Asian Journal of Pharmaceutical and Clinical Research
Vol. 4, Issue 1, 2011 ISSN - 0974-2441

Review Article

DEVELOPMENT OF ANTI-MIGRAINE DRUGS -CURRENT STATUS AND FUTURE PERSPECTIVES

G.MOWNIKA[1] DR.SADANANDAM.M[2]

Department of Pharmaceutics, Sri Venkateshwara College of Pharmacy, Madhapur, Hyderabad, Andhrapradesh, India. E-mail: drpssvcp@gmail.com

ABSTRACT

Migraine is a chronic neurological disorder resulting in a range of symptom profiles, burden and disability. The pharmacological treatment includes preventive and acute strategies. A better understanding of the discovery of novel molecular targets has lead to a growing number of upcoming therapeutic proposals by choosing a broad range of pharmaceutical and non-pharmaceutical options. Some new molecules are being investigated as possible new therapies and others have already led to the creation of drugs that are currently in clinical trials. This review focuses on the current approaches and future scope in the migraine treatment.

Key words: Migraine, Triptans, CGRPantagonist, Aura, 5HT, CSD.

INTRODUCTION

Migraine is a familial disorder characterized by recurrent attacks of headache widely variable in intensity, frequency and duration. Attacks are commonly unilateral and are usually associated with anorexia, nausea and vomiting .The term migraine is derived from the Greek word *hemicranias* (Galen about 200AD).[1] Migraine headaches are a common and painful experience for many young adults. They are two and half times more prevalent in women, occurring in 6% of all males and 15-17% of females.[2] They are more likely to strike those aged between 25 and 44. With 90% of migraine patients reporting their first attack before age 40 .Migraine prevalence is similar in western countries and the USA.[3-4]

Migraine prevalence varies by age, sex, ethinic origin, and income. Before puberty, migraine prevalence is about 4 %. After puberty, prevalence increases more rapidly in girls than boys.The headache classification committee of the international headache society (IHS) published the classification and diagnostic criteria for headache disorders (international headache society, 2004). The terms 'common migraine' and 'classical migraine' have been replaced by 'migraine without aura 'and 'migraine with aura' respectively.

Migraine has an enormous impact on society. Recent studies have evaluated the indirect and direct costs of migraine. Indirect costs include the aggregate effects of migraine on productivity at work (paid employment), in performance of household work and in other roles. It was estimated that productivity losses due to migraine cost American employers 13 billion dollars per years.[5]

Migraine is characterized by episodes of head pain that is often throbbing and frequently unilateral and may be severe. In migraine without aura (previously known as common migraine) attacks are usually associated with nausea, vomiting or sensitivity to light, sound or movement and when treated, the attacks typically last 4 to 72 hrs. A recent survey by world health organization (WHO), rates severe migraine, along with quadriplegia, psychosis, and dementia, as one of the most disabling chronic disabling chronic disorders. This ranking suggests that in the judgment of WHO, a day with severe migraine is disabling as a day with quadriplegia.[5]

High levels of free fatty acids and an increase in blood lipid levels lead to increase in serum lipid level profile and increase in platelet agregability. Several factors are responsible for high levels of free fatty acids: high dietary fat intake, obesity, insulin resistance, vigorous exercise, hunger, consumption of alcohol, coffee and other caffeinated beverages, oral contraceptives with high oestrogenic activity, smoking and stress.[6]

The migraine aura was thought to be cause by cerebral vasoconstriction and headache by reactive vasodilation. However, it was later established that headache often begins while cortical blood flow is reduced thus, headache is not caused by simple reflex vasodilation.The immediate precursors of vasodilation are serotonin i.e. it is called as low-serotonin syndrome. Plasma serotonin levels decrease during increased platelet aggregation, leading to vasodilation with accompanying migraine headache.[7] Foods high in fat are also high in linoleic acid, a precursor of prostaglandins. PGE1 is one of the most powerful known vasodilators.

