International Journal of Research and Development in Pharmacy and Life Sciences
Available online at http//www.ijrdpl.com
August - September, 2013, Vol. 2, No. 5, pp 553-558
ISSN: 2278-0238

Review Article

ROLE OF ACE INHIBITORS & AT-II RECEPTOR ANTAGONISTS IN MIGRAINE PROPHYLAXIS : AN OVERVIEW

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(Received: March 18, 2013; **Accepted:** May 02, 2013**)**

ABSTRACT

Migraine is a chronic neurological disorder characterized by recurrent moderate to severe headaches, associated with a number of autonomic nervous system symptoms. Migraine constitutes 16% of primary headaches affecting 10-20% of general population according to International Headache Society. Typically the headache is unilateral (affecting one half of the head) and pulsating in nature, lasting from 2 to 72 hours. Associated symptoms may include nausea, vomiting, photophobia, phonophobia and the pain is generally aggravated by physical activity. Globally, approximately 15% of the population is affected by migraine at some point in life. Initial recommended management is with simple analgesics such as ibuprofen and acetaminophen for the headache, an antiemetic for the nausea, and the avoidance of triggers. Specific agents such as triptans or ergotamines may be used by those for whom simple analgesics are not effective. All the already available drugs have certain limitations. Either they are unable to produce complete relief or 30-40% patients are no responders or drugs produce adverse effects. A new class of drugs like angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin II receptor antagonists have recently been studied for their off label use in prophylaxis of migraine. Studies done so far, have shown results in favour of their clinical use because of the ability to reduce number of days with headache, number of days with migraine, hours with migraine, headache severity index, level of disability, improved Quality of life and decrease in consumption of specific or nonspecific analgesics. This article reviews the available evidence on the efficacy and safety of these drugs in prophylaxis of migraine. Relevent literatures were chosen, examining the efficacy of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) for migraine prophylaxis.
Keywords: Migraine, ACE Inhibitors, AT II Receptor blockers, Clinical trial, Prophylaxis.

INTRODUCTION

Migraine

A migraine is a relatively common medical condition that can severely affect the quality of life of the sufferer[1]. Almost 8% of Canadians over the age of 12 have been diagnosed with migraine, of which 75% are women and 25% are men. Migraine is most commonly experienced by both men and women between the ages of 25 and 39[2].

There are two different types of migraines: migraines without aura and migraines with aura. A migraine without aura is a condition characterized by moderate to severe throbbing and unilateral pain. The pain is worsened by movement and accompanied by at least one of the following symptoms[3]:

- Nausea, loss of appetite and/or vomiting
- Photophobia (increased sensitivity to light)
- Phonophobia (increased sensitivity to sound)

Migraines without aura are characterized by sudden onset and can have a major impact on the sufferer's daily life. On average, untreated migraine episodes last from 4 to 72 hours[4].

A migraine with aura involves any number of different sensations that range from visual disturbances to physical sensations[3]. The aura symptoms usually occur in alternating sites during different attacks. Almost always preceding the headache, the aura symptoms can last between 5 and 60 minutes[3]. Some people report having a prodrome, a feeling of strangeness a day or two before the attack begins. Prodromes are characterized by mood changes, food cravings, feeling tired or hyperactive, or excessive yawning. Some people may also experience fatigue, stiffness in the neck and/or difficulty concentrating body[4].

Signs and symptoms

Migraines typically present with self-limited, recurrent severe headache associated with autonomic symptoms. About 15-30% of people with migraines experience migraines with an aura and those who have migraines with aura also frequently have migraines without aura. The severity of the pain, duration of the headache, and frequency of attacks is variable. A migraine lasting longer than 72 hours is termed **status migrainosus**. There are four possible phases to a migraine, although not all the phases are necessarily experienced[5].

1. The prodrome, which occurs hours or days before the headache,
2. The aura, which immediately precedes the headache,
3. The pain phase, also known as headache phase,
4. The postdrome, the effects experienced following the end of a migraine attack.

RARE TYPES OF MIGRAINE

There are also some rare types of migraine.

Basilar type migraine

This is named after the basilar artery, a blood vessel in the back of the head, although it is unclear whether this blood vessel is actually involved. This type of migraine usually involves a headache at the back of the head rather than on one side. This is accompanied by, an aura which may involve problems with vision or hearing, speaking difficulties, tingling in the hands and feet (on both sides) and dizziness or problems with co-ordination[6].

