

The role of Ace inhibitors in prophylaxis of migraines: a randomized prospective placebo controlled trial

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A. Lay Abstract

This study attempts to determine if a class of medications called Ace inhibitors can decrease the amount of migraine headaches that a person with migraines gets and also to see if the amount of various elements in the blood that are affected by Ace inhibitors can predict if a person will benefit from the medication. Several pilot studies show a benefit.

Migraine headaches are very painful often affecting one side of the brain and are throbbing and attacks can last hours to days. This often leads to not being able to go to work or school and often need to lie down in dark areas. These headaches are very common affecting 10-20% of people with the most common age group being age 25-34. It is believed that migraine attacks lead to the loss of 6-17 billion dollars a year because of people not being able to carry out activities.

This study will take people who have several migraine attacks a month and give them either an Ace inhibitor called lisinopril or a control drug called a placebo which they will take every morning for 6 months. Then the number of days affected by migraines will be determined for each patient comparing the number of days a month before and after the medicine is started. Lisinopril is a medicine routinely used to treat high blood pressure and heart failure.

Also before the drugs are given the patients will have some blood drawn during migraine attacks. The blood will be examined for the amount of specific parts of the blood called renin, angiotensin II, and bradykinin. These blood elements are known to be affected by the medicine lisinopril. This study will see if having more of any of these blood elements during a migraine makes it more likely that a person will have improvement by taking lisinopril.

The study patients will be men and woman between ages 20-50 who have 2-10 migraine attacks a months. The people should be relatively healthy without kidney, liver or heart disease and should not be pregnant because lisinopril can harmfully affect development of a fetus. The patients will be recruited through the clinic system and doctors offices at CPMC and also through newspaper advertisements in NYC. They will be recruited by the doctor who normally take care of the patient and if the patient is interested the researchers involved in the study will provide more details.

The study will require visits to study doctors at several times after the drug is started. This will be 2 and 4 weeks after and then once a month for 6 month total. During this time the doctor will assess how the patient's headaches are and check if the patient is keeping a daily diary of when migraines are occurring and for how long. Also blood will be drawn to check for kidney function and for potassium amount in the blood which can be affected by lisinopril. Also the blood pressure and heart rate will be measured each visit.

There are no ethical problems appreciated with this study.

B. Study Purpose and Rationale

The purpose of this study is to determine if Ace inhibitors can act as effective prophylactic agents in patients with migraine headaches and if the levels of various factors altered by Ace inhibitors can predict a given patient's response. Lisinopril approved for heart failure and hypertension will be used.

The primary outcomes will be change in days affected by migraines and the predictive value of angiotensin II, renin, and bradykinin levels during a migraine attack in determining responsiveness to an Ace inhibitor.

Secondary outcomes will be change in headache severity and in the use of abortifacants.

C. Study Design and Statistical Analysis

The study is a longitudinal prospective randomized placebo controlled double blinded parallel-arm trial. Patients will be randomly assigned to a control placebo arm or to a lisinopril 10 mg qd arm. Initially all subjects will undergo a 3 month run in period taking placebo tablet and keeping a diary of headaches. In the diary will be recorded the number of days with migraine, severity on 1-10 scale with 10 most intense, and the use of abortifacants. During the first 3 migraine attacks during this period the patients will be instructed to call the study coordinator and either the patient will be instructed to come to a blood drawing center or if not possible a study representative will go to the patient to draw blood levels of renin, angiotensin II, bradykinin. These samples will be sent to a designated lab and results not made available to the investigators until completion of the study. Participants who do not keep a diary, miss more than 20% of their pill doses (assessed by pill counting), are urine ICON positive or who average fewer than 2 or more than 8 migraine attacks per 30 days will not be included in the randomization phase.

After the run in period participants will be randomly assigned to the control or treatment arm and followed for 6 months. During this time the patients will continue recording their diary. They will be evaluated by a blinded study physician every 4 weeks to check compliance by pill counting and to check that diaries are being kept. During these meetings patients will be asked about potential adverse effects of lisinopril, will have blood drawn to check the creatinine and potassium which can be adversely affected by the study medicine, and will have their heart rate and blood pressure measured.

Data will be evaluated by a two-sided T test to evaluate for statistical significance of differences in days affected, severity, and abortifacant use between the placebo and treatment groups. For each patient the days affected following randomization minus the days during the run in period (per 30 days) will be calculated and then the averages in the treatment and control groups compared by the T-test.

Secondly patients in the treatment arm will be divided into two groups- those with greater than a 20% decrease per 30 days in the days with migraine verses those with less than a 20% change. Two sided T-tests will be performed to determine if the renin, angiotensin II, or bradykinin levels drawn during migraine attacks differ significantly ($p < .05$) between the 2 groups.

Using the unpaired t-test parallel arm in order to obtain 80% power to detect an effect of 0.2 and a standard deviation of 0.4 the study will need 65 patients in each arm. Assuming 20% of the subjects in the run in period will not fulfill criteria described above to enter the randomization phase a total of 156 people will need to enter the run in period.

