

Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study

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Abstract

Objective To determine the efficacy of an angiotensin converting enzyme inhibitor in the prophylaxis of migraine.

Design Double blind, placebo controlled, crossover study.

Setting Neurological outpatient clinic.

Participants Sixty patients aged 19-59 years with migraine with two to six episodes a month.

Interventions 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.

Main outcome measures 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.

Results 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 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.

Conclusion The angiotensin converting enzyme inhibitor, lisinopril, has a clinically important prophylactic effect in migraine.

Introduction

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, the anti-epileptic drug sodium valproate, the 5-hydroxytryptamine receptor antagonists pizotifen and methysergide, flunarizine, and several non-steroidal anti-inflammatory drugs have shown some prophylactic effect. 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.

We had observed an impressive improvement in migraine in a patient treated with lisinopril for hypertension. This effect has already been described in a case series.¹ Furthermore, we had obtained anecdotal evidence for the efficacy of lisinopril in 10 women who had migraine, eight of whom reported fewer attacks during treatment. We carried out a randomised, double blind, placebo controlled, crossover study to investigate the prophylactic effect of the angiotensin converting enzyme inhibitor lisinopril.

Participants and methods

The study followed the guidelines recommended by the International Headache Society's committee on clinical trials in migraine² and was carried out between April 1998 and December 1999. Of the 60 randomised patients, 35 were recruited from an outpatient clinic and 25 responded to advertisements in a local newspaper.

Inclusion criteria were diagnosis of migraine with and without aura according to the criteria of the International Headache Society,³ men and women aged between 18 and 60 years, presence of migraine for more than a year, onset of migraine before the age of 50 years, and attacks of migraine occurring two to six times a month. Exclusion criteria were interval headache that the patient was unable to differentiate from migraine, use of prophylactic drugs for migraine in the four weeks before randomisation, pregnancy or inability to use contraceptives, decreased renal or hepatic function, hypersensitivity to angiotensin converting enzyme inhibitors, history of angio-neurotic oedema, and psychiatric disorder. The study was performed in accordance with the Declaration of Helsinki. The study protocol was approved by the regional ethics committee for medical research, and all patients gave written, informed consent before enrolment.

Study design

The design is reported in the longer version of this paper on the *BMJ's* website. After a four week placebo run-in period to verify the frequency of attacks, patients were randomly allocated to take one tablet daily containing either 10 mg lisinopril (active) or placebo (inactive).

The participants kept a daily diary in which they recorded the presence, severity, and, if appropriate, duration of symptoms in hours. Quality of life was assessed with a standardised questionnaire (SF-36).⁴ Primary end point variables were number of hours with headache; number of days with headache, irrespective of duration and severity; and number of days with migraine, irrespective of duration and severity. Secondary end point variables were headache severity index, calculated by multiplying headache

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hours with the reported maximum severity that day (grade 1-4) and subsequently adding the results for all headache days during 12 weeks of either treatment period; doses of triptans and doses of analgesics; acceptability of treatment; days of sick leave; and health related quality of life variables.

After each treatment period participants were also asked about the acceptability of the treatment ("If you could receive this treatment on prescription, would you like to continue with the treatment that you have used in the past 12 weeks?"). Participants were defined as compliant with treatment if they had adhered to the drug regimen (>80% of the tablets taken as determined by a tablet count at the end of the treatment period) and had given complete data in the diary.

