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The role of triptans in the management of migraine

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ABSTRACT

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Migraine is one of the most prevalent disorders seen in clinical practice today and also a major cause of disability in the workplace. The prevalence of migraine is highest during the years of peak productivity, ie, between the ages of 25 and 55 years. The triptans are a group of selective 5-hydroxtriptamine $(HT)_1$ serotonin receptor agonists that activate the $5\text{-}HT_{1B/1D}$ receptor and possibly also the $5\text{-}HT_{1A}$ dan $5\text{-}HT_{1F}$ receptors. To date 7 subclasses of serotonin receptors have been identified, namely subclasses $5\text{-}HT_1$ to $5\text{-}HT_7$. Triptan causes cranial vasoconstriction, inhibits peripheral trigeminal activity and the trigeminal afferents. With its triple action, triptans can control acute attacks of migraine. Triptan is contraindicated in patients with previous ischemic or coronary artery disease, cerebral or peripheral vascular disease and other cardiovascular disorders. Triptans should be given immediately after an acute attack of migraine. The triptans are useful in the management of an acute migraine, but are not indicated for preventive therapy of migraine. Several new advances in migraine management have been made in regard to the recognition of the disease, the pathogenesis of migraine, and the phenomenon of central sensitization. More treatment options become available to patients and prescribers, the impact of such therapy on worker productivity will become more important in determining the value of such interventions.

Keywords: Tiptans, migraine, serotonin reseptor

INTRODUCTION

Migraine is a neurological syndrome characterized by changes in body perception, headaches and nausea. The most commonly encountered clinical manifestations are periodically recurrent headaches, the attacks of which initially are unilateral, but at some point in time may become bilateral or total. Migraine occurs as a result of trigeminovascular abnormalities.[1] For clinical purposes, the International Headache Society (IHS) has divided headaches into 2 categories, i.e. primary and secondary headaches. Migraine is classified as a primary headache, i.e. not due to organic or structural abnormalities.[2]

Migraine affects 17% of women and 6% of men in the United States. Before puberty, the prevalence and incidence is higher in boys than in girls. In those aged over 12 years, there is an increased prevalence of migraine in females and males. At ages over 40 the incidence declines, except in perimenopausal women. Overall, the prevalence in females is higher than in males. The ratio of females to males increases from 2.5:1 at puberty to 3.5:1 at the age of 40 years, then decreases. The incidence of migraine with aura reaches a peak in boys at around 5 years of age and in girls at around 12-13 years. In the United States, the incidence of migraine in white females is higher than in Asian females.[2] Poor socio-economic conditions are said to be associated with migraine. Studies have shown that migraineurs experience lower quality of life than the general population,[3,4] and that attack frequency is inversely related to quality-of-life scores.[5] Studies have also shown that effective treatment of migraine has a positive impact on health-related quality of life.[6]

On the basis of the clinical manifestations, there are 3 distinctive phases in migraine, namely triggering of acute attacks, aura and headaches.[7] Migraine with aura is a hereditary disorder, in which several genes are involved. In familial hemiplegic migraine, a dominant hereditary disorder, the locus has been identified in the 19q gene. The 19q gene codes for P/Q calcium channels CACNA1A. A second gene, ATP1A2, located on chromosome 1Q23, was discovered several years ago. The ATP1A2 gene encodes an á-subunit of the sodium/ potassium pump located in the neuronal membrane.[8]

One complication associated with migraine is stroke, because migraine is associated with an increased risk of ischemic stroke. Other complications of migraine comprise mental health problems, such as depression, manic depression, anxiety and panic disorders.

For aborting acute attacks of migraine, anti-migraine drugs may be used, such as nonsteroidal anti-inflammatory drugs, triptans, or ergotamine. On the other hand, for the prevention migraine attacks, the drugs used are beta blockers, calcium channel inhibitors, antidepressants, and anticonvulsants.[9] Through continuous research in migraine, scientists have been able to identify the serotonin receptors.