Mechanism of headache probably results from the activation of meningeal and bloodvesel nociceptors combined with a change on central pain modulation. The trigeminal vascular comlplex is strongly implicated in the pathogenesis. The activation of this system leads to release of inflammatory mediators like substancep, neurokinin and CGRP recently there has been a lot of focus on CGRP and its role in migraine. There is definitive role of CGRP in migraine and antagonists to CGRP receptors have shown good response in migraine therapy. Some other neurotransmitters are also implicated in the pathogenesis along with serotonin like dopamine.[1]

Acute therapy involves many drugs like acetaminophen aspirin, NSAIDS, barbital, caffeineanalgesics, opiods, neuroleptics, dihydroergotamine, intranasal therapy, ergotamine tablets, and triptans.Preventive therapy involves βblockers, antiserotonin drugs like pizotifen, methysergide, calcium channel blockers, serotonin specific reuptake inhibitors, MAO inhibitors, anticonvulsants.

LITERATURE

Currently, mild migraine attacks are most frequently treated with analgesics like NSAIDS. Moderate to severe attacks are treated with ergots or specific 5HT1B/D agonists, the so called triptans.[8]

The main drawbacks of all current treatment options are latency until improvement of headache, incomplete and inconsistent pain relief, as well as recurrence of headache. Furthermore, the medications exhibit the risk of cardiovascular or intestinal sideeffects, therefore, there is much room for improvement of abortive migraine treatment.[9] Over the last years, neuropeptides and their receptors gained much interest as new treatment options since various neuropeptides are co-released with classical neurotransmitters like glutamate and play important role in generation of hyperalgesia and pain.[10] Medications for the prophylaxis of migraine are available, but such drugs (topiramate) cause unwanted effects and only reduce number of attacks without suppressing completely. To overcome these drawbacks, novel treatment options would be desirable.[11] Tremendous amount of work is being done in the development of drugs for migraine therapy and newer approaches are being investigated on a routine basis.

Rebeck et.al.(1994) have studied the selective 5HT1Dα serotonin receptor gene expression in trigeminal ganglia and observed that agonists bind selectively to the 5HT1Dα receptor subtype could lead to more specific antimigraine therapies with less potential risk of complications relating to constriction of vascular smooth muscle. The antimigraine drug sumatriptan binds with high affinity to 5HT1Dα and 5HT1Dβ recognition sites suggesting that its actions may be well mediated by one or more receptor subtypes. [12-13]

Skaer et.al.(1996) proposed that sumatriptan exhibits consistent efficacy and is generally well tolerated. Potential adverse effects of sumatriptan are transient. However, it is contraindicated in patients with history of ischemic heart disease, myocardial infarction, angina, or uncontrolled hypertension. There has been no change in tachyphylaxis and no change in tolerability profile of sumatriptan when used for acute treatment of migraine over several months. Moreover, a second dose of sumatriptan will neither prevent migraine recurrence nor prove useful if the patient does not respond to first dose. Sumatriptan was developed specifically as an antimigraine medication based on assumption that serotonin receptors located on the cranial vasculature play a critical role in mechanisms of migraine attack.[14-16]

Harold fisher (1995) proposed the use of intravenous haloperidol for the patients with migraine in dose of 5mg following 500 to 1000cc bolus of normal saline. Headache was completely or substantially relieved in 25 to 65 minutes after administration. Side effects were minimal. Haloperidol may work by its effects on 5HT receptor as well. In addition, it possesses a potent antiemetic effect by virtue of its action on central chemo receptors. This effect is a useful feature for drugs used in migraine therapy associated with low recidivism and less expensive.[17-19]

Alexander Mauskop and Jerome Goldstein (1997) proposed that development of newer 5HT1D receptor agonists and the route of administration being oral is easiest i.e. tablets being ideal method of administration. Rectal administration certainly is less use are friendly, but there is better absorption. Intranasal administration usually is easy, but because of nasal decongestion or nasal conditions there may be variable absorption. Best route is subcutaneous route which involves a needle injection but however, it is not well tolerated.[20-21]The newer 5HT1D agonists like zolmitriptan, naratriptan, alnitidan, MK-462, BMS-180048 have overcomed the drawbacks of sumatriptan like low oral bioavailability, significant headache recurrence, and contraindication in patients with coronary artery disease. The newer 5HT1D receptor agonists have little effect on heart rate or blood pressure. Sumatriptan does not penetrate the Blood Brain Barrier (BBB), but zormitriptan does appear to penetrate the Blood Brain Barrier.[20]

Magnesium is also found to have a role in control of NMDA receptors, which play important role in transmission of pain through nervous system. Magnesium plus calcium NMDA receptor prevents calcium from entering into the cell. Lowering magnesium concentration facilitates activation of NMDA receptor, which allows calcium to enter cell and show its effects. It is impractical to treat migraine attacks with an intravenous infusion of magnesium sulfate, oral magnesium supplementation may be beneficial in a significant proportion of patients with frequent migraine. Many available Mg preparations are poorly absorbed.[22-23]

