REVIEW ARTICLE

Role of Triptans in the Management of Acute Migraine: A Review

Patel Nazema[1], Adil Patel[1,2]

[1]Department of Pharmaceutics, Shree Dhanvantary Pharmacy College, Kim, Surat, Gujarat, India, [2]Department of Pharmaceutics, School of Pharmacy, RK University, Rajkot-360001, Gujarat, India

Abstract

The common episodic headache disorder known as a migraine is mainly characterized by attacks comprising various combinations of a headache as well as neurological, gastrointestinal, and autonomic symptoms. This condition can be symptomatic of a distinct pathologic process or can occur without underlying causes. As per the report of American Migraine Prevalence and Prevention Study indicate that 17.1% of women and 5.6% of men in the United States experience one or more migraine headache per year. Most recurrent headaches are the result of a benign chronic primary headache disorder. The serotonin receptor agonists or triptans play a key role in migraine pharmacotherapy. The first and second generation of triptans is reported to give quick relief from migraine headache compare to other medication available. The importance of triptans is also reinstated by the fact that they are appropriate first line therapy for patients with mild to severe migraine and are used for rescue therapy when nonspecific medications are ineffective.

Key words: Migraine, pharmacokinetic, recurrent headaches, sumatriptan, triptans,

INTRODUCTION

Migraine is common episodic headache disorder that is characterized by attacks comprising various combinations of a headache and neurological, gastrointestinal, and autonomic symptoms. Headache is one of the most common complaints encountered by health-care practitioner and among top three principle reasons given by adults 18 years of age and older for visiting emergency department in U.S.[1] Most recurrent headaches are result of benign chronic primary disorder.[2] Less often headache is symptomatic of a serious underlying medical condition such as infection, cerebral hemorrhage, or brain mass lesions. The peak prevalence of tension-type and migraine headache, the most common of primary headache disorders, occurs during most productive years of life (20-25 years of age).[3] The updated classification of headache disorder and diagnostic criteria by the International Headache Society (IHS) [Table 1] provides more precise definitions and standardized nomenclature for both the primary (tension-type, migraine, and cluster headache) and secondary (symptomatic of organic disease) headache disorders.[4]

The positive and negative symptoms of migraine are caused by neuronal dysfunction. The neurologic changes of the aura parallel to those that occur during cortical spreading depression.[5] Migraine pain is believed to result from activity within the trigeminovascular system. Activation of trigeminal sensory nerve triggers the release of vasoactive neuropeptides which interact with dural blood vessels to promote vasodilation and dural plasma extravasation resulting in neurologic inflammation.[6,7] Orthodromic conduction along trigeminovascular fibers transmits pain impulses to the trigeminal nucleus caudalis, where information is relayed further to higher cortical pain centers. Continued afferent input can result in sensitization of these central sensory neurons, producing a hyperalgesic state that responds to previously innocuous stimuli and maintains headache.[8] However, the pathogenesis of migraine may be related to a defect or dysfunction in the activity of neuronal calcium channel mediating serotonin and excitatory neurotransmitter release in brainstem nuclei that modulate cerebral vascular tone and nociception. This dysfunction may result in vasodilation of the trigeminovascular system.[7,9]

Address for correspondence:
Dr. Adil Patel, Department of Pharmaceutics Shree Dhanvantary Pharmacy College, Kim, Surat, Gujarat, India. E-mail: adil1487@gmail.com

Received: 26-07-2016
Revised: 23-08-2016
Accepted: 29-08-2016

Table 1: International headache society classification system[2]

Migraine	
Migraine without aura	
Migraine with aura	Typical aura with migraine headache (aura lasting<1 h) Typical aura with nonmigraine headache Typical aura without headache Familial hemiplegic migraine Sporadic hemiplegic migraine Basilar-type migraine
Childhood periods syndromes that are commonly precursors of migraine	
Cyclical vomiting (self-limiting episodic conditions)	Abdominal migraine (episodic midline abdominal pain attacks lasting 1-72 h) Benign paroxysmal vertigo of childhood (brief episodic vertigo)
Retinal migraine (repeated attacks of monocular visual disturbance)	
Complications of migraine	Chronic migraine (occurring on ≥15 days/month for>3 months) Status migrainous (debilitating attack lasting>72 h) Persistent aura without infarction (symptoms persisting>1 week) Migrainous infarction (aura symptoms associated with an ischemic brain lesion) Migraine-triggered seizure
Probable migraine	Probable migraine without aura Probable migraine with aura Probable chronic migraine
Tension-type headache	
Cluster headache and other trigeminal autonomic cephalalgias	
Other primary headache	Headache attributed to head and/or neck trauma Headache attributed to cranial or cervical vascular disorder Headache attributed to nonvascular intracranial disorder Headache attributed to a substance or its withdrawal Headache attributed to infection Headache attributed to disorder of homeostasis Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structures Headache attributed to psychiatric disorder Cranial neuralgias and central causes of facial pain Other headache, cranial neuralgia, central or primary facial pain