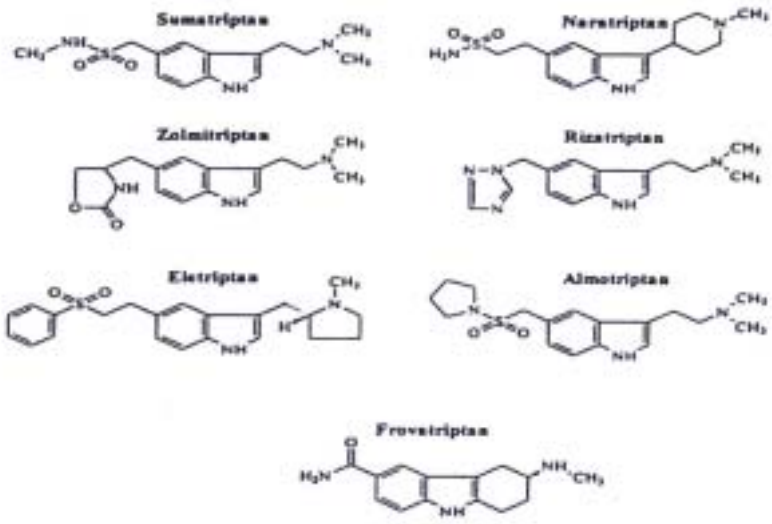

Figure 1. Chemical structure of triptans[12]

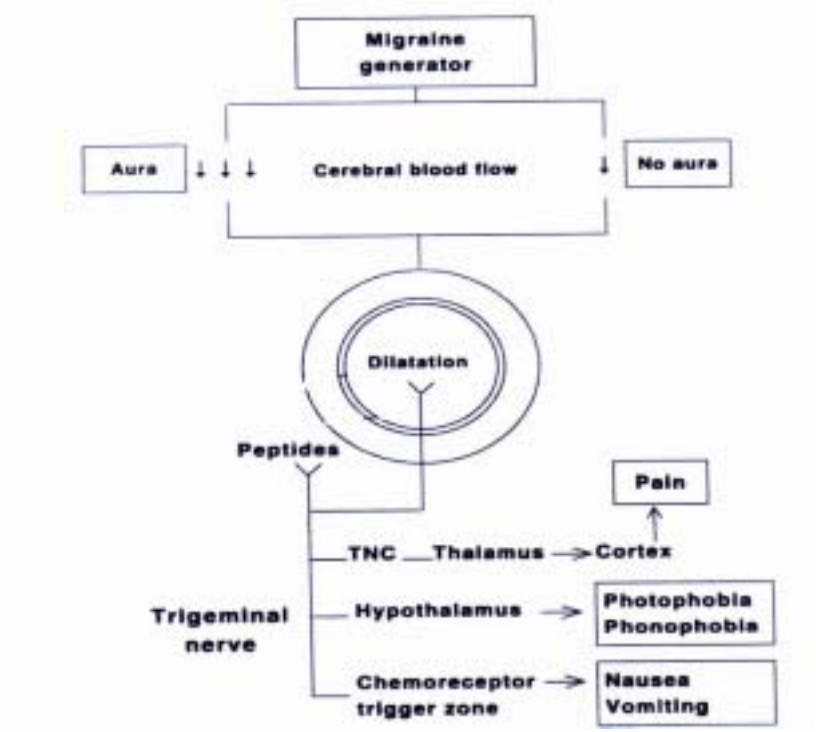

Figure 2. Pathophysiology of migraine[7]

Currently there are 7 recognized subclasses of serotonin receptors, i.e. subclasses 5-hydroxtriptamine $(HT)_1$ to $5\text{-}HT_7$. The $5\text{-}HT_1$ receptor consists of 5 subtypes, namely A, B, D, E and F.[10] The accumulated knowledge about serotonin receptors ultimately led to the discovery of triptans.