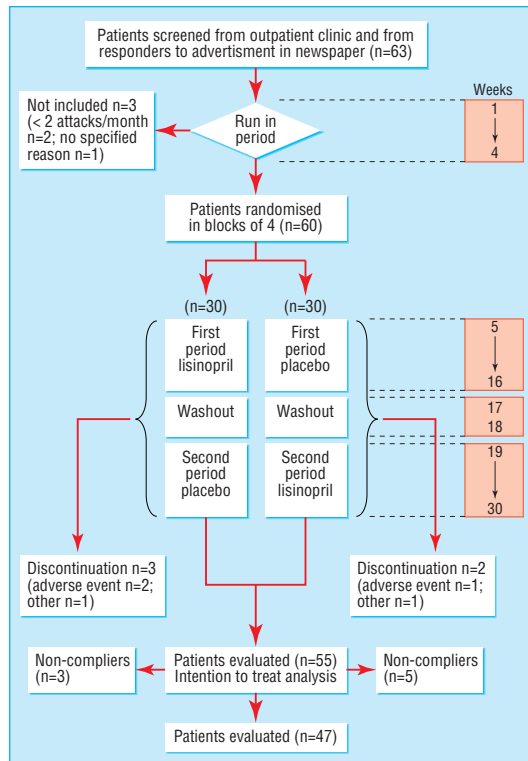
Statistical analysis

We used the Wilcoxon signed rank test to compare end point variables. For comparison of adverse events and acceptability we used a McNemar's matched pairs test. A two-sided P<0.05 was considered significant. A paired study including 55 subjects will have about 80% power to detect a group mean difference of 0.5 SD (with Student's *t* test).⁵

Results

Participants

Of the 60 patients who were randomised, three withdrew from the study because of adverse events (fatigue, dizziness and fatigue, exanthema, and monoarthritis), one declined to continue, and one had an inadequate response on placebo (see figure). Eight patients did not comply with treatment but kept a diary



Trial profile in study of prophylactic treatment of migraine with lisinopril

Table 1 Adverse events in 60 participants with migraine treated with lisinopril or placebo*

	Lisinopril	Placebo
Coughing	8	3
Fatigue	3	3
Dizziness	7	4
Tendency to faint	3	0
Others	3	3
Total	24	13

*P=0.07 (McNemar's matched pairs test) for comparison of pooled effects: no adverse events v at least one symptom (2x2 table).

Table 2 Efficacy parameters in 47 participants with migraine during treatment periods of 12 weeks. Figures are means (SD)

	Lisinopril	Placebo	Mean % reduction (95% CI)
Primary efficacy parameter			
Hours with headache	129 (125)	162 (142)	20 (5 to 36)
Days with headache	19.7 (14)	23.7 (11)	17 (5 to 30)
Days with migraine	14.5 (11)	18.5 (10)	21 (9 to 34)
Secondary efficacy parameter			
Headache severity index	297 (325)	370 (310)	20 (3 to 37)
Triptan doses	15.7 (15)	20.2 (17)	22 (7 to 38)
Doses of analgesics	14.5 (23)	16.2 (20)	11 (-16 to 37)
Days with sick leave	2.30 (4.32)	2.09 (2.50)	-10 (-64 to 37)
Bodily pain*	63.7 (29)	53.8 (23)	-18 (-35 to -1)
General health*	73.6 (20)	74.1 (21)	1 (-6 to 7)
Vitality*	61.1 (24)	58.2 (21)	-5 (-18 to 8)
Social functioning*	81.4 (25)	79.5 (23)	-2 (-11 to 6)

*From SF-36.

Table 3 Intention to treat analysis of primary efficacy parameters in 55 participants during treatment periods of 12 weeks. Figures are means (SD)

	Lisinopril	Placebo	Mean % reduction (95% CI)
Hours with headache	138 (130)	162 (134)	15 (0 to 30)
Days with headache	20.7 (14)	24.7 (11)	16 (5 to 27)
Days with migraine	14.6 (10)	18.7 (9)	22 (11 to 33)

for the whole study period. The 47 remaining participants (38 women, mean (SD) age 41 (9) years; nine men, 43 (5) years) provided complete data for final evaluation of efficacy. Table 1 shows the adverse events in the 60 randomised patients.

Outcomes

There was a significant difference in favour of lisinopril for hours with headache, number of days with headache, number of days with migraine, and headache severity index (table 2). There was a reduction of at least 50% in symptoms in 14 (30%) participants for days with migraine and 15 (32%) for headache severity index during lisinopril compared with placebo treatment. In the intention to treat analysis in 55 patients, significant differences were retained for the primary efficacy end points (table 3).

Mean (SD) blood pressure was 128/83 (14/10) and mean (SD) heart rate was 71 (8) beats/min during the 12 week placebo period. During the lisinopril period mean blood pressure was 121/78 (13/10) (P<0.0001 for systolic and diastolic pressure) and mean heart rate 69 (6) beats/min. Acceptability of treatment was 35/47 for lisinopril versus 14/47 for placebo (P<0.0001). Except for bodily pain, which showed a reduction with

lisinopril, health related quality of life scales showed no significant differences.