Genetic factors seem to play an important role in susceptibility to migraine attacks. Attack occurrence and frequency are governed by CNS sensitivity to migraine specific triggers or environmental factors.[10] Low levels of magnesium or dopamine and increased levels of excitatory amino acids such as glutamate and alterations in levels of extracellular potassium also can affect the migraine threshold and initiate and propagate the phenomenon of critical spreading depression.[11]

The migraine attack has been divided into several phases. Premonitory symptoms are experienced by approximately 20-60% of migraineurs in the hours or days before the onset of headache.[2,12] Premonitory symptoms vary widely among migraineurs but usually are consistent within an individual. Neurologic symptoms, e.g., phonophobia, photophobia, hyperosmia, and difficulty in concentration are most common, but psychological symptoms, e.g., anxiety, depression, euphoria, irritability, drowsiness, hyperactivity, and restlessness; automatic, e.g., polyuria, diarrhea, and constipation; constitutional symptoms, e.g., stiff neck, yawning, thirst, food carving, and anorexia are also reported.[13]

General approach to treatment

Nonpharmacologic and pharmacologic interventions are available for the management of migraine headache. However, drug therapy remains the mainstay of treatment for most patients. Treatment strategies must address both immediate and long-term goals. Acute migraine therapies should provide consistent, rapid relief, and enable the patient to resume normal activities of patients. Recurrence of symptoms and treatment-related adverse effects should be minimal. Goals of long-term and acute treatment of migraine are listed in Table 2.[14,15]

Nonpharmacologic therapy of acute migraine headache is limited but can include the application of ice to the head and period of rest or sleep usually in a dark, quiet environment. Abortive or acute therapies can be migraine specific, e.g., ergots and triptans or nonspecific, e.g., analgesics, antiemetics, NSAIDs, and corticosteroids are most effective at relieving pain and associated symptoms.[15,16]

Table 2: Goals of therapy in migraine management

Goals of long-term migraine treatment
Reduce migraine frequency, severity, and disability
Reduce reliance on poorly tolerated, ineffective, or unwanted acute pharmacotherapies
Improve quality of life
Prevent headache
Avoid escalation of headache medication use
Educate and enable patients to manage their disease
Reduce headache-related distress and psychological symptoms
Goals for acute migraine treatment
Treat migraine attacks rapidly and consistently without recurrence
Restore the patient's ability to function
Minimize the use of backup and rescue medications
Optimize self-care for overall management
Be cost effective in overall management
Cause minimal or no adverse effects

Serotonin receptor agonists (triptans)

Triptans are a family of tryptamine-based drugs used as abortive medication in the treatment of migraines and cluster headaches. They were first introduced in the 1990s. While effective at treating individual headaches, they do not provide preventative treatment and are not considered a cure. Triptans play very advance and significant role in migraine pharmacotherapy. The first member of this class, sumatriptan, and the second-generation agents such as zolmitriptan, naratriptan, rizatriptan, almotriptan, frovatriptan, and eletriptan are selective agonist of the 5-HT_{1B} and 5-HT_{1D} receptors. Three main key actions are responsible for relief from migraine headache: Normalization of dilated intracranial arteries through enhanced vasoconstriction, peripheral neuronal inhibition, and inhibition of transmission through second order neurons of the trigeminocervical complex.[17,26,28] The triptans are appropriate first line therapy for patients with mild to severe migraine and are used for rescue therapy when nonspecific medications are ineffective.[7]

The first generation triptan, sumatriptan is the most extensively studied acute therapy. Sumatriptan is available for subcutaneous, oral, and intranasal administration.[28] Subcutaneous sumatriptan is capable of alleviating migraine headache and associated symptoms with relief reported in 69% of patients at 1 h in a meta-analysis of placebo-controlled studies.[7] Advantage of subcutaneous sumatriptan is capable of providing enhanced efficacy and more rapis onset of action compare to the oral formulation.[28] Sumatriptan is produced and marketed by various drug manufacturers