Chemical structure of triptans

Triptans are serotonin (5-HT) receptor agonists, that are selective for $5\text{-}HT_1$. Triptans activate the $5\text{-}HT_{1B/1D}$ receptors and possibly also the receptors for $5\text{-}HT_{1A}$ dan $5\text{-}HT_{1F}$.[10,11] These drugs are derivatives of indol, with substitutions at positions 3 and 5. The chemical structure of triptans is shown in Figure 1.[12]

A number of studies have concluded that the trigger for the initial attacks of migraine involves the brain stem as migraine generator, which is associated with genetic abnormalities. In the phase following the initial attack, auras and headaches develop. When the migraine generator is triggered, the cerebral blood flow will be reduced, followed by supression of cortical wave propagation. In patients with a reduction in cerebral blood flow below a critical level, the symptoms of aura will appear. In addition to noradrenaline and acetylcholine, immunohistochemical studies have uncovered several vasodilation transmitters in perivascular nerves that supply the intracranial blood vessels, including serotonin (5-HT), vasoactive intestinal peptide (VIP), nitric oxide (NO), substance P, neurokinin A dan CGRP. NO may be involced in the pathophysiology of migraine, and inhibition of NO synthesis may be used in the treatment of migraine. In several cases, vasodilation causes changes in blood volume, followed by changes in cardiac stroke volume, with consequent enhanced pulsation of the blood vessels. Enhanced pulsation will be detected by receptors in the vessel wall and

results in increased activity of the perivascular sensory trigeminal nerves, which causes headaches and other symptoms (Figure 2).[7]

According to additional evidence, serotonin and dopamine stimulate the stage of the inflammatory process that involves endothelial cells, mast cells and platelets. This inflammatory reaction causes vasodilation and perivascular reaction. Receptors for 5-HT are recognized as being the most important receptors in the mechanism of headache. Several symptoms associated with migrainous headaches, such as nausea (80%), yawning, irritability, hypotension and hyperactivity may be linked to dopamine receptor activation.[1,13]

There are 2 hypotheses that may explain the mechanisms of action of triptan in the pathogenesis of migraine. The first hypothesis states that the 5-HT_{1B} receptor has the ability to induce vasoconstriction of intracranial blood vessels, including arteriovenous anastomoses. In migraine there is dilatation of carotid arteriovenous anastomoses in the head, the causes of which are currently still not known with certainty. A total of 80% of the carotid arterial flow is reportedly shunted through anastomoses located in the scalp and the ears. There will be extravasation of blood from the capillaries, which subsequently causes cerebral ischemia and hypoxia. According to this version of the pathophysiology of migraine, an effective antimigraine drug must be able to close the shunt and reverse the cerebral blood flow.[10,11,13] Triptan interacts with 5-HT_{1D} and 5-HT_{1B} receptors and has no or only low affinity for other 5-HT receptors. The drug is not active against α1-, α2-, and β-adrenergic, dopamine, cholinergic muscarinic and benzodiazepine receptors. The effective dose of triptan is determined by its affinity for the 5-HT_{1B} and 5-HT_{1D} receptors, whilst the affinity of triptan for 5-HT_{1A} or 5-HT_{1E} receptors has no influence on its effective dose.[7,10]

The second hypothesis states that 5-HT_{1D} agonists inhibit release of proinflammatory neuropeptides on perivascular nerve terminals. In the pathophysiology of migraine, headaches are not solely caused by cranial vasodilation, but also involve an inflammatory mechanism known as neurogenic inflammation. Arterial dilatation causes traction on the perivascular nerve fibers, resulting in depolarization of the fibers, which induces an action potential that is conducted to the central nervous system. In addition, depolarization also results in the release of neuropeptides from the nerve fibers around the artery. The released neuropeptides are substance P from the C fibers and calcitonin gene-related peptide (CGRP) from the Aδ fibers, ultimately causing increasing dilatation of the artery and producing pain.[10,11,14,15]

