Headache in Mild-to-Moderate Hypertension and Its Reduction by Irbesartan Therapy

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**Background:** Although it is generally acknowledged to be a problem in severe hypertension, headache has not been consistently associated with mild-to-moderate hypertension.

**Patients and Methods:** In 7 randomized, double-blind, placebo-controlled trials, which included 2673 patients with mild-to-moderate hypertension (defined as seated diastolic blood pressure of 95-110 mm Hg), patients were randomized to receive twice-daily treatment with irbesartan, an angiotensin II receptor blocker (n=1987), or placebo (n=686). The data were pooled and analyzed retrospectively to determine whether the level of hypertension was associated with headache and whether antihypertensive therapy reduced the incidence of headache.

**Results:** Factors found to be predictive of headache incidence were diastolic blood pressure, sex (female), and age (<50 years). In comparison with placebo, the use of irbesartan was associated with a significant reduction in the incidence of headache (P = .003).

**Conclusions:** These data suggest that mild-to-moderate hypertension is not asymptomatic and that the incidence of headache can be reduced by antihypertensive treatment with a favorable adverse effect profile.

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**Headache May be the Most Frequently Mentioned Complaint that Accompanies Hypertension.**

As early as 1913, in a review of more than 7800 patients, Janeway concluded that headache was the most common of the various symptoms reported by patients with hypertension, a position supported by other investigators. In a study of 400 patients with hypertension (diastolic blood pressure [BP] >110 mm Hg), 55% of patients reported headache as a consequence of their hypertension. For diastolic BP between 95 and 125 mm Hg, the incidence of headache has been reported to be between 15% and 20% in patients with hypertension who are untreated.

Despite the early recognition of an association, the link between headache and hypertension has often been attributed to anger, anxiety, or the adverse effects of drug therapy. Indeed, the reporting of headache has been used in an “anger scale” that predicted hypertension in the Framingham Study. According to another report, anxiety-induced hyperventilation has been considered a common cause of headache in hypertension. Other investigators have attributed the development of headache in hypertension to the adverse effect of diuretics, calcium channel blockers, and angiotensin-converting enzyme (ACE) inhibitors. Confounding the situation further, pain of any cause, including headache, may elevate BP.

Some reports have indicated that the treatment of hypertension reduces the frequency of headache. Additional indirect evidence was provided by Cooper et al, who found that headache frequency increased following drug withdrawal from all classes of antihypertensive agents except calcium channel blockers, indicating that BP control with well-tolerated agents may reduce the frequency of headache. The recently developed angiotensin II receptor blockers (ARBs) may reduce BP as effectively as other antihypertensive medications, while providing a tolerability profile similar to that of placebo. Thus offering the means to test the hypothesis as to whether the reduction of BP without the imposition of adverse events reduces the frequency of headache in hypertension.

Irbesartan is an angiotensin II receptor antagonist; in an integrated analysis, it was shown to possess a clear dose response in antihypertensive effectiveness for both diastolic and systolic BP. Furthermore, this integrated analysis of 9...
PATIENTS AND METHODS

PATIENTS

Patients were men or women (surgically sterile or post-menopausal) 18 years or older (irbesartan therapy, n=1987; placebo, n=686). All patients had newly discovered or established mild-to-moderate hypertension (defined as seated diastolic BP of 95-110 mm Hg) and were randomly assigned to a treatment or placebo group in each of the 7 studies. (Reports on 6 of these studies have been previously published.24–29) Exclusion criteria were related to specific concomitant diseases that would present safety hazards or to concomitant medications that might interfere with the assessment of safety or efficacy of irbesartan and were highly consistent across all studies. Each study was approved by an institutional review committee, and each patient gave informed consent before study enrollment. There were no statistically significant differences in baseline characteristics between the irbesartan therapy and placebo groups. Most patients (80%) were white, and more than half (63%) were men, with a median age of 53 years and mean baseline BP of 154/101 mm Hg.

