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Isradipine Twice Daily Lowers Blood Pressure Over 24 H

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The objective of this study was to compare the effects of isradipine and placebo on blood pressure (BP) at the end of the dosing interval ('trough'). Following a three-week placebo period, 187 patients who had previously shown a response to treatment with isradipine (based on office BP measurements) were randomized to double-blind treatment with 2.5 mg isradipine twice daily or placebo for six weeks. Four of these patients withdrew from the study during the double-blind phase because of adverse events (one taking isradipine and three taking placebo). Blood pressure during the double-blind study was always measured 12 h after drug administration (trough values). The rate of normalization [defined as diastolic BP (DBP) ≤ 90 mm Hg] was 52/96 (54%) in the isradipine-treated group compared with 30/87 (33%) in the placebo group. A further 12/96 (12%) patients taking isradipine showed a fall in DBP of ≥10 mm Hg, although their DBP was still not < 90 mm Hg, compared with 5/87 (6%) patients receiving placebo. This difference was statistically significant ($P = .003$). Thus, isradipine in a dose of 2.5 mg twice daily lowers blood pressure over 24 h. Am J Hypertens 1991;4:131S-134S

KEY WORDS: **Isradipine, trough blood pressure, duration of action, placebo.**

Isradipine is a dihydropyridine characterized as a potent inhibitor of calcium channel influx with a high specificity for vascular smooth muscle as opposed to cardiac muscle. In anesthetized cats and dogs, isradipine produces vasodilatation and increased coronary, cerebral, and skeletal blood flows. Cardiac output and myocardial contractility are increased whereas myocardial oxygen consumption is reduced. Isradipine has been evaluated in several randomized, double-blind, parallel-group trials in the treatment of patients with essential hypertension. These trials used doses of 1.25 to 10 mg twice daily. The results of these trials indicated that 1.25 mg twice daily is effective in reducing blood pressure and that a dose-response relationship applies with doses up to 7.5 mg twice daily. No additional antihypertensive benefit was apparent with doses above 7.5 mg twice daily. Thus, using doses higher than those required to lower blood pressure served only to increase the frequency and/or severity of side effects.

Most of these results, however, were based on blood pressure measurements taken 4 to 6 h after drug administration (office measurements, as is the usual practice). Relatively few data are available from studies in which blood pressure was measured at the end of the 12 h dosing interval (trough measurements), although what data there are did show that the therapeutic effect lasts for 12 h with isradipine at a dose of 2.5 mg twice daily. Because the inclusion of patients not responding to treatment was thought to make the evaluation of the duration of effect less accurate, the study was carried out double-blind and placebo-controlled in patients who had already shown a clinical response to 2.5 mg isradipine twice daily.

PATIENTS AND METHODS

Patient Selection The following were the criteria for entry into the placebo phase of the study. Patients had

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to have received treatment with 2.5 mg isradipine twice daily as monotherapy for at least four weeks and had to have a documented diastolic blood pressure (DBP) <95 mm Hg or a reduction in DBP of at least 10 mm Hg during the isradipine treatment. Patients were to show no clinically relevant abnormal laboratory test results. To qualify for entry into the double-blind phase, patients were to have a resting, sitting DBP of at least 95 mm Hg, but not >115 mm Hg, at the end of the placebo phase.

Study Design A multicenter, double-blind, parallel-group, placebo-controlled study design was used. Total duration of the study per patient was nine weeks as follows: weeks 1 to 3, placebo wash-out phase; weeks 4 to 9, 2.5 mg isradipine twice daily or placebo. Patients whose response to isradipine had been demonstrated in a preceding clinical study directly entered the placebo phase of the comparative study. Patients who had not already shown a response with 2.5 mg isradipine twice daily initially received placebo for two weeks to establish the diagnosis of hypertension; this was followed by 2.5 mg isradipine twice daily for four weeks to establish the response to treatment before entering the placebo phase.

Patients eligible for the study received one placebo tablet twice daily (at 9