From both of the above hypotheses and several studies that have been conducted, it may be concluded that triptan has 3 mechanisms of action, namely induction of cranial vasoconstriction, inhibition of peripheral trigeminal activity, and inhibition of trigeminal afferents.[11,14,16] With these three actions, triptan can control acute attacks of migraine. The following illustration shows the site of action of triptan in the trigeminovascular system (Figure 3).[11]

Another benefit of triptan is its ability to relieve the nausea and vomiting which frequently accompany migraine. This is because triptan acts on the 5-HT_{1D} receptor that is located in the solitary tract nuclei, thus inhibiting the centers for nausea and vomiting.[10,14]

There are seven kinds of triptans that have been studied and synthesized for use as acute antimigraine drugs, i.e. sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan and frovatriptan.[7,10] With the increasing numbers of available drugs, some guidance is necessary in the selection of

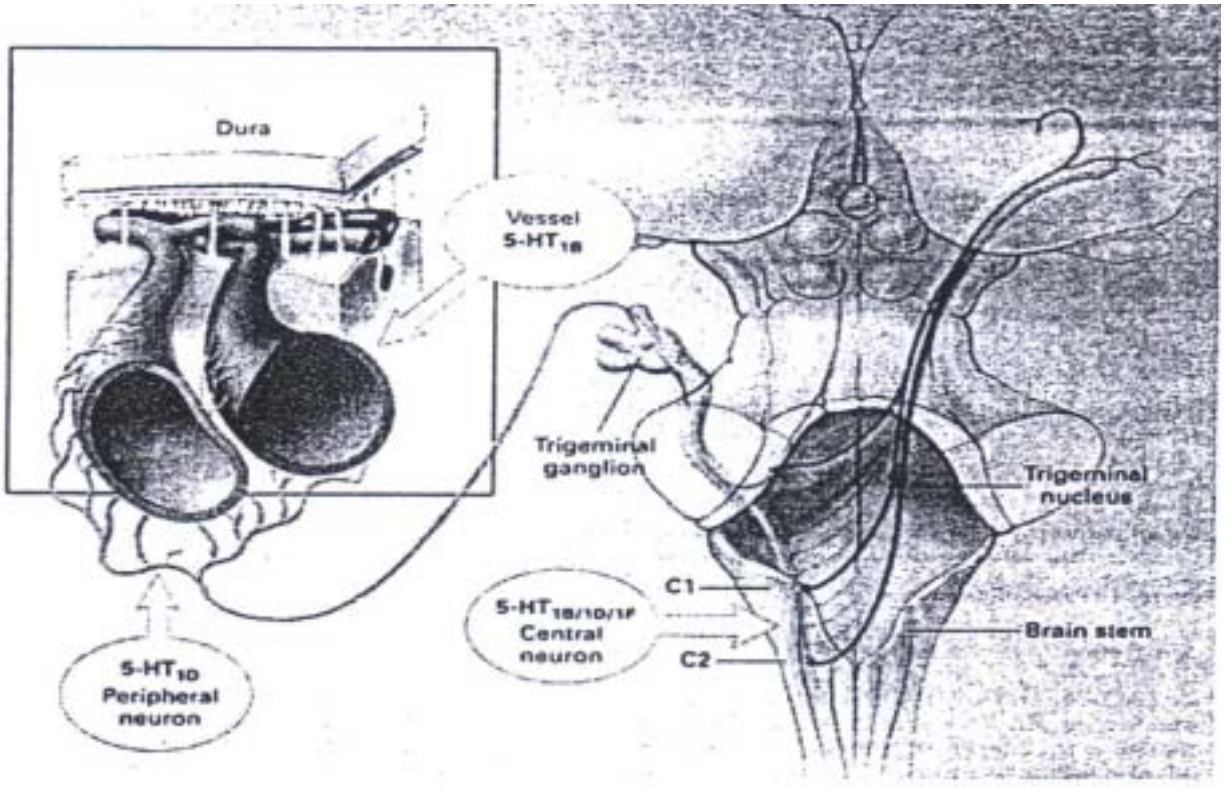

Figure 3. Site of action of triptan[11]

those triptans that have the greatest chances of success in the management of acute migraine. Sumatriptan reaches a peak plasma concentration within 12 minutes after subcutaneous administration and 1-2 hours after oral administration. The bioavailability of subcutaneous preparations approach 97%, whilst for oral or intranasal preparations it is only 14-17%. The elimination half-time of the drug is 1-2 hours. Sumatriptan is metabolized mainly by MAO-A, and its metabolites are excreted in the urine. The plasma protein binding of sumatriptan is around 14%.[7,10,17,18]