CONTRIBUTING STUDIES

All 7 studies began with a 4- to 5-week single-blind placebo lead-in period. Following the lead-in period, eligible patients were randomized to receive placebo or irbesartan in fixed doses, ranging from 1 mg to 900 mg for a period of 8 or 12 weeks. (These studies also included an extension period30 or randomization arms31,32 in which patients could receive hydrochlorothiazide or irbesartan combination therapy; these patients and groups were excluded from this analysis.) Blood pressure was measured with a standard, calibrated mercury sphygmomanometer and analyzed according to standardized protocol. Blood pressure was determined by calculating the mean of 3 to 5 measurements taken 1 minute apart, following 5 to 10 minutes of rest in the seated position at 24±3 hours after the previous day’s morning dose. Only the baseline (end of placebo lead-in period) and final BP measurements at the completion of the double-blind period were used in the current analysis.

Safety monitoring at each clinic visit (every 2-6 weeks) included evaluation by open-ended questioning regarding health status. Investigators recorded any change in health status as well as specific information on onset, severity, cause, treatment required, and resolution of any adverse event on a standardized case-report form. Accordingly, headache was detected by spontaneous adverse event reporting and relied on patient recall. Furthermore, reporting of headache as an adverse event captured data on new or worsening headache only; data on stable headache were not captured. Physical examinations, electrocardiograms, and tests on blood and urine samples were also performed individually.

STATISTICAL ANALYSIS

In this pooled analysis, the relationship between headache and age, sex, baseline diastolic and systolic BP, last recorded diastolic and systolic BP, and active drug treatment was analyzed by logistic regression. A backward elimination method was employed to determine the relative importance of each factor to headache incidence. P<.05 was considered statistically significant.

RESULTS

Among patients who received placebo alone, sex (female) and last measured diastolic BP were significant predictors of headache incidence during the double-blind period. Figure 1 shows the cumulative incidence of new or worsening headache in men (18%) and women (29%) (P<.001 vs men in logistic regression). The last diastolic BP measurement of less than 90 mm Hg, 90 to 99 mm Hg, and 100 mm Hg or greater was associated with headache in 19%, 21%, and 27% of cases, respectively (P=.03 in logistic regression) (Figure 2). There was no observed relationship between the last systolic BP measurement and headache incidence. There was a statistically significant trend toward decreasing frequency of headache with increasing age (P=.02 in logistic regression) (Figure 3). Table 1 summarizes odds ratios for headache among patients who received placebo by age, sex, and last diastolic BP measurement. Similar trends were also seen among patients who were treated with irbesartan.

In both the placebo and irbesartan groups combined, the mean BP after randomization was 142/92 mm Hg and the baseline BP was 154/101 mm Hg. When all patients were analyzed, the same factors remained predictive of headache incidence, namely sex (female) and the last diastolic BP measurement. Increasing age was also significantly correlated with a decreasing incidence of headache (Table 2). Active drug treatment was a significant independent predictor of decreased headache. Patients receiving irbesartan had a significantly lower incidence of headache compared with patients receiving placebo (17% vs 22%; P=.003).
The following statements from the 14th edition of *Harrison’s Principles of Internal Medicine* succinctly present the “classic” opinion about the relationship between mild-to-moderate hypertension and headache:

Most patients with hypertension have no specific symptoms referable to their blood pressure elevation... Though popularly considered a symptom of elevated arterial pressure, headache is characteristic only of severe hypertension...30 Similarly, the 15th edition of *The Merck Manual of Diagnosis and Therapy* states that:

Primary hypertension is asymptomatic until complications develop... Dizziness, flushed face, headache, fatigue, episcleritis, and nervousness are not caused by uncomplicated hypertension...31

There are findings, however, including those from the current analysis, that indicate a more direct association between headache and hypertension, ie, that patients with hypertension who receive treatment have a lower incidence of headache than those who do not receive treatment.11,12 In the present analysis, patients with mild-to-moderate hypertension (diastolic BP, 95-110 mm Hg) who were treated with irbesartan had a significantly reduced incidence of headache compared with patients receiving placebo (17% vs 22%; \( P=.04 \) in logistic regression). In fact, the magnitude of the effect could be greater since the studies were not designed to capture headache specifically. Additionally, a potentially greater effect from treatment might be realized at doses higher than the 75- to 150-mg oral dose of irbesartan that was used in most of the 7 studies.