Discussion

Our results show that lisinopril has a clinically relevant prophylactic effect in migraine. Compared with the placebo period, there was a reduction of about 20% in primary efficacy parameters during lisinopril treatment. A comparison of the effect of lisinopril with those reported for other prophylactic drugs for migraine is difficult because of differences in study designs and ways of reporting results.⁶ A meta-analysis of the effect of propranolol 160 mg indicated an improvement of 33% with regard to the headache index on active medication compared with placebo, but this analysis included both open and controlled studies.⁷ For this parameter we saw an improvement of 20%, and we consider this to be a promising result in a study performed with an up to date and robust methodological design. To assess the relative efficacy, safety, and tolerability of different drugs reliably, however, only direct comparisons in a single study are valid.

Study strengths

The main strength of our study is that it was performed according to the guidelines for controlled trials of drugs in migraine.² We chose the crossover design for this single centre study because fewer patients were needed than for a parallel group design. There are known disadvantages of the crossover design,⁸ but we found no period effect and no carry over effect. The drop out rate was low (8%), despite the relatively long duration of the study (31 weeks).

We did not use the “number of attacks” as an efficacy end point because participants would have had to record when the headache started and stopped. As the headache diary was already quite extensive we were concerned that this might cause a higher drop out rate. In addition, the frequent use of effective triptans modifies the attack pattern and makes it hard to assess the true attack rate as defined by the International Headache Society. Furthermore, we are not aware of any other studies that have detailed data on individual attacks such that the attack frequency could be reliably assessed according to the International Headache Society guidelines and comparisons made between studies. We therefore used the less ambiguous end points of number of days with migraine, number of days with headache, and number of hours with headache.

Why it might work

Lisinopril has various pharmacological effects that may be relevant in migraine. In addition to blocking the conversion of angiotensin I to angiotensin II, it also alters sympathetic activity, inhibits free radical activity, increases prostacyclin synthesis,⁹ and blocks the degradation of bradykinin, enkephalin, and substance P.¹⁰ Of great relevance may be the recent finding that migraine without aura seems to be more common in people with the angiotensin converting enzyme DD gene, and migraineurs with this gene also have higher angiotensin converting enzyme activity and a higher frequency of attacks than other migraine sufferers.¹¹

What is already known on this topic

Many drugs recommended for prophylaxis of migraine are not suitable for long term use

What this study adds

The angiotensin converting enzyme inhibitor lisinopril is an effective prophylactic treatment for frequent migraine attacks

Lisinopril significantly decreased hours with headache, days with headache, days with migraine, headache severity index, and doses of triptan

Lisinopril is well tolerated and adverse events are mild or moderate

Safety and tolerability

Lisinopril was well tolerated, as can be seen from the acceptability and the quality of life scores, and the adverse events observed in this study were those known to be associated with angiotensin converting enzyme inhibitors.¹² Symptoms associated with hypotension (dizziness and tendency to faint) may be minimised by reducing the intake of lisinopril to its lowest effective dose. Cough, a side effect not related to dose, was severe enough to prohibit further use in three patients.

In contrast with β blockers, lisinopril can be used in patients with asthma, intermittent claudication, and conduction defects, and it is not associated with sexual dysfunction.¹³ Angiotensin converting enzyme inhibitors are known to cause fetal and neonatal morbidity and mortality in the second and third trimesters of pregnancy,¹⁴ but in contrast with valproic acid, lisinopril is considered relatively safe during organogenesis in the first trimester. This may allow for a cautious use in women of childbearing age as the drug can be discontinued when pregnancy is diagnosed.

Lisinopril is widely prescribed for various cardiovascular conditions and has a well established safety profile. Doctors are already familiar with prescribing angiotensin converting enzyme inhibitors. Thus, given the limitation of this being one relatively small study, albeit with a robust double blind and placebo controlled design, the positive outcomes and good tolerability support the use of lisinopril as a useful prophylactic treatment for migraine patients.