For zolmitriptan, the peak plasma concentration occurs about 1.5-2 hours after administration of the oral preparation, which has a bioavailability of around 40%. Zolmitriptan is converted into the N-desmethyl form, an active metabolite that has an affinity for 5-HT_{1B} and 5-HT_{1D} receptors several times higher than that of zolmitriptan. The half-life of zolmitriptan and is metabolite is 2-3 hours.[7,10,17,18]

Rizatriptan has its peak plasma concentration in 1-1.5 hour after oral administration. Its bioavailability is around 45%, and the main metabolic pathway is through oxidative deamination by MAO-A. Plasma protein binding of rizatriptan is about 14 %.[7,10]

Almotriptan and eletriptan reach their respective peak plasma concentrations in 1.4-3.8 and 1-2 hours after administration of the oral preparation. The bioavailability of the oral preparation of almotriptan is 80%, whilst that of eletriptan is 50%. The elimination half-times of almotriptan and eletriptan are 3.3-3.7 and 3.6-5.5 hours, respectively. Almotriptan is metabolized by cytochrome P-450 and MAO-A, and eletriptan by CYP3A4.[11,14]

For frovatriptan the characteristics are as follows: peak plasma concentration is reached in 2-4 hours after oral administration; bioavailability of the oral preparation is 24-30%; elimination is through the kidneys and liver, with a half-time of 25 hours and over; the drug is not metabolized by MAO-A.[7,11,18]

The side effects of the administration of 5-HT1 agonists may be serious or minor. Serious side effects rarely occur, and may take the form of coronary arterial vasospasm, myocardial ischemia, atrial and ventricular arrhythmias, or myocardial infarction. These side effects usually occur in patients with underlying risk factors for coronary heart disease. However, generally the side effects of triptan in the treatment of acute migraine are minor. Oral administration of triptan may cause paresthesia; asthenia and weakness; flushing of the face; sensations of oppression, fullness or pain in the chest, neck and lower jaw; drowsiness; nausea; vertigo and diaphoresis. On subcutaneous administration, the majority of patients has reported minor pain and burning sensation at the injection site.[10,11,14,16]

Triptan is contraindicated in patients with a history of ischemia or vasospasm of the coronary arteries, peripheral or cerebral vascular disease, or other cardiovascular disorders. However, triptan is still safer than other drugs commonly used for managing migraine, e.g. ergot preparations, which are nonspecific serotonin agonists. The vasoconstrictive effect of the coronary arteries are mediated by 5-HT2A receptors, whilst triptan has only weak activity for these receptors.[7,9-11]

Triptan is also contraindicated in patients with uncontrolled hypertension, as it causes an acute, albeit usually small, rise in blood pressure. On the other hand, triptan is not contraindicated in patients with controlled hypertension. Naratriptan is contraindicated in patients with severe renal or hepatic disorders, for which rizatriptan may be given, but under special monitoring.[7,9]

Use of triptans in migraine

Triptan is the drug of choice for aborting attacks of migraine. It is reportedly effective, safe and well-tolerated in migraine. Treatment with triptan should be given immediately after the onset of a migrainous attack. Triptan is effective in the treatment of acute migraine, with or without aura, but it is not indicated for use in the prevention of migraine. The oral preparations are the safest, but difficult to use in patients suffering from nausea or vomiting during the attacks of migraine.[19-21] The individual responses to triptan are unpredictable, therefore selection of a suitable drug for a patient is usually on a trial-and-error basis. If the selected triptan does not succeed in effecting a cure or if there are side effects limiting its use, the patient could possibly have a better response to another triptan.[9]