Hemiplegic migraine

Hemiplegia means paralysis on one side of the body and weakness and is a key symptom of this type of migraine. Other symptoms might include numbness or pins and needles, visual problems, confusion and speech problems. These problems usually go within 24 hours, but they may last a few days. This type of migraine can be particularly frightening as the symptoms are similar to a stroke but in hemiplegic migraine they usually develop more slowly, whereas a stroke is usually a sudden event[6].

ACE INHIITORS & ANGIOTENSIN II RECEPTOR ANTAGONISTS,

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-II receptor antagonists (AIIRAs), both target the renin-angiotensin system. ACE inhibitors inhibit the conversion of angiotensin I to angiotensin II. AIIRAs antagonise the binding of angiotensin II to the AT1 receptor which mediates most of the antihypertensive effects usually associated with angiotensin II. Angiotensin II is important as it has numerous effects, including stimulation of the sympathetic nervous system, vasoconstriction, increasing aldosterone release and sodium retention, which can result in hypertension. Currently there are 11 ACE inhibitors, seven combination ACE inhibitors, seven AIIRAs and six combination AIIRAs availale. Although ACE inhibitors and AIIRAs work at different steps of the renin-angiotensin system, they are broadly indicated for similar conditions and the National Institute for Health and Clinical Excellence (NICE) offers guidance on the use of these drugs in the following areas: Heart Failure, Hypertension, Myocardial Infarction (Secondary Prevention), Type 2 Diabetes, and Chronic Kidney Disease[7].

Despite treatment of symptomatic migraine with triptans many patients experience only partial relief of symptoms. Furthermore, about 30-40% do not respond, and in some triptans induce headache. For these patients and for those who do not respond to non-specific treatments, prophylactic drugs are indicated for people who experience two or more attacks a month. Some β blockers and the anti-epileptic drug sodium valproate have shown some prophylactic effect. There is some evidence for the efficacy of the 5-hydroxytryptamine receptor antagonists pizotifen and methysergide as well as for flunarizine and several non-steroidal anti-inflammatory drugs. Most of the recommended drugs, however, cause adverse events that preclude long term treatment. Thus, there is a need for new prophylactic drugs that have greater efficacy and are better tolerated[8].

ACE INHIBITORS AND AT-II RECEPTOR ANTAGONISTS IN MIGRAINE PROPHYLAXIS,

A new target which has recently caught the attention of researchers in migraine is Renin Angiotensin System (RAS). RAS has neurophysiological, chemical and immunological effects that are relevant to pathophysiology of migraine. This fact directed the scientists to explore the usefulness of angiotensin-converting enzymes inhibitors (ACE inhibitors) /Angiotensin II receptor antagonists in the management of migraine. These drugs are extensively used for treatment of hypertension and congestive heart failure. The use of ACE inhibitors as prophylactic agents in headache was first proposed by Siceturi in 1981. Dramatic improvement was seen in 50% patients experiencing improvement in headache and 31% had partial relief. The rationale for this was inhibition of carboxypeptidase, an enkephalin-inactivating enzyme. This hypothesis was further supported by **Baldi *et* al**., in 1986[9].

Silberstein *et* al., (2012): In the 2000 guideline, there were no studies testing the efficacy of angiotensin receptor blockers or angiotensin converting-enzyme (ACE) inhibitors for migraine prevention. Since that publication, 3 reports have been published.

Candesartan. In a Class II crossover study (12-week treatment separated by 4-week washout), the mean number of headache days was 18.5 with placebo (26.3% reduction from baseline) vs 13.6 with candesartan (45.6% reduction from baseline; *p* _ 0.001).6 Selected secondary endpoints also favoured candesartan: headache hours (139 vs 95; *p* _ 0.001), migraine days (12.6 vs 9.0; *p* _ 0.001), migraine hours (92.2 vs 59.4; *p* _ 0.001), and headache severity index (293 vs 191; *p* _ 0.001). No serious adverse events (AEs) occurred. The most common AEs were dizziness (31%), "symptoms of the musculoskeletal system (21%), and fatigue (14%); none occurred significantly more often than with placebo.