Contributors: HS had the original idea for the study and is the guarantor. HS and LJS were the principal investigators and designed the protocol, assessed the patients, and wrote the manuscript. GH assisted in the design of the study, recruitment of the patients, and data collection and analysis. TS helped to draw up the protocol and participated in the statistical analysis. TS and GH contributed to the revision of the manuscript. GB participated in planning the study, assessment of patients, and revision of the manuscript. He also advised on the study design and the statistical analysis. The database was managed by the investigators who performed the statistical analyses of the data.

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Competing interests: HS and GB have been reimbursed by AstraZeneca, one of the manufacturers of lisinopril, for attending conferences. These conferences were unrelated to the present study.

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Existence and quality of written antenatal screening policies in the United Kingdom: postal survey

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The assessment of antenatal care of women at increased risk of having a baby with Down's syndrome, neural tube defect, thalassaemia, and cystic fibrosis that was undertaken by the national confidential inquiry into counselling by non-geneticists revealed several problems, including poor record keeping.¹ These problems were reported to the Department of Health in five specific papers and four summary, peer reviewed papers and on the internet.² The Royal College of Obstetricians and Gynaecologists then issued guidelines recommending that antenatal units have written policies for screening for Down's syndrome and for neural tube defect and that haemoglobinopathy screening be offered to all patients whose ethnic origin makes them susceptible.³ There is less consensus on screening for cystic fibrosis (UK National Screening Committee, joint meeting of the antenatal and child health screening subgroups, cystic fibrosis workshop, London, 2 June 1999). We assessed the response among antenatal staff to the outcomes of the national confidential inquiry.

Methods and results

In 1999 directors of obstetrics and midwifery throughout the United Kingdom were asked to complete an

anonymous questionnaire concerning their awareness of the national confidential inquiry and its effects on practice. (Copies of the questionnaires are available on the *BMJ's* website.) Midwives were also asked to submit their unit's written policies, which we assessed using the royal college's criteria (table).³

A total of 242 obstetricians were sent questionnaires, 181 (75%) of whom responded. Of these, 29 (16%) were aware of the inquiry (four having supplied information to it), 13 (7%) were aware of the specific recommendations for Down's syndrome, 7 (4%) those for neural tube defects, and 6 (3%) those for cystic fibrosis. Four obstetricians stated that they had implemented recommendations, and one was auditing their effect on practice. Of the 273 midwives who were sent questionnaires, 160 (59%) responded; 33 (21%) were aware of the inquiry, 27 (18%) were familiar with the recommendations for Down's syndrome, 13 (9%) those for neural tube defects, and 9 (6%) those for cystic fibrosis. The figures for obstetricians and those for midwives are not evidently related.

Thirty nine units (24%) lacked local and regional policies for Down's syndrome, 55 (34%) for neural tube defect, 104 (65%) for haemoglobinopathy, and 125 (78%) for cystic fibrosis; 55 units updated their policies annually, 36 "[when] required", one every five years,

Adherence of midwifery units' written policies to Royal College of Obstetricians and Gynaecologists' guidelines on screening*

Royal College guidelines criterion	No (%) of policies fulfilling criterion	Comments
Clear statement of which test is available	61 (94)	Missing in one policy on Down's syndrome and three on haemoglobinopathy
Clear statement of which patients are routinely to be offered test	45 (69)	11 offer testing for Down's syndrome to all, 9 to women aged 30-38; three offer haemoglobinopathy testing to unspecified ethnic groups, one universally; both policies covering cystic fibrosis state family history as basis for screening
Personnel responsible for offering screening or counselling are specified	13 (20)	Unrelated to condition to which policy referred
Clear statement of cut-off values for normality	22 (34)	In 4/14 of policies for both Down's syndrome and NTD, 5/20 for Down's syndrome, 5/11 for NTD, and 8/18 for haemoglobinopathy
Clear guidelines on referral for abnormal screen	26 (40)	9/18 of policies covering haemoglobinopathy, 1/2 covering cystic fibrosis

*Of 65 written policies, 20 covered Down's syndrome, 11 neural tube defect (NTD), 14 both Down's syndrome and NTD, 2 cystic fibrosis, and 18 haemoglobinopathy.

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Copies of the questionnaires are available on the *BMJ's* website