Macro pappagallo (2003) explained treating migraine with a variety of newer antiepileptic drugs(AED'S). The newer AED'S like topiramate, levetiracetam have received approval for migraine treatment and useful for preventive treatment. Valproic acid has got FDA approval in 2002 and topiramate has got FDA approval in 2004 for the treatment of migraine.[24]

Zonisamide is being investigated for the treatment of migraine headaches and neuropathic disorders.[25]

Stefanjust et.al.(2006) explained the role of neuropeptides in the treatment of migraine. Most clinical trails are investigating the role of neuropeptide receptor ligands in the treatment of migraine. The only new entity showing promise is olcegepant (BIBN4096BS) a potent and selective antagonist of the calcitonin-gene related peptide (CGRP) receptor.[26]

PeterJ.goads et.al. explained number of targets developed for the treatment of migraine like 5HT1F and 5HT1D receptors ,A1 receptors, nociceptin, vanilloid TRPV1 receptors, anandamide CB1 receptors including CGRP blockade are shown to be effective acute antimigraine strategy.[27]

5HT1Ftarget: The potent specific 5HT1F agonist LY334, 370 was developed, to block neurogenic plasma protein extravasation in the rat duramatter. LY334,370 was found effective in acute migraine, albeit at dose with CNS side effects. No cardiovascular problems were seen in these studies.[28-30]

5HT1D target: One compound that went to clinical studies PNU142633 was ineffective. It was a weak agonist when compared to sumatriptan in invitro studies and found poor brain penetration. This compound was developed using gorilla receptors.[31-33]

Adenosine A1 target: Purine adenosine may have some role in nociception. Antinociceptive effects of adenosine are mediated through the A1 receptor. It has been shown that two highly selective adenosine A1 receptor agonists, GR79236 and GR190178, can inhibit trigeminovascular activation, both in trigeminal nucleus and by inhibition of the release of CGRP in cranial circulation.[34-36]

Nociception-ORL-1 receptors: A novel neurotransmitter referred to as opiod receptor like ORL1.The suppression of neurogenic dural vasodilation and the cardiovascular effects of nociception are reversed by ORL-1 receptor antagonist [Nphe ^{1}]N/OFQ-(1-13)-NH_2 .[37]

Vanilloid receptors: Vasodilation was being inhibited by TPRV1 antagonist capsazepine to a modest degree. Civamide in intranasal route was able to provide headache relief in 55% of patients at 2hrs (Diamond et.al.2000).[39-39]

Anandamide receptors: Akerman et.al. have shown that anandamide dural vasodilator effect was attenuated by specific TPRV1 receptor antagonist capsazepine .

CGRP target: Local micro iontophoresis of CGRP receptor antagonist BIBN4096BS inhibit trigeminocervical neurons .The major challenge for acceptance of BIBN4096BS as an anti-migraine treatment is its intravenous administration. Searching for a more suitable administered formulation, Williams *et al.* identified 10 different benzodiazepinones as CGRP antagonists with different affinities for the human CGRP receptor. Among these, benzodiazepinone piperindinyldihydroquinazoline had the higher affinity. The anti-migraine properties have need to be studied thoroughly although it has been shown to be orally bioavailable in rats.[40-41]

Carh G.H.Dahlof et.al.(2004) compared patient preference for zolmitriptan nasal spray to their current acute therapies for migraine and evaluated efficacy of zolmitriptan nasal spray.[42]

Ho.et.al(2008) studied and found the oral CGRP receptor antagonist Telcagepant for acute migraine treatment in a randomized , double blind, parallel group trial with a two stage, adaptive dose ranging 25-600 mg. 300mg dose was most promising. The proportion of patients experiencing pain relief at 2 hrs was 68.1%. PhaseIII trials are positive with results similar to those with zolmitriptan (5mg) and adverse effects profile lower than zolmitriptan.[43-44]

Steven J.siegelet.al(2007) have done studies on iontophoretic patch for optimal transdermal delivery of sumatriptan which uses an electric current to propel sumatriptan across intact skin and into underlying tissue . Unique prototype iontophoretic sumatriptan patch conditions were compared to 6mg subcutaneous injection and an oral 50mg tablet of sumatriptan succinate. They proposed that it may be possible to maintain therapeutically appropriate steady state drug levels for longer intervals than those with either 50mg oral or 6mg injectable formulations.[45]