The injectable preparation sumatriptan 6 mg is the most effective treatment of acute migraine, but also has more frequent side effects, and requires skill in injecting the drug. The injection may be repeated once in one 24-hour period if the initial dose fails to abort the attack.[7,10,22]

The onset of action of sumatriptan nasal sprays is approximately 15 minutes. The recommended dosage is between 5-20 mg, which may be repeated after 2 hours, until the maximal dose of 40 mg/24 h is reached.[10]

The recommended oral dose of sumatriptan is 25-100 mg, which may be repeated after 2 hours until a total dose of 200 mg in one 24-hour period is reached. Zolmitriptan is given orally with a dose of 1.25-2.5 mg, repeatable after 2 hours, up to the maximal dose of 10 mg/24 h. On the other hand, the oral dose of naratriptan is 1-2.5 mg, which must not be

repeated until 4 hours have passed since the previous dose was given. The maximal dose in one 24-hour period must not exceed 5 mg.[7,9,17,18]

The recommended oral doses of rizatriptan and almotriptan are 5-10 mg and 6.25-12.5 mg, respectively, to be repeated if necessary after 2 hours, up to the maximal dose of 30 mg/24 h for rizatriptan and 25 mg/24 h for almotriptan.

The triptans are not recommended for concomitant administration with ergot preparations or other triptans within one 24-hour period, because all of them stimulate the serotonergic receptors of the cerebral and coronary blood vessels.[7] Sumatriptan, rizatriptan and zolmitriptan are contraindicated in patients on monoamine oxidase inhibitors such as moclobemide.[23] The group of monoamine oxidase inhibitors retard the metabolism of sumatriptan, rizatriptan and zolmitriptan, and raise the peak blood concentration of these triptans. Naratriptan, eletriptan, and frovatriptan are not metabolized by monoamine oxidase and as such are not contraindicated for concomitant administration with monoamine oxidase inhibitors. Almotriptan is mainly eliminated through the kidneys and metabolized by cytochrome CYP 450, and only a small percentage is metabolized by monoamine oxidase, and thus is also not contraindicated for use with monoamine oxidase inhibitors.[7,9,18]

Propanolol increases the blood concentration of rizatriptan through its effect on the monoamine oxidase-A system, such that the dose of rizatriptan needs to be reduced if adiministered with propanolol. A dose of 5 mg of rizatriptan on concomitant administration with propanolol results in an equal blood concentration as a dose of 10 mg rizatriptan given without propanolol. The maximal dose of rizatriptan is also modified to 15 mg/24 h on concomitant administration with propanolol, whilst in patients without propanolol the maximal dose is 30 mg/24 hours. This interaction does not occur between rizatriptan and other b-blockers or between other triptans and propanolol.[14,16]

Eletriptan is metabolized mainly by cytochrome P-450 CYP3A4 and eliminated from the brain by the P-glycoprotein pump. Drugs that induce or inhibit this system may modify the pharmacokinetics of eletriptan, although the clinical importance of this interaction is not fully understood.[16]

The US FDA has now reported the serotonin syndrome in a number of people taking triptans concurrently with some antidepressants, particularly selective serotonin and serotonin–norepinephrine reuptake inhibitors (SSRIs and SNRIs, respectively).[24] The serotonin syndrome is an idiosyncratic reaction that may occur when triptan is combined with serotonin-specific reuptake inhibitors (SSRIs). The serotonin syndrome consists of changes in the triad of mental status (e.g. confusion), dyautonomia (e.g. diaphoresis, diarrhea, hypertension, and fever, and neuromuscular symptoms (e.g. myclonus and tremor), but this syndrome occurs only rarely.[14,16,25] The symptoms of the serotonin syndrome (Box 1)[25] often have a rapid onset, usually within hours of the initiation or dose change of a drug, but occasionally up to several weeks after.[26,27]

