentially no increase in adverse effects.[38] Even at doses above 10 mg, adverse events were generally mild and well tolerated. This underscores its potential off-label suitability for dosing on consecutive days such as in a short-term preventative paradigm used in menstrual migraine.

Clinical studies of frovatriptan in treatment of migraine

Clinical efficacy trials

Frovatriptan was studied in three randomized placebo-controlled double-blind clinical trials that included 2,676 subjects.[38,41,42] Statistically significant headache response was achieved for frovatriptan 2.5 mg versus placebo at 2 and 4 hours after dosing moderate-to-severe headache. Resolution of migraine-associated symptoms also was statistically superior for frovatriptan versus placebo. Headache recurrence, defined as achieving relief at 4 hours with subsequent return to moderate or severe pain within 24 hours, was low and ranged between 10% and 25%.

Long-term safety and tolerability studies

Tolerability of frovatriptan over 12 months was studied in 13,878 migraine attacks treated by 496 patients.[43] Frovatriptan was well tolerated regardless of age, sex, race, concomitant medications, or the presence of cardiovascular risk factors.

Early intervention and frovatriptan

Frovatriptan is more efficacious when provided early in the course of a developing migraine.[42] Time to meaningful relief of migraine occurred 3.5–4 hours earlier when migraine was

treated during mild headache versus severe headache and 1.5 hours earlier when migraine headache was moderate. Recurrence rates were low (15%) and unaffected by the intensity of headache at the time of treatment. This might be predicted since the time to maximum concentration (Tmax) for frovatriptan is 2–4 hours, which is somewhat longer than for other triptans.

A second randomized placebo-controlled comparison of frovatriptan versus placebo initiated at onset of mild headache demonstrated statistical efficacy for early treatment.[42] It also demonstrated that early treatment with frovatriptan limited migraine disability.

Early clinical uses of frovatriptan

Frovatriptan is often promoted for acute treatment of migraine of longer duration and in particular, menstrual-related migraine (MRM). While all triptans have efficacy as acute treatment for MRM, in most studies frovatriptan has demonstrated a similar initial efficacy and a statistically significant lower rate of recurrence. An interesting exception is a combination of dexketoprofen/frovatriptan, which improved early response versus frovatriptan alone.[45]

Triptan as preventive therapy in MRM

Earlier studies suggested that MRM could be prevented by pretreatment with triptans. Newman et al provided an open label study demonstrating 25 mg of sumatriptan initiated prior to onset of menstrual migraine could prevent the predicted MRM.[46] Further, placebo-controlled studies with naratriptan demonstrated efficacy for the 1 mg dosage of naratriptan twice a day, but failed to reach statistical efficacy for the 2.5 mg twice a day dosage.[47] This paradox combined with concerns that migraine might be delayed rather than prevented, kept this treatment strategy from being widely promoted. However, a large clinical trial with frovatriptan as a short-term preventive therapy of MRM demonstrated positive efficacy for frovatriptan in short-term prevention of MRM.[48]

Frovatriptan as short-term prevention of menstrual migraine trial

Frovatriptan has been studied in a multicenter, randomized, double-blind, placebo-controlled, three way crossover study for prevention of menstrual migraine.[49] The study population comprised of 427 women aged older than 18 years with regular menses who experienced a migraine with at least three-quarters of their menstrual periods within the previous year. Subjects were randomized into three groups: placebo, frovatriptan 2.5 mg once daily, or frovatriptan 2.5 mg twice daily (bid) and instructed to begin treatment 2 days before anticipated onset of menses and continue treatment for 6 days. The primary endpoint for the study was the difference in number of MRM attacks between active and placebo groups. Secondary endpoints included MRM severity, duration, associated symptoms, and patient satisfaction. The occurrence of MRM was 69% in the placebo group, 52% in the frovatriptan daily group, and 41% in the frovatriptan 2.5 mg bid group. Both active groups reached statistical significance. There was a statistically significant reduction for headache severity and associated symptoms. Statistical significance was also achieved between the frovatriptan daily versus frovatriptan bid group. Patient satisfaction was significantly greater for active drug over placebo with the greatest patient satisfaction occurring in the frovatriptan bid dosage group. There were no differences in the incidence or severity of adverse events for either active group. The type and frequency of adverse events were similar for frovatriptan and placebo. There was no evidence that migraine was delayed rather than prevented.

