CLINICAL UPDATE

Lisinopril for migraine

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.

Background: Migraine, which affects an estimated 18% of women and 6% of men,[1] results in significant costs to individuals and society. Current prophylactic therapies can be associated with potential side effects, but a recent observational study suggests that angiotensin-converting-enzyme (ACE) inhibitors may be effective when used prophylactically.

Question: Does lisinopril, an ACE inhibitor, prevent migraine headaches?

Design: This was a double-blind, placebo-controlled, crossover study. All patients were aged 18 to 60 years, met the diagnostic criteria for migraine established by the International Headache Society, had migraine for more than a year, had onset of migraine before the age of 50 and experienced at least 2 to 6 migraine attacks monthly. Patients who could not differentiate migraine from other forms of headache, who had used prophylactic medication recently or who had contraindications to ACE inhibitor therapy were excluded. A 4-week placebo run-in period verified the frequency of attacks. At randomization, half of the patients were assigned to receive lisinopril for 12 weeks, followed by a 2-week washout period, and then were given placebo for a final 12 weeks; the other half were given placebo first, followed by a washout period, and then lisinopril. The dosage of lisinopril was 10 mg once daily for the first week, followed by 20 mg once daily for the remaining 11 weeks.

All patients were asked to keep a daily symptom diary and were followed closely during the study period. The primary study outcomes were number of days with migraine, number of days with headache and number of hours with headache. Secondary outcomes included headache-severity index, doses of triptans and analgesics, acceptability of treatment, number of days of sick leave and quality-of-life index.

Results: Of the 60 patients eligible for randomization after the run-in period, 5 withdrew from the study and another 8 were noncompliant with the study protocol. This left 47 patients for a final evaluation of efficacy and 55 patients for an intention-to-treat analysis. The mean number of days with migraine was 6.8 during the 4-week run-in period; afterward, the mean number was 6.2 days with placebo and 4.8 with lisinopril, representing reductions of 9% (95% confidence interval [CI] –3% to 21%) with placebo and 29% (95% CI 15% to 42%) with lisinopril. The mean number of days with headache was reduced by 16% (95% CI 4% to 28%) with placebo and 30% (95% CI 19% to 42%) with lisinopril; the reductions in the mean number of hours with headache were similar. Significant differences favouring lisinopril remained when the drug was compared directly with placebo in the intention-to-treat analysis. As well, the headache-severity index and the mean doses of triptans were significantly lower with lisinopril than with placebo, and the acceptability of treatment was significantly greater with lisinopril than with placebo. There was no significant difference between the 2 drugs in the other secondary outcomes. Three patients stopped taking lisinopril because of cough.

Commentary: This crossover study, using patients both as treatment and control subjects, was able to demonstrate statistically significant differences in the primary outcomes. Potential bias due to a carry-over effect appears to have been avoided because of the washout period. The lack of difference in the number of days of sick leave, however, is disappointing. This may reflect the small size of the study, or perhaps a learned behaviour associated with a long-standing history of migraine.

Practice implications: None of the currently recommended prophylactic medications for migraine is ideal.[2] The serendipitous finding that lisinopril is efficacious is therefore most welcome. ACE inhibitors are generally well tolerated in selected patients and, unlike alternative prophylactic agents such as valproic acid, are familiar to most physicians. In considering lisinopril prophylaxis, one must consider contraindications to ACE inhibitor therapy (e.g., pregnancy), as well as nonpharmacologic approaches to migraine management.[3] The efficacy of lisinopril relative to other prophylactic drugs awaits future studies. — *Benjamin H. Chen*

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References

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