Lisinopril. One Class II study reported significant reduction in all 3 primary endpoints with lisinopril vs placebo (headache hours: 129 vs 162 [mean change in hours 20, confidence interval (CI) 5–36]; headache days: 19.7 vs 23.7 [20, CI 5–30]; migraine days: 14.5 vs 18.5[21, CI 9–34]). AEs included cough (26%; 10% discontinued treatment due to cough), dizziness (23%), and "tendency to faint" (10%). No serious AEs were reported.

Telmisartan. In a single Class II placebo controlled trial, telmisartan 80 mg did not show a significant difference from placebo for reduction in migraine days (_1.65 vs _1.14).

Lisinopril and candesartan are possibly effective for migraine prevention (1 Class II study each). Telmisartan is possibly ineffective for reducing the number of migraine days (1 negative Class II study)[10].

Paterna *et* al.,(1992) found the utility of captopril in preventing migraine. These initial steps strongly led to further research on the use of these drugs in migraine. There is no clear underlying mechanism of action relating, as the effect produced by them is probably not due to their effects on blood pressure. It has been suggested that the effect of ACE inhibitors can be related to their ability to increase norepinephrine and serotonin action on vascular tone. The postulated pharmacological effects which can be relevant in migraine are inhibition of conversion of angiotensin I to angiotensin II, inhibition of free radicals, alteration of sympathetic activity, increase in prostacyclin synthesis, inhibition of degradation of bradykinin, enkephalin and substance P.

Thus angiotensin, by its multifaceted actions, is involved in pathogenesis of migraine providing one additional mechanism by virtue of which ACE inhibitors and angiotensin II receptor antagonists possess prophylactic role in migraine. Recently it has been found that genetic basis of migraine contributes a lot to define the role of ACE inhibitors/Angiotensin II receptor antagonist in migraine prophylaxis.

Studies have shown that ACE inhibitors (enalapril, lisinopril) as well as angiotensin II receptor antagonists (candesartan, telmisartan) have proved to be effective in reducing frequency as well as severity of migraine attacks with minimal side effects. Outcome measures studied in most of trials showed decrease in number days of headache, number of days with migraine, hours with migraine, headache severity index, level of disability, improved quality of life and decrease in consumption of specific or nonspecific analgesics.

Case series, open label studies, randomized controlled

clinical trials and meta-analysis have been done so far evaluating the role of ACE inhibitors/angiotensin II receptor antagonists for prevention of migraine[11].

In a meta-analysis, data from 27 studies involving 12,110 patients were included. The risk of headache was about one-third lower in patients taking an angiotensin II receptor

Table 1: Clinical studies of ACE inhibitors and Angiotensin II receptor antagonists in prophylaxis of migraine[9].

Authors	Number of Patients (n)	Duration of Therapy	Drugs	Type of study	Outcomes	Adverse effects
Schrader *et* al., (2001)[8].	47	12 weeks	Lisinopril (10mg for 1 week, 20 mg for 11 weeks	A randomized double blind study	20% Reduction in hours of headache	Cough Hypotension Dizziness
Schuh Hofer *et* al., (2007)[14].	21	12 weeks	Lisinopril 2.5 mg/day for 1 week, 5mg/day for 11 weeks	Open study	50% Decreased frequency of attacks	Cough, Dizziness
Bender WI, (1995)[15].	17	3 Months to 3 Years	Lisinopril/Enalapril (10-25 mg/day)	Open study	59% Decreased Migraine attacks	Cough
Tronvik *et* al., (2003)[16].	57	12 weeks	Condesartan 16 mg/day or placebo daily	A randomized double blind study	Hours with migraine(59.4 vs 92.2 p<0.001), days with migraine (9 vs 12.6 p<0.001)	ADR similar to Placebo
Owada (2004)[17].	10	Variable	Condesartan 8 mg/day	-	MIDAS* decreased from 29.4 to 9	Not Significant
Diener *et* al., (2009)[18].	95	12 weeks	Telmisartan 80 mg/day or placebo daily	A randomized, placebo-controlled trial	Reduction in migraine days(38% vs 15% with placebo, P value=0.03) and no. Of responders(40% vs 25% in placebo, P value=0.07)	ADR similar to Placebo
Sonobolestan *et* al (2013)[19].	40	2 Months	Enalapril 10 mg/day	A randomized double blind placebo study	Reduction in migraine attack more than 50% at first and second months (*P*=0.016)	-

antagonist than in those taking placebo (RR 0.69; 95% confidence interval [CI]: 0.62 to 0.76; the test of heterogeneity was negative, *P* value 0.2). The odds ratio for having a headache per unit dose of the reference drug losartan was 0.81(95% CI: 0.68-0.93) (**Etminan *et* al. 2002,).**

Relevant studies predicting the clinical efficacy and tolerability of ACE inhibitors/Angiotensin II receptor antagonists are summarized in [Table1].