Amjad alhalaweh et.al developed zolmitriptan chitosan microparticles by spray drying for nasal delivery i.e mucoadhesive dry powders in combination with natural polymer chitosan and succeded with a narrow particle size range and high drug loading.[46]

Goadsby PJ et.al. found that intensive running acts on blood vessels and thus eliminates the pain on the microlevel. This observation might be connected to the human hormonal system, since the migraine itself is connected to the human hormonal system, if one eliminates the trigger factors such as emotional stress changes in sleep patterns ,skipping meals etc. The migraine attack appears

quite regular. Therefore, migraine is probably connected to the internal human biological clock. The migraine attack begins probably when concentration of certain harmones passes through their minimal or maximal and running can lead to increase or decrease of this level so, 2-3 km of running eliminates the headache completely.[47]Antimigraine drugs applicable using NDDS have been approached using fast mouth dissolving tablet for formulation of drugs like DHE mesylate , ergotamine tartarate, methysergide maleate, pizotifen maleate, and sumatriptan succinate.[48]

RECENT DEVELOPMENTS IN PREVENTIVE THERAPY

Cortical spreading depression (CSD) inhibitors similar to the available preventive agents, tonabersat, a novel potential preventive agent that has recently been investigated in three Phase II studies, also inhibits CSD. In addition ,it reduces CSD –induced NO release and trigeminovascular response was found.[49-50]

Neuromodulation : Neuromodulatory approaches are currently focused on stimulation of the greater occipital nerve (GON). In case of GON stimulation, the targeted synapse and neurons are located in the trigeminocervical complex and receive convergent input from the GON as well as from the trigeminal nerve. Moreover, functional imaging studies have shown that central processing of migraine pain signals in the thalamus could be modified by GON stimulation.[51]

Botulinum toxin typeA: Experimental studies showed anti-nociceptive properties in some standard models such as rats with formalin-induced pain which provided the rationale for its development in headache prevention. Accordingly, a recent meta-analysis of these studies concluded that BTA is not significantly better than placebo for the preventive treatment of episodic migraine. With regard to chronic daily headaches, two large studies have been reported, and both were negative on the primary endpoint of headache days. Recently, two PhaseIII studies of BTA in chronic migraine have been completed (PhaseII research evaluating migraine prophylaxis therapy) with botulinum toxin typeA (PREEMPT1) in North America and PREEMPT2 in NA and Europe. A pooled analysis of data from PREEMPT1 and PREEMPT2 also showed a significant benefit of BTA over placebo with regard to headache days and headache episodes. [52-53]
Patent foramen ovale closure: An epidemiological relation seems to exist between patent foramen ovale and migraine with aura, but not migraine without aura. Open label studies suggest that PFO closure could cure or substantially improve migraine.[54-55]

Recently, a study suggested that acupuncture might also be useful for the treatment of acute migraine attacks, however, the absolute treatment effect was small and it is questionable whether this can be considered clinically relevant.[56]

Nanoemulsion of antimigraine durgs:

RS Bhanushali et.al. developed intranasal and gel formulations for rizatriptan benzoate for prolonged action . Nanoemulsion formulations were prepared by constructing pseudo-ternary phase diagrams using lipophilic and hydrophilic surfactants and water and found that brain targeting through intranasal delivery has a potential for treatment of migraine. [57] A new way to treat migraine attacks with aura is by single-pulse transcranial magnetic stimulation. Lipton et.al. reported on the use of a handheld device that delivers two pulses of transcranial magnetic stimulation(TMS) to treat migraine in the aura phase. The results of this study are important for two reasons: They show that TMS is effective for pain relief in patients with migraine with aura and support the current theory underlying the pathogenesis of migraine with aura. Cortical spreading depression has long been thought of as the physiological equivalent to migraine with aura, and this concept is supported by functional imaging studies. The use of TMS could be a major step forward in the treatment of migraine with aura, particularly in patients in whom presently available drug treatment is ineffective , poorly tolerant or contraindicated.[58]