In the current analysis, the incidence of headache was related to diastolic but not to systolic BP. However, our analysis used only the last recorded BP measurement. More comprehensive measurements, such as ambulatory BP data, could be more effective in identifying an independent relationship between systolic BP and headache.
The findings of the current analysis agree with the findings of other studies, indicating that a pharmacologic reduction in BP may result in improved quality of life and a reduced incidence of headache. Cooper et al studied 11,710 patients with newly diagnosed or poorly controlled hypertension (seated diastolic BP of 95-120 mm Hg). Following a 2-week washout period, patients received treatment with an ACE inhibitor. Prior to treatment with the ACE inhibitor, the highest prevalence of headache was noted in the previously untreated group, which also had the highest BP at baseline. Throughout the trial, headache incidence was related to increasing levels of BP for both diastolic and systolic BP. During treatment with the ACE inhibitor, the overall frequency of reports of headache was lower, but the same relationship was observed. The Treatment of Mild Hypertension Study (TOMHS), which included 902 men and women with borderline hypertension (average baseline BP of 140/91 mm Hg), found a nonsignificant trend toward a reduction in the incidence of headache among patients receiving treatment compared with those receiving placebo.

More recently, the Hypertension Optimal Treatment (HOT) Study found that intensive BP lowering was associated with improved quality of life. Despite the aggressive use of antihypertensive agents, a study of patients participating in the HOT Study (n=610) demonstrated that intensive BP lowering improved quality of life and significantly reduced the incidence of headache. Furthermore, 2 self-administered questionnaires—the Psychological General Well-Being Index and the Subjective Symptoms Assessment Profile—indicated that the lower the diastolic BP achieved, the greater the improvement in well-being reported by patients. More intensive antihypertensive therapy was also associated with a significant reduction in the incidence of headache. In the HOT Study, 18,790 patients with hypertension (mean diastolic BP of 105 mm Hg) were randomized to 1 of 3 target BP groups (≤90, ≤85, and ≤80 mm Hg). In the HOT Study, the incidence of headache was reduced in all target groups (P<.001) and was associated with an elevated BP rather than with adverse events resulting from treatment. Although the findings of the current study are generally consistent with the overall results of the HOT Study and TOMHS, it included additional analyses of the relationship between BP and headache. It used a multivariate method to control for the effects of age and sex, it differentiated diastolic and systolic BP in terms of their ability to predict the incidence of headache, and it identified a significant relationship between diastolic BP while receiving treatment and new or worsening headache in patients receiving placebo only.

In the current studies, the relationship between headache and BP may have been more easily identified because of the excellent tolerability profile of irbesartan therapy. Irbesartan therapy has been shown to have a tolerability profile that is comparable with placebo, with no relationship between irbesartan dose and the overall incidence of adverse events or adverse drug events. With other agents, a more confusing picture may emerge in analyzing adverse event reports, and the adverse effects of hypertension may be difficult to separate from the adverse effects of the antihypertensive agent, particularly as the doses are likely to be higher among patients with higher levels of BP.

The reduction in the incidence of headache with irbesartan therapy may have important implications for the clinical use of ARBs. Classes of antihypertensive agents that are thought to be more tolerable, such as ACE inhibitors, are associated with lower rates of discontinuation from therapy compared with agents that are thought to be less tolerable, such as calcium channel blockers and diuretics. Although long-term, large-scale, comparative studies evaluating discontinuation rates with ARBs are lacking, the superior tolerability of these agents may translate into improved quality of life and, consequently, into improved compliance and long-term BP control.

**CONCLUSIONS**

In this pooled analysis of 7 double-blind, placebo-controlled trials of irbesartan therapy, the incidence of headache was directly associated with the level of attained diastolic BP. Factors predictive of increased headache incidence were sex (female), younger age, and receiving placebo. These data indicate that treatment with irbesartan lowered the incidence of headache. Thus, mild-to-moderate hypertension may not be an asymptomatic condition; furthermore, reduction of BP with irbesartan therapy is associated with a reduced incidence of headache. The results of the analysis suggest that physicians should take patient reports of headache seriously and take steps to aggressively reduce BP, preferably with agents that have superior tolerability profiles, to improve overall quality of life.

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Dr Smith has been an investigator in clinical trials sponsored by Bristol-Myers Squibb Co, Princeton, NJ, and Dr Hansson has been a consultant to Bristol-Myers Squibb Co.

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