Results of the above-mentioned studies clearly indicate the effectiveness and safety of ACE inhibitors/angiotensin II receptor antagonists, providing a new hope for chronic migraineurs. A special indication for the use of ACE inhibitors and angiotensin II receptor antagonists is migraineurs with bronchial asthma, intermittent claudication and conduction defects. Pregnancy is a known contraindication to the use of these drugs because of their ability to produce teratogenic effects in second and third trimester. Regarding tolerability, these drug classes have well established safety profile[12].

A preventative trials evaluating ACE inhibitors consist of a case series, 2 open-label trials, and a placebo-controlled trial. Lisinopril reduced headache hours 20%, headache days 17%, and migraine days 21% versus placebo in the controlled trial ($p < 0.05$). Clinically significant (>50%) reductions in migraine measures were more common (52-66%) in open-label ACE inhibitor trials than in the controlled (32-36%) trial. Preventive trials evaluating ARBs consist of a meta-analysis, an open-label trial, and 2 placebo-controlled trials. Candesartan reduced headache hours 31%, headache days 26%, and migraine days 28% versus placebo in the first controlled trial ($p \leq 0.001$). Telmisartan did not reduce any prespecified primary or secondary outcome measures in the second controlled trial. Clinically significant reductions (>50%) in migraine measures were more common (54-88%) in open-label ARB trials than in the controlled (26-38%) trials. A prescription database review found that ACE inhibitor or ARB therapy halved the use of abortive migraine agents compared to diuretic therapy. **(Gales *et* al.2010,)**

Conclusion drawn from the (**Gales *et* al. 2010,)** preventive trial that, ACE inhibitors and ARBs have migraine prophylaxis activity similar to that of some currently utilized agents. Low-dose lisinopril or candesartan may be reasonable second- or third-line agents, particularly in patients with other indications for ACE inhibitor or ARB therapy. Further controlled clinical trials are needed to delineate the role of these agents in migraine prevention[13].

(Schrader *et* al. 2001,) determine the efficacy of an angiotensin converting enzyme inhibitor and angiotensin receptor antagonists in the prophylaxis of migraine by designing Double blind, placebo controlled, and crossover study in Neurological outpatient clinic involves Sixty patients aged 19-59 years with migraine with two to six episodes a month.

The intervention of the study was that, the treatment period of 12 weeks with one 10 mg lisinopril tablet once daily for one week then two 10 mg lisinopril tablets once daily for 11 weeks, followed by a two week wash out period. Second treatment period of one placebo tablet once daily for one week and then two placebo tablets for 11 weeks. Thirty participants followed this schedule, and 30 received placebo followed by lisinopril.

The main outcome measures in this study is that, the primary end points: number of hours with headache, number of days with headache, number of days with migraine. Secondary end points: headache severity index, use of drugs for symptomatic relief, quality of life and number of days taken as sick leave, acceptability of treatment.

The result of the study was that, in the 47 participants with complete data, hours with headache, days with headache, days with migraine, and headache severity index were significantly reduced by 20% (95% confidence interval 5% to 36%), 17% (5% to 30%), 21% (9% to 34%), and 20% (3% to 37%), respectively, with lisinopril compared with placebo. Days with migraine were reduced by at least 50% in 14 participants for active treatment versus placebo and 17 patients for active treatment versus run-in period. Days with migraine were fewer by at least 50% in 14 participants for active treatment versus placebo. Intention to treat analysis of data from 55 patients supported the differences in favour of lisinopril for the primary end points[8].