There has been tremendous development in the administration of antimigraine drugs in different dosage forms like transdermal patches, oral inhalers of dihydroergotamine, nasal sprays. Some of the future approaches include sodium channel blockers(lacosamide, a slow sodium channel blocker),novel antiepileptics, GABA enhancers and analog, 5HT-2A and 5HT7antagonists, Brain –derived neutrophic factor (BDNF) modulators, Orexin-melatonin pathway modulators, Dopamine antagonists by oral inhalation (prochlorperazine and loxapine), potassium current modulators, sigma receptor agonists(Dextromethorphan and others), COX-3 inhibitors (dipyrone in Brazil),Peripheral cannabinoid agonists(CB1-dronabinol),New 5HT1B/1D agonists, Astrocytic calcium wave inhibitors.[59]

DISCUSSION

Although many of the drugs presented in the article provide effective migraine relief, they may not completely be termed or qualified as candidates for an ideal antimigraine medication. Most of the current prophylactic agents have not been studied in randomized controlled trials with an acceptable number of subjects. Although effective, most of the current options for acute therapy do not offer consistent and fast pain-free endpoints in all patients. Acting simultaneously in different pathophysiologic mechanisms of a migraine attack, such as inflammation and “low serotonin” is an attractive goal.[60]

The major and necessary goal is targeting on the actions of specific and different neurotransmitter systems by combining pharmacologic agents. Currently by a single agent, multimodal pharmacotherapy cannot be provided, since migraine is multifactorial disease. To improve the evidence base of the current approaches, a lot of work remains to be done, particularly in the management of chronic migraine, and elucidation of their mechanisms since effective treatment is possible in most of the patients. The mainstay of migraine treatment is still medical therapy, but migraine is a complex disorder for which patient preferences have to be taken into account.To improve patient satisfaction and to reduce the disease burden non-pharmacological treatments can certainly help .An individualized approach to migraine management is thus warranted and will be appreciated by the patient. Future pharmacological developments for the treatment of acute migraine attacks, such as new triptan formulations, non-vasoconstrictor CGRP antagonists, and 5HT1F agonists, show hope in further improvement of therapeutic efficacy in helping severely affected patients.

REFERENCES

1. Dr Sujit Rajagopalam, Dr Debashish Hota Drugs Bulletin vol.XXXIII no.3.
2. Stewart WF, Schechter A, Rasmuss B K. Migraine prevalence: a review of population- based studies. Neurology 1994; 44(6suppl4): S17-S23.
3. Stang P E, Osterhaus J T. Impact of migraine in the united states: data from the National Health Interview Survey. Headache 1993;33:29-35.
4. Selby G, Lance J W. Observation on 500 cases of migraine and allied vascular headache. J Neurol Neurosurg psychiatry 1960; 23: 23-32.
5. Migraine: Current concepts and emerging therapies by D.K Arulmozhi, A.veeranjaneyulu and S.L.Bodhankar 2005.
6. Z.BIC, G. G. BLIX, H. P. HOPP, F. M.LESIE. Medical hypothesis (1998) 50, 1-7.
7. Davidoff R A. Migraine: Manifestations, Pathogenesis, and Management. Philadelphia: Davis, 1995.
8. Gallagher, R. (2004) what do patients want from acute migraine treatment? cephalalgia 24, 8-15.
9. Lipton, R.B. and Stewart , W.F. (1999) Acute migraine therapy: Do doctors understand what patients with migraine want from therapy? Headache: J head face pain 39, S20-S26.
10. Goadsby, P.J.et.al. (1990) vasoactive peptide release in the extracerebral circulation of humans during migraine headache. Ann.Neurol.28, 183-187.
11. Krymchantowski, A.V.et.al. (2002) New and emerging prophylactic agents for migraine. CNS drugs 16, 611-634.
12. G.William Rebeck, KennethI.maynard, Bradley T. Hyman, and Michael A.moskowitz Neurobiology. Vol. 91, pp. 3666-3669,April1994.