An effect of 0.2 was chosen as the current chief prophylactic agent B-blockers provide in numerous studies a 20-30% benefit, a pilot study with lisinopril showed a 20% reduction in days with migraines, and the realization that less significant reductions may not have substantial clinical utility. Prior study has shown a group mean difference of 0.4 standard deviation between placebo and lisinopril treatment in percent reduction of days with migraines by lisinopril.

a. Outline

- Patients screened from outpatient clinics and newspaper advertisements
- Run in period 60 days - take placebo, headache diary of number of days with migraine, use of abortants, severity on 1-10 scale.
- If do not keep diary, urine ICON positive, fewer than 2 or greater than 8 migraines per 30 days, or take less than 80% of pills then excluded.
- During first 3 attacks blood drawn for renin, angiotensin II, bradykinin
- Randomization - double blinded
- Placebo verses lisinopril 10 mg po qd Follow for 6 months
- Continue diary
- Follow up visits with study physician weeks 2, 4, 8, 12, 16, 20, 24

- During each visit diary checked, pill counting, heart rate and pulse determined. Blood samples sent to check potassium and creatinine.

b. Study Procedures

- Procedures being done solely for research purposes include the drawing of blood samples during migraine attacks and during follow up visits (in this case to monitor for adverse drug effects).
- Each patient will have blood drawn during his or her first three migraine attacks. Blood samples will be tested for levels of renin, , angiotensin 11, and bradykinin. All three blood tests are radioimmunoassays to be done at Quest Diagnostic Laboratories.
- During follow-up after randomization blood samples will be checked at 2 and 4 weeks and then every four weeks to check potassium and creatinine levels.
- The study should take 9-12 months with each patient participating for 9 months (3 month of run in period and 6 months of randomization phase).

D. Study Drugs

Lisinopril 10 mg a day will be used. The medicine will be given orally. This Ace inhibitor is approved for use in hypertension and congestive heart failure. It is investigational in treatment of migraines.

Rational for use: Several studies have shown that Ace inhibitors may be an effective prophylactic agent in treating migraine headaches. A pilot study by Bender (1995) treated 17 migraine patients with enalapril or lisinopril over 3 months to three years. He found marked improvement in 10 patients, moderate in 6, and slight in 1.

Schrader et al. (2001) designed a double blind, placebo controlled, crossover study comparing placebo to lisinopril in migraine prophylaxis. They found that lisinopril treatment reduced hours with headache by 20%, days with headache by 17%, days with migraine by 21 %, and headache severity index by 20%.

Furthermore Paterna et al. (2000) found that migraine without aura is more common in people with the angiotensin converting enzyme DD allele and that patients with migraines who have this allele have increased angiotensin converting enzyme activity and more frequent migraine attacks than migraine patients with other alleles.

Currently migraine prophylaxis is indicated for patients suffering two or more attacks a month. Most of the current prophylactic agents cause significant side effects precluding long term use. The most common class of agents are B blockers. Other agents include amitriptylene, calcium channel B blockers, valproate, and methysergide. Usage of B blockers is precluded in patients with asthma, peripheral vascular disease and can cause significant side effects including impotence. Lisinopril does not exacerbate asthma attacks and does not increase impotence risk. Lisinopril was well tolerated in the studies referenced above with the predominant side effects being cough, hypotension, and dizziness. These are all known side effects associated with Ace inhibitors. In 60 patients receiving 10 mg a day of lisinopril for migraines 8 developed cough, 3 fatigue, 7 dizziness, 3 tendency to faint. Oral administration of lisinopril is a standard route of administration and the 10 mg dose is a standard starting dose for treating hypertension.

Ace inhibitors however are contraindicated during pregnancy because of teratogenic effects in the second and third trimesters but not during organogenesis during the first trimester. Females of childbearing age will need to use contraception and stop treatment when pregnant.

E. Medical devices

No devices used specifically for this study

F. Study Subjects

The study will include men and woman ages 20-50 who have migraines with or without aura as defined by the International Headache Society. They should have more than 2 migraine attacks a month but no greater than 8 attacks.

Exclusion criteria include use of prophylactic medications within the 4 weeks prior to the study start date, pregnancy, unwillingness to use contraceptives, renal failure (elevated creatinine), known renal artery stenosis, liver enzyme abnormalities, elevated potassium (>5), psychiatric disorder, known allergy to Ace inhibitors, SBP<100, and interval headaches that the patient cannot clearly distinguish from migraines, use of Ace inhibitor, use of migraine prophylactic medicine within 30 days prior to the start of the study. A "vulnerable" population included is woman of childbearing age because of the teratogenic effects of Ace inhibitors during the 2nd and 3rd trimesters of pregnancy. Therefore all females in the study who menstruate must use oral contraceptives for at least 6 months prior to the study (to avoid confounding effects on migraine frequency of starting the contraceptive at the time of the study) and have a negative pregnancy test (urine ICON) prior to entry.

G. Recruitment of subjects

Subjects will be identified by responses to advertisements in newspapers in New York City and by referral from clinicians at Columbia Presbyterian medical Center.

The patient's primary physician need to agree that the patient is suitable for participation in the study and should ascertain whether the patient is willing to discuss the study with the research team

H. Confidentiality of Study Data

All study data will be coded by random code numbers of six digits and will be stored in a secure location accessible only to the investigators.

I. Potential Conflict of Interest

No conflict of interest is recognized

J. Location of the Study

This will be based at CPMC at the outpatient clinical area.

K. Potential risks

Risks include the side effects described above but preliminary studies suggest equal efficacy of Ace inhibitors to B blockers in prophylaxis and there is no evidence suggesting worsening of migraine intensity or frequency.

L. Potential Benefits

This includes prophylaxis, potentially safer side effect profile than B blockers, the development of a prediction model for determining if a migraine sufferer will benefit from lisinopril.