The majority of triptan clinical trials has a similar research design, i.e. randomized, double blind, and controlled, and thus meta-analyses may be conducted using data from these trials. In 2001 a meta-analysis was done on 53 triptan clinical trials involving 24,089 patients in the age group of 18-65 years with moderate and severe attacks of migraine according to the International Headache Society criteria. The patients had been treated with one oral triptan preparation in a predertermined therapeutical dose. In the meta-analysis, all

Box 1. Signs and symptoms of serotonin syndrome[25]

Autonomic hyperactivity
- Abnormal blood pressure:
  - In moderate cases, severe hypertension
  - In severe cases, hypotension
- Dilated pupils
- Diarrhea
- Fever, diaphoresis, shivering
- Tachycardia, tachypnea, dyspnea

Mental status changes
- Agitation, nervousness, hypervigilance, insomnia
- Confusion, agitated incoherent speech, delirium
- Semicoma or coma

Neuromuscular abnormalities
- Akathisia, mydriasis, impaired coordination
- Myoclonic twitching, tremors, ataxia, rigidity, hyperreflexia, clonus (including ocular clonus)
- Seizure

Table 1. Comparison of oral sumariptan 100 mg with other oral triptans.[28]

Drug and dose	Recovery in 2 hours	Pain-free in 2 hours	Consistency	Tolerability
Sumatriptan 50 mg	=	=	= or –	=
Sumatriptan 25 mg	-	= or -	-	+
Zolmitriptan 2.5 mg	=	=	=	=
Zolmitriptan 5 mg	=	=	=	=
Naratriptan 2.5 mg	-	-	-	++
Rizatriptan 5 mg	=	=	=	=
Rizatriptan 10 mg	+	+	++	=
Eletriptan 20 mg	-	-	-	=
Eletriptan 40 mg	= or +	= or +	=	=
Eletriptan 80 mg	+	+	=	-
Almotriptan 12.5 mg	=	+	+	++

Legend:
- The equal sign (=) signifies a value equal to that of sumatriptan 100 mg; the plus sign (+) means superior or higher than sumatriptan 100 mg; two plusses (++) signify increased superiority; the minus sign (-) means inferior or less than sumatriptan 100 mg
- Recovery in 2 hours: indicates that the patient responded to treatment by recovering from moderate or severe pain into having mild pain or none at all.
- Pain-free in 2 hours: the patient became pain-free within 2 hours without additional drugs and there was no recurrence of the headache within 24 hours.
- Consistency: the patient responded in minimally 2 out of 3 treated attacks of migraine.
- Tolerability: in how far the patient could tolerate the side effects of the drug which medically were not important but clinically disturbing, e.g. flushing of the face and sensations of oppression in the chest.

triptan preparations with differing dosages were compared as to efficacy, consistency, and tolerability, with sumatriptan 100 mg as the standard. Frovatriptan was excluded from the meta-analysis, because the data were not available and its efficacy was considered to be less than that of other triptans.[28,29]

The safety of a drug is not identical to its tolerability. The occurrence of side effects of the drug in patients on triptan therapy is related to its tolerability and does not affect its safety. Absence of side effects does not imply increased safety. The safety of triptan should be placed in the context of endangering patients at risk for underlying cardiovascular disease. From various studies the fact emerged that long-term use of triptans is safe in patients without contraindications.[16]

CONCLUSIONS

Migraine is a disorder with a sufficiently high prevalence which affects both women and men. The management of migraine is divided into management for aborting the acute attack and management for prevention of attacks of migraine. The triptans are one group of the drugs of choice in acute attacks of migraine. The triptans are all effective in aborting migraine headaches, as they have similar pharmacodynamic effects. The oral preparations rizatriptan 10 mg, eletriptan 80 mg, and almotriptan 12.5 mg have a better efficacy than do other oral triptan preparations in the management of acute migraine.

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