13. Weinshank,R. L., Zgombick, J.M., Macchi, M.J., Branchek, T. A. & Hartig, P. R. (1992) Proc. Natl. Acad. Sci. USA 89, 3630-3634.
14. Tracy L.Skaer, Clinical therapeutics vol.18, No.2, 1996.
15. Doenicke A, Brand J, Perrin.VL. Possible benefit of GR43175, a novel 5HT1 like receptor agonist for acute treatment of severe migraine. Lancet. 1988; 1: 1309-1311.
16. PerrinVL, Farkkila M, Gosguen J, et.al. Overview of initial clinical studies with intravenous and oral GR43175 in acute migraine. Cephalalgia. 1989; 9(suppl9): 63-72.
17. N Engl J Med. The subcutaneous sumatriptan study group: the treatment of migraine attacks with sumatriptan 1991; 325: 316-21.
18. Harold Fischer, MD, MCFP(EM), DABEM, The journal of emergency medicine, vol 13, No.1, pp 119-122, 1995.
19. Goodman and Gillman's. The pharmacological basis of therapeutics, 8th ed. Elmsford, Newyork:pergamon press; 1990: 386-404, 926, 1683.
20. Alexander Mauskop and Jerome Goldstein. Current Pain and Headache Reports 1997, 1: 246-250.
21. Becker WJ : A placebo controlled, double –dose defining findings of the sumatriptan nasal spray in the acute treatment of migraine. In proceedings of the seventh International migraine congress, Toronto, Canada , 16-30 september, 1995.
22. Altura BT, Shirley T, Young cc, et al.: A new method for rapid determination of ionized mg^{2+} in whole blood, serum and plasma. Meth find exp clin pharmacol. 1992, 14: 297-304.
23. Altura BT, Shirley TL, Young cc, et al.: Characterasation of a new ion selective electrode for ionized magnesium in whole blood, plasma, serum and aqueous samples. Scand J Clin Lab Invert 1994, 54(supp 217): 21-36.
24. Marco Pappagallo, MD clinical therapeutics vol.25, No.10,2003.
25. William B. Young, MD, Hua Chiang Siow, MD, and Stephen D.Silberstein, MD Current Pain and Headache Reports 2004, 8: 244-250.
26. Stefan Just, Kriten Arndt, Thomas Weiser, Henri Doods; Drug discovery today: Disease mechanisms. vol.3, No.3 2006.
27. Peter J. Goadsby, MD Current Pain and Headache Reports 2004, 8: 393-398.
28. Phebus LA, Jhonson KW, Zgombick JM, et al.: Characterization of LY334370 as a pharmacological tool to study 5HT1F receptor-binding affinities, brain penetration, and activity in the neurogenic dural inflammation model of migraine. Life sci 1997, 61:2117-2126.
29. Jhonson KW, Schaus JM, Durkin MM, et al.: 5HT1F receptor agonists inhibit neurogenic dural inflammation in guinea pigs. Neuroreport 1997, 8: 2237-2240.
30. Goldstein DJ, Roon KI, Offen WW, et al.: Selective serotonin 1F {5-HT(1F)} receptor agonist LY334370 for acute migraine: a randomized, controlled trial. Lancet 2001, 358:1230-1234.
31. Gomez-Mancilla B, Cutler NR, Leibowitz MT, et al.: Safety and efficacy of PNU-142633, a selective 5-HT1D agonist, in patients with acute migraine. *cephalalgia* 2001, 21:727-732.
32. Pregenzer JF, Alberts GL, Im WB, et al.: Differential pharmacology between the guinea-pig and the gorilla 5-HT1D receptor as probed with isochromans (5-HT1D selective ligands) Br J pharmacol 1999, 127: 468-472.
33. McCall RB, Huff R, Chio CL, et al.: Preclinical studies characterizing the anti-migraine and cardiovascular effects of the selective 5-HT1D receptor agonist PNU-142633. cephalagia 2002 , 22:799-806.
34. Gurden MF, Coates J, Ellis F, et al.: Functional characterization of three adenosine receptor types. BrJ Pharmacol 1993, 109: 693-698.
35. Scheehan MJ, Wilson DJ, Cousins R, Giles H: Relative intrinsic efficacy of adenosine A1 receptor agonists measured using functional and radioligand binding. Br J pharmacol 2000, 131:34P
36. Goadsby PJ, Hoskin KL, Storer RJ, et al.: Adenosine (A1) receptor agonists inhibit trigeminovascular nociceptive transmission. Brain 2002, 125:1392-1401.
37. Bartsch T, Akerman S, Goadsby PJ: The ORL-1(NOP1) receptor ligand nociceptin /orphanin FQ (N/OFQ) inhibits neurogenic vasodilation in the rat. Neuropharmacology 2002, 43: 991-998
