ACE Inhibitors for Migraine Prophylaxis

Schrader H, Stovner LJ, Helde G, et al. Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study. BMJ 2001:322:1–5.

Study Overview

Objective. To determine whether lisinopril effectively prevents migraine headaches.

Design. Randomized, double-blind, placebo-controlled, crossover study with single-blind run-in and washout periods preceding treatment periods.

Setting and participants. Patients recruited from an outpatient clinic (n = 35) and a newspaper advertisement (n = 25) were randomized if they had migraine with or without aura (using the International Headache Society criteria [1]), with attacks occurring 2 to 6 times per month. Subjects also met the following inclusion criteria: age between 18 and 60 years, presence of migraine for at least 1 year, and onset of migraines before age 50 years. Exclusion criteria were interval headaches indistinguishable from migraines, use of medications for migraine prophylaxis in the 4 weeks prior to randomization, pregnancy or inability to use contraceptives, renal or hepatic insufficiency, hypersensitivity to angiotensin-converting enzyme (ACE) inhibitors, history of angioneurotic edema, or psychiatric disorder. The study was carried out in a single center in Norway.

Intervention. During the 4-week run-in period, patients were instructed to take 1 tablet containing either 10 mg of lisinopril or an identical-appearing placebo and to record the frequency of migraine attacks in a headache diary. Researchers informed patients that they would continue in the study only if their headache diaries documented 2 to 6 attacks in this period. Patients not excluded after the run-in period (n = 60) were randomized to receive either 10 mg of lisinopril for 12 weeks and placebo for another 12 weeks or the opposite (lisinopril followed by placebo in two 12-week intervals). Half of subjects received lisinopril first. A 2-week washout period occurred between the 2 treatment periods; all patients received placebo during this time.

Main outcome measures. Primary outcomes were number of hours with headache, number of days with headache, and number of days with migraine. Duration and severity of headache episodes were not included in the primary outcomes. Secondary outcomes were a headache severity index (calculated using headache hours and severity scores), doses of triptans and analgesics, days of sick leave, SF-36 scores [2], and acceptability of treatment (a binary variable assessed by the question "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?").

Main results. 63 patients were enrolled in the run-in period. (The authors do not state how many people were screened to recruit 63 subjects.) After 4 weeks, 2 patients were eliminated from the study because they had had less than 2 migraine attacks and 1 declined to participate for an unspecified reason. Of the remaining subjects, 5 dropped out of the study (3 because of adverse events, 2 for other reasons) and were not included in any analysis, and 8 were noncompliant (took less than 80% of doses). Most of the noncompliance occurred during the active treatment period (63%, P not reported). Overall, lisinopril was associated with more adverse reactions than placebo, although the difference did not reach statistical significance (24 versus 13, P = 0.07).

The intention-to-treat analysis showed a 14% to 20% greater decrease in all primary endpoints compared with placebo ($P < 0.05$). This decrease was 29% to 34% compared with baseline. Patients had a lower mean headache severity index during active treatment (20% compared with placebo [95% confidence interval (CI), 3% to 37%]) and used fewer triptan doses (22% [95% CI, 7% to 38%]). Other secondary measures did not differ between active and placebo periods. The authors found no evidence of a period or carry-over effect resulting from crossover design.

Conclusion

Lisinopril appears to be modestly effective as a prophylactic agent for patients with migraine who experience more than 1 attack per month.

Commentary

This study was small but generally well designed.

However, there were some problems with how the study was reported and how outcomes were analyzed. Schrader et al provided no descriptive data regarding subjects. Information on previous prophylactic treatments, use of narcotics for headaches, and presence of comorbidities (especially nonmigraine headaches) would have been helpful in assessing the study's generalizability. Many studies of therapies for migraine prophylaxis report the number of subjects improved, with improvement usually defined as a greater than 50% decrease in headache days or hours. Without this information, we cannot assess the number needed to treat for benefit, and therefore the overall usefulness of the treatment remains unclear. The meaningfulness of treatment response, as reported by Schrader and colleagues, is difficult to evaluate. (In the study, the mean number of hours with headache during active treatment periods was still more than 10 per week and the number of days with headache was 1.2 per week.)

Applications for Clinical Practice

While Schrader et al's results do not suggest that lisinopril should replace better studied and probably more effective first-line agents such as propranolol and valproic acid, lisinopril can be considered when more established agents have not been effective. At what point a course of lisinopril should be tried (ie, as third-, fourth-, or fifth-line treatment) will need to be established through further research (preferably) or clinical experience (more likely).

References

1. Classification and diagnostic criteria for headache disorders, cranial neuralgias, and facial pain. Headache Classification Committee of the International Headache Society. Cephalalgia 1988;8 Suppl 7:1–96.
2. Ware JE, Gandek B. The SF-36 health survey: development and use in mental health research and the IQOLA project. IQOLA project group. Int J Mental Health 1994;23:49–73.