DISCUSSION

Migraine prevention by substances influencing the RAS such as ACEIs or ARBs was first shown by an open study on Captopril in 1981. Then, **Bender** in a small open study and **Paterna *et* al**., in a small randomized double-blind study showed that Enalapril, Lisinopril, and Captopril can prevent

migraine attacks, and also some circumstantial studies in hypertensive patients indicated the preventive effect of RAS-related drugs. One of these studies was a meta-analysis which showed the Odds Ratio for having headache per unit dose of the reference drug Losartan (as an ARB) equal to 0.81 (95% CI: 0.68–0.93). Two other randomized, controlled, and blinded studies were performed by **Schrader *et* al**., and **Tronvik *et* al**., on Lisinopril as an ACEI and Candesartan as an ARB, respectively. Recently, an open label study on low-dose Lisinopril indicated the efficacy of this drug close to that of beta-blockers with good tolerability.

CONCLUSION

The angiotensin converting enzyme inhibitors and angiotensin receptor antagonists has a clinically important prophylactic effect in migraine. ACE inhibitors and Angiotensin II receptor antagonists show a potential in prophylactic management of migraine. Patients with frequent headaches who do not respond to conventional prophylactic agents or in whom these drugs are contraindicated, trial of ACE inhibitors/Angiotensin II receptor antagonists can be useful. Their use should be considered as a long-term therapeutic approach to migraine prophylaxis. Further assessment by larger studies is warranted in future to evaluate whether the positive effects are shared by all ACE inhibitors/angiotensin II receptor antagonists.

REFERENCES

1. Frediani F et al. Measure of negative impact of migraine on daily activities, social relationships and therapeutic approach. Neurol Sci 2004;25 Suppl 3:S249-250.
2. Martin S. Prevalence of migraine headache in Canada. CMAJ 2001;164:1481.
3. Ferrari MD. Migraine. Lancet 1998;351:1043-1051.
4. The International Classification of Headache Disorders, 2nd edition. Cephalalgia 2004;24 (Suppl 1):1-152.
5. Bartleson JD, Cutrer FM (May 2010). "Migraine update. Diagnosis and treatment". *Minn Med* 93 (5): 36–41.
6. Stroke Association Factsheet 28, version 01 published April 2012, stroke.org.uk
7. http://www.nhsbsa.nhs.uk/Documents/July-Sept 09 ACE Inhibitors and AIIRAs.pdf
8. Schrader H, Stovner LJ, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study. BMJ 2001; 322:19-22.
9. Nandha R, Singh H. Renin angiotensin system: A novel target for migraine prophylaxis. Indian J Pharmacol 2012;44:157-60.
10. Silberstein S.D., Holland S., Freitag F., Dodick D.W., Argoff C., Ashman E, New Guidelines on Treating Migraine, American Academy of Neurology APRIL 23, 2012 2012;78:1337–1345.
11. Paterna S, Di Pasquale P, Martino S, Arrostuto A, Ingurgio NC, Parrinello G, *et al*. Captopril versus Placebo in the prevention of hemicranias without aura-A randomized double blind study. Clin Ter 1992;141:475-81.
12. Etminan M, Levine MA, Tomlinson G, Rochon PA. Efficacy of angiotensin II receptor antagonists in preventing headache systematic overview and meta-analysis. Am J Med 2002;112:642-6.
13. Gales BJ, Bailey EK, Reed AN, Gales MA. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for the prevention of migraines. 2010 Feb; 44(2):360-6.
14. Schuh-Hofer S, Flach U, Meisel A, Israel H, Reuter U, Arnold G. Efficacy of lisinopril in migraine prophylaxis□-□An open label study. Eur J Neurol 2007;14:701-3.
15. Bender WI. ACE inhibitors for prophylaxis of migraine headaches, Headache 1995;8:470-1.
16. Tronvik E, Stovner LJ, Helde G, Sand T, Bovim G Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. Department of Neurology and Clinical Neurophysiology, Norwegian University of Science and Technology JAMA. 2003 Jan 1;289(1):65-9.
17. Owada K. Efficacy of candesartan in the treatment of migraine in hypertensive patients. Hypertens Res 2004;27:441-6.
18. Diener HC, Gendolla A, Fruersenger A, Evers S, Straube A, Schumacher H, *et al*. Telmisartan in migraine prophylaxis: A randomized, placebo-controlled trial. Cephalalgia 2009;29:921-7.
19. Sonbolestan SA, Heshmat K, Javanmard SH, and Saadatnia M Efficacy of Enalapril in Migraine Prophylaxis: A Randomized, Double-blind, Placebo-controlled Trial Int J Prev Med. 2013 January; 4(1): 72–77.