38. Akerman S, Kaube H, Goadsby PJ: Vanilloid type1 receptor (VR1) evoked CGRP release plays a minor role in causing dural vessel dilation via the trigeminovascular system. Br J pharmacol 2003, 140: 718-724.
39. Akermans S, kaube H, Goadsby PJ: Anandamide shows both cannabinoid and vanilloid properties in an invivo model of trigeminovascular mediated head pain. Cephalagia 2003, 23: 646.
40. P.L. Durham, CGRP receptor antagonist: A new choice for acute treatment of migraine?, Curr. Opin. Investig. Drugs **5** (2004), pp. 731–735
41. T.M. Williams et al., Non-peptide calcitonine-gene related peptide receptor antagonist from a benzodiazepinone lead, Bioorg. Med. Chem. Lett. **16** (2006), pp. 2595–2598. |
42. Carl G.H. Dahlof, Mattias Linde, Erika Kerekes; J Headache pain (2004) 5: 237-242.
43. Ho TW, Ferrari M, Dodick DW, et al. Acute antimigraine efficacy and tolerability of the novel oral CGRP receptor antagonist telegepant. Headache 2008; 48 (supp1): 7-8.
44. Ho TW, Mannix LK, Fan X, et al. Randomized controlled trial of an oral CGRP receptor antagonist , MK-0974, in acute treatment of migraine. Neurology 2008; 70: 1304-12.
45. Steven J. Siegel, Carol O'Neill, Louise M.Dube, Peter Kaldeway, Russell Morris, David Jackson and Terri Sebree. Pharmaceutical research, vol.24, No.10, October 2007
46. Amjad Alhalweh, Staffan Andersson, SitaramP.Velaga. European journal of pharmaceutical sciences 38(2009) 206-214.
47. Goadsby PJ et al. Migraine – current understanding and treatment . New Engl J Med 2002; 346:257-70.
48. Shailesh Sharma: Fast dissolving tablet: the future of compaction; pharmainfo.net, vol.5 issue 2 2007.
49. Smith MI, Read SJ, Chan WN, et al. Repetetive cortical spreading depression in a gyrencephalic feline brain: Inhibition by the nivel benzoylamino-benzopyran SB- 220453. Cephalalgia 2000; 20: 546-53.
50. Read SJ, Smith M1, Hunter AJ , Upton N, Parsons AA. SB-220453, a potential novel antimigraine compound , inhibits nitric oxide release following induction of cortical spreading depression in the anaesthetized cat. Cephalalgia 1999; 20: 92-99.
51. Ellrich J, Lamp S. Peripheral nerve stimulation inhibits nociceptive processing : an electrophysiological study in healthy volunteers. Neuromodulation 2005; 8: 225-32.
52. Silberstein SD, Stark SR, Lucas SM, Chrristie SN, Degryse RE, Turkel CC. Botulinum toxin typeA for the prophylactic treatment of chronic daily headache : a randomized ,double blind, placebo-trial. Mayo clin proc 2005; 80: 1126-37.
53. Mathew NT, Frishberg BM, Gawel M, Dimitrova R, Gibson J, Turkel C. Botulinum toxin typeA(BOTOX) for the prophylactic treatment of chronic daily headache : a randomized , double-blind, placebo-controlled trial. Headache 2005; 45: 293-307.
54. Diener HC, Kurth T, Dodick D. Patent foramen ovale and migraine. Curr Pain Headache Rep 2007; 11: 236-40.
55. Wilmshurst PT, Nightingale S, Walsh KP, Morrison WL. Effect on migraine of closure of cardiac right-to-left shunts to prevent recurrence of decompession illness or stroke or for haemodynamic reasons. Lancet 2000; 356: 1648-51.
56. Li Y, Liang F, Yang X, et al. Acupuncture for treating acute attacks of migraine: a randomized control trial. Headache 2009; 49: 805-16.
57. RS Bhanushali, MM Gatne, RV Gaikwad, AN Bajaj, MA Morde. Indian journal of pharmaceutical sciences Volume : 71 Issue : 6 Page : 707-709 Year : 2009.
58. Lipton RB, Dodick DW, Silberstein SD, et al. Single –pulse transcranial magnetic stimulation for acute treatment of migraine with aura: a randomized, double-blind, parallel-group, sham controlled trial. Lancet Neurol 2010; published online march 4. DOI:10.1016/S1474-4422(10)70054-5
59. A.Rapoport Neurol Sci (2009) 30 (supp 1): S49-S54.
60. Marcelo E.Bigal, MD, Msc, PhD; Abouch V. Krymchantowski, MD, Msc, PhD. Medscape General Medicine. 2006;8(2):31.