Preemptive or short-term prophylaxis of migraine

Numerous clinical studies have been conducted on treatment of migraine before the headache is moderate-to-severe in intensity and demonstrated improved efficacy over delaying treatment until the headache is moderate-to-severe. This raises the question of whether acute treatment can be optimized even further through treatment of earlier phases of migraine such as the premonitory phase or even the vulnerability phase of the attack.[7,44]

A small pilot study has been conducted using naratriptan administered during the premonitory period of a migraine attack and demonstrated positive results over placebo.[19]

A second pilot study compared frovatriptan administered during the promontory phase of a migraine attack to daily administration of topiramate.[50] Both drugs were associated with a statistically significant reduction of both migraine and headache days though a slight superiority was observed for daily topiramate. On the other hand, the dropout rate was 18% for topiramate and 4% for frovatriptan. Implications from this study open the door to the new treatment paradigm for triptan drugs as short-term preventive medication for migraine and possibly for other forms of predictable migraine. This includes the off-label use of frovatriptan as a preemptive prophylaxis of migraine.

Putting it altogether: which patient profile might suggest a trial of frovatriptan

Pattern

A clinically challenging population of migraineurs includes those with frequent episodic or CM. Utilizing frovatriptan with its long half-life and low recurrence rate potentially could reduce overall medication use and provide a longer duration of protection to the nervous system. Many studies[30–37] have demonstrated that, compared to other triptans, frovatriptan produces less recurrence of migraine at 48 hours post-dose.

Phenotype

Ideally a slow onset migraine of long duration (>12 hours) would align with the longer Tmax and longer half-life noted with frovatriptan. Frovatriptan might also be considered for a patient with a phenotype of predictable ultra-long duration migraine (>48 hours), also as off-label preemptive treatment for highly predictive migraine, and of course as short-term prophylaxis for MRM.

Another phenotype of migraine where frovatriptan had superior efficacy to rizatriptan, zolmitriptan, and almotriptan was in treatment of migraine with aura.[51]

Patient

Frovatriptan might be appropriate for patients with obesity. A study by Saracco et al[52] compared responses to frovatriptan, rizatriptan, zolmitriptan, and almotriptan in obese and nonobese patients and noted that the rate of headache relapse was significantly less for frovatriptan than with the other triptans.

A study comparing triptan response between normotensive and hypertensive patients found a decreased response to zolmitriptan, almotriptan, and frovatriptan in hypertensive patients.[53] While efficacy at early time points was similar for all the medications, the relapse rates within 48 hours were significantly less for frovatriptan.

Other patient profiles to consider are patients with mild renal or hepatic impairment or patients utilizing drugs with known hepatic or renal toxicity such as NSAIDs. Patients with risk factors for cardiac disease might also be another patient population to consider bearing in mind that if significant coronary heart disease exists, then all triptans are contraindicated.

Pharmacology

Given the low rate of migraine recurrence associated with frovatriptan, it might be an ideal acute intervention for patients requiring multiple doses of medication to manage their attacks of migraine. This may in turn reduce the risk of MOH and/or be a useful bridge therapy in lessening patients' reliance on offending drugs.

Also patients on multiple medication may benefit from frovatriptan given its lack of drug–drug interactions and having both renal and hepatic excretion pathways.

Precipitants

An area that distinguishes frovatriptan is the treatment of predictable migraine. The most promising arena is MRM, but other predictable migraines warrant serious study. Also future studies should consider frovatriptan as a preventive agent based on premonitory symptoms or possibly predictable migraine triggers.

Summary

It has been nearly 25 years since triptans were first introduced as treatment for acute migraine. They have proven themselves to be an effective safe treatment for migraine, yet there have been no new indications for these products. Frovatriptan is a novel triptan with a unique molecular signature and potential clinical applications. Hopefully, future research will be conducted that will advance the utility and benefit of this important product.

Frovatriptan, with its unique half-life, low potential for drug interactions, and excellent tolerability over a wide dose range is a logical choice for continued research in the onset of short-term prevention for predictable migraine attacks. Given that 60% of female migraineurs suffer from MRM, this population is the obvious group for continued study of the short-term preventive paradigm with triptans. However, other migraine attacks are also highly predictable. This includes attacks associated with specific triggers such as air travel or alterations in sleep schedules as well as migraines predicted by premonitory symptoms. Hopefully, the study of triptans will continue even in light of new and exciting developments in migraine.

Disclosure

The authors report no conflicts of interest in this work.

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