Table 3: Drugs for migraine

Route	Generic name	Trade name	Dose
Oral	Acetaminophen+codeine	Empracet®, tylenol 3®, generic	300 mg+30 mg
	Ibuprofen	Motrin®, generic	400-1200 mg
	ASA+metoclopramide	ASA+emex®, maxeran®, reglan®, generic	1000 mg+10 mg
	Naproxen	Naprosyn®, generic,	750
	Diclofenac	Voltaren®, generic	50 g
	Sumatriptan	Imitrex®	25-100 mg
Parenteral	Meperidine/pethidine	Demerol®, generic	75-100 mg IV/SC
	Chlorpromazine	Largactil®, generic	25 mg IV
	Metoclopramide	Maxeran®, Reglan®, generic	10 mg IV
	DHE	Dihydroergotamine®	0.5-1 mg IV/SC
	Nalbuphine	Nubain®	10 mg IM
	Methotrimeprazine	Nozinan®	37.5 mg IM
	Ketorolac	Toradol®	60 mg IM
	Sumatriptan	Imitrex®	6 mg SC
Intranasal	DHE	Migranal®	0.5-1 mg IN
	Butorphanol	Stadol NS®	1 mg IN
	Sumatriptan	Imitrex®	20 mg IN

Table 4: Pharmacokinetic and efficacy profile of triptans

Name	Formulation	Recommended dose (mg)	Tmax (h)		Cmax (mg/L)	Protein binding (%)	Vd (L/kg)	$t_{1/2}$ (h)	Bioavailability (%)	AUC (mg/L h)	CLR (ml/min)
			Outside attack	During attack							
Sumatriptan	Oral	100	2.5		54	14-21	2.4	2-2.5	14	158	260
	Subcutaneous	6	0.25	-	72	-	-	2	96	90	220
	Intranasal	20	-	-	13	-	-	2	-	48	210
Zolmitriptan	Oral	2.5	2	2.5	3.3	25	7	3	40	78	193
Naratriptan	Oral	2.5	1.5-2	3.5	12.6	28-31	170	5-6	63	98	193
	Subcutaneous	1	0.2	0.2	-	-	-	5	-	-	-
Rizatriptan	Oral	10	1	1	19.8	14	110-140	2-2.5	47	50	414
Eletriptan	Oral	80	1.5	2.8	246	-	-	4-5	50	1661	-
Almotriptan	Oral	12.5	2.5	-	49.5	-	-	3.6	70	266	-
Frovatriptan	Oral	2.5	2-4	2-4	4.2	-	-	25	24	94	-

with many different trade names such as Imitrex, Imigran, Sumatran, Sumatriptanum, and Sumax and also as Treximet as a combination product with naproxen.

The second generation triptans appear to offer an improved pharmacokinetic and pharmacodynamics profile compared with oral sumatriptan. These agents have demonstrated higher oral bioavailability and longer half-lives compare to oral sumatriptan.[7,16,28] Frovatriptan and naratriptan have the longest half-lives and slower onset of action compared with other triptans. At all marketed dose, triptans are effective and well tolerated. Across studies for sumatriptan 100 mg, mean result was a 2 h headache response of 59%, with 29% pain free at 2 h, 20% sustained pain free, and 67% consistency. Compared with sumatriptan 100 mg, rizatriptan 10 mg showed better efficacy and consistency and similar tolerability. Eletriptan 80 mg showed better efficacy similar consistency but lower tolerability. Almotriptan 12.5 mg showed similar efficacy at 2 h but better other results. Naratriptan 2.5 mg and eletriptan 20 mg showed lower efficacy and better tolerability, and zolmitriptan 2.5 and 5 mg, eletriptan40 mg, and rizatriptan 5 mg all showed similar results.[7,17,18]

Mechanism of action

It has been observed that mechanism of action of triptans includes constriction of dilated cranial blood vessels, inhibition of neurogenic inflammation around the blood vessels,[19] and inhibition of impulse transmission centrally within trigeminovascular system.[20,21] Many researchers believe that the triptans cause constriction of dilated cranial extracerebral blood vessels, most likely via 5-HT1B receptors.[3,22,23] One such study reported that during migraine attacks the middle cerebral artery was dilated on the headache side which was reversed by intravenous sumatriptan. Other studies have reported that there was an increase in middle cerebral artery blood flow velocity after subcutaneous injection of sumatriptan during migraine attack.[24,25] Triptans are also capable of reducing neuropeptide release and plasma protein extravasation across dural vessels[26] and also inhibit impulse transmission centrally within the trigeminovascular system.[27,28] The role of 5-HT1D receptors in producing a neuronal effect by the mediation of triptans is unsure because PNU-142633F, a selective 5-HT1D receptor agonist, has not proved ineffective in the treatment of migraine.[29]

Pharmacokinetics of triptans

The effectiveness of migraine treatment entirely depends on the pharmacokinetic profile of triptans. Most desirable characters of any effective migraine drug are rapid absorption, passage through CNS, rapid onset of action, high bioavailability, and the ability to prevent recurrence of migraine attacks. Considerable amount of research work has been done to develop most effective treatment for migraine treatment with good drug pharmacokinetic profile.

