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Lisinopril: a New Prophylactic Agent for Migraine Headache

ANNE D. WALLING, M.D.

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Even with optimal therapy, many patients with migraine obtain only partial relief and could benefit from prophylactic therapy. The long-term use of common prophylactic agents, such as beta blockers, valproate and nonsteroidal anti-inflammatory drugs, is limited by adverse effects. This situation has prompted the search for new agents to reduce the number and severity of migraine attacks. Based on observational and anecdotal evidence, patients taking lisinopril for hypertension were believed to have fewer migraine attacks. Schrader and colleagues conducted a randomized, placebo-controlled, crossover study to examine the prophylactic effect of lisinopril on migraine.

Participants 18 to 60 years of age who met International Headache Society criteria for migraine were recruited from an outpatient clinic and through local newspaper advertising. Participants had to report having two to six migraine episodes per month for at least one year beginning before the age of 50. Exclusion criteria included use of prophylactic medications, pregnancy or lack of contraception, decreased hepatic or renal function, or contraindication to the study medication.

All participants kept a symptom diary for a four-week placebo run-in period to establish the number and characteristics of migraine attacks. The 60 participants were then randomly assigned to treatment with lisinopril or an identical placebo for 12 weeks. Participants treated with lisinopril were given one 10-mg dose per day for one week, then two 10-mg doses per day for 11 weeks. Participants treated with placebo followed a similar regimen. Following a second placebo "wash-out" period of two weeks, the treatments were reversed for each patient for an additional 12 weeks. Throughout the study, participants kept a daily symptom diary and

completed a quality-of-life questionnaire. Outcomes measured included the number of days and hours of headache, headache severity, use of medications and time lost from work. Participants were also asked about the acceptability of treatment.

Data were complete on 38 women and nine men. The main reason for not completing the study was noncompliance. Only three participants withdrew because of side effects. During lisinopril therapy, 24 of 60 participants reported an adverse effect. The principal adverse effect was cough, which was reported by eight participants during lisinopril therapy and three during placebo therapy. Other adverse effects included dizziness in seven participants taking lisinopril and four participants taking placebo, and fatigue in three participants during both therapies. During placebo periods, mean blood pressure was 128/83 mm Hg and mean pulse was 71 beats per minute. During lisinopril therapy, the corresponding figures were 121/78 mm Hg and 69 beats per minute. While taking lisinopril, participants reported a reduction in body pain, but otherwise the health and quality-of-life scores were comparable during both treatment periods.

The number of hours and days with headache was significantly reduced during lisinopril treatment *(see accompanying table)*. About one third of participants reported at least a 50 percent reduction in symptoms, number of days with migraine and severity of attacks.

The authors conclude that lisinopril has a clinically significant prophylactic effect in migraine. This could be caused by several mechanisms, including altered sympathetic activity, inhibition of free radical activity, increased prostacyclin synthesis and alteration of the metabolism of various neurochemicals. It is also known that migraine without aura is more common in persons with the angiotensin-converting enzyme DD gene and that carriers of this gene have higher angiotensin-converting enzyme activity and more frequent attacks, suggesting a genetic mechanism. Lisinopril is well tolerated and may prove to be a useful prophylactic agent for migraine if the results of this study can be confirmed.

Efficacy Parameters in 47 Participants with Migraine During Treatment Periods of 12 Weeks

	Lisinopril	*Placebo*	*Mean % reduction (95% CI)*
Primary efficacy parameter			
Hours of headache	129 (125)	162 (142)	20 (5 to 36)
Days with headache	19.7 (14)	23.7 (11)	17 (5 to 30)

	Lisinopril	*Placebo*	*Mean % reduction (95% CI)*
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 the SF-36 Health Survey (SF-36).*

Reprinted with permission from 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;322:20.

editor's note: Migraine prophylaxis is notoriously difficult to study because of the placebo effect, the episodic nature of the condition and the subjective element in symptoms. This well-designed study provides credible evidence that lisinopril has a prophylactic effect and proposes several plausible explanations. For a practicing physician, however, the really interesting prospect is being able to match prophylaxis to specific types of migraine. Currently, we consider patient characteristics to make the initial medication selection, then face a long period of monitoring and adjusting the dosage until the optimal balance of reduction in migraine and "nuisance" of daily medication is reached. Many physicians and patients abandon this frustrating process. If certain types of migraine are more responsive to specific agents, we may be more successful. The link between blood pressure and migraine is also fascinating. I noted that most migraine patients appear to have low blood pressure but did not know about the increased angiotensin-converting enzyme activity in migraine without aura. Could this activity explain the lower cardiovascular disease rates in persons with migraine? Is it worth suffering migraine pain earlier in life to prevent the possibility of cardiac disease later? How could these observations about blood pressure be reconciled with the slightly increased risk of stroke in women with migraine? Obviously, there is much to learn about this painful and disruptive condition.—a.d.w.

Author Information

ANNE D. WALLING, M.D.

Reference(s)

1. Schrader H, et al. Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study. *BMJ.* January 6, 2001;322:19-23.