A detailed study was carried out in both healthy human volunteers and in patients with migraine to check the pharmacokinetic characteristics of triptans. Rapid absorption followed by maximum plasma concentration (t_{max}) of 10 min with average bioavailability was observed after subcutaneous sumatriptan (6 mg).[30,31] The oral administration of 100 mg sumatriptan produced bioavailability as low as 14% coupled with longer t_{max} of 1.5 h.[32,33] No significant change in any parameter was observed after intranasal and rectal administration.[34-36] New triptans have exhibited good oral bioavailability specially naratriptan and almotriptan because of their lipophilic nature. Values of t_{max} of zolmitriptan, naratiptan, eletriptan, almotriptan, and frovatriptan after oral administration are not similar to or longer than that of sumatriptan.[36-38] In case of rizatriptan, the time taken to reach c_{max} is less compare top sumatriptan.[39] A comparative study where the t_{max} was 1.3 h in case of rizatriptan and 2.5 h of shumatriptan also confirms the faster oral absorption of rizatriptan than sumatriptan.[40] It has been observed that the unbound c_{max} values of new triptans are lower than that of sumatriptan. Reasons for such are lower therapeutic concentration are required as these drugs have a higher affinity at 5-HT1B/1D receptors, and these drugs have been better titrated. Except rizatriptan, the newer triptans degrade more slowly compare to sumatriptan.[41] Unlike sumatriptan and naratriptan metabolites of zolmitriptan, rizatriptan, and eletriptan have shown pharmacological activity.[42-44] In case of almotriptan and frovatriptan, the activity of metabolites are not reported anywhere.

To check the interaction of triptans with drugs used for migraine prophylaxis or dugs coadministered in the treatment of migraine have been investigated in healthy volunteers. The pharmacokinetic profile of sumatriptan remains unchanged by concomitant administration of propranolol, pizotifen, flunarizine, dihydroergotamine, paroxetine, butorphanol, or naratriptan.[9] No significant change in clinical profile of zolmitriptan was observed when administered concomitantly with dihydroergotamine, propranolol, pizotifen, fluoxetine, metoclopramide, or paracetamol (acetaminophen). Similarly, no significant change in pharmacokinetic profile of naratriptan was observed when coadministered with ergotamine and dihydroergotamine.[46,45] An increase in mean plasma concentration by 70% was seen in case of rizatriptan when coadministered with propranolol. No such effect was observed in case of nadolol and metoprolol when administered along with rizatriptan.[47] No change in plasma concentration was observed when paroxetine and rizatriptan administered together. The presence of rizatriptan did not affect the plasma concentration of ethinylestradiol and norethisterone.[48,49] The monoamino oxidase-A selective inhibitor was responsible for increase in plasma concentration of sumatriptan, zolmitriptan, and rizatriptan.[50,51]

Therapeutic efficacy and consistency in headache recurrence

The goal of having an ideal antimigraine drug can be achieved by finding a drug which can show good preclinical performance and help to overcome shortcomings of the available treatments specifically sumatriptan which is known as the current gold standard.[1] The new generation of triptans have good lipid solubility and thus show good oral bioavailability. Triptans with greater lipophilicity had shown better therapeutic response when lipophilicity was plotted against a measure of clinical effects such as headache therapeutic gain at 2 h.[52] The oral bioavailability problem can be avoided in case of sumatriptan and naratriptan without altering the lipophilicity by parenteral administration. The t_{max}, which seems to correlate well with efficacy within formulations of sumatriptan, is only 1 h for eletriptan, rizatriptan, and zolmitriptan. It is unclear why, given its physicochemical properties, the t_{max} for naratriptan is prolonged compared with each of these and even compared with sumatriptan. A shorter t_{max} is likely to bring an earlier onset of action, which of course would be highly desirable in the treatment of patients with migraine pain. Many new triptans such as almotriptan (80%) and naratriptan (74%) have shown better oral bioavailability compare to sumatriptan. However, it is not clear that good oral bioavailability translates into more consistent clinical response in individual patients. An excellent consistency in terms of clinical efficacy has been achieved under rizatriptan development program by administering 10 mg dose.[53] Perhaps, this can be attributed to both its 45% bioavailability and relative lipophilicity compared with sumatriptan.

CONCLUSION

When numbers of therapeutic approaches are available for the treatment of migraine the role of triptans is under great scrutiny from researchers. Till date, considerable amount of research in terms of clinical trials and dosage form development has been reported by many researchers. There is no doubt about the therapeutic efficacy of both first generation and second generation triptans, but the pharmacokinetic and pharmacodynamic data show lots of variation among the test population. Such variation leads to the different type of results in terms of the therapeutic response of an individual and the overall efficacy in preventing recurrent headache. However, modern day dosage forms have tried to maximize the effect of triptans by various novel techniques of delivering drugs in the human body. Nevertheless, the undeniable performance of triptans in the treatment of migraine makes them choice of drug for prescription and further research and development.

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Source of Support: Nil. **Conflict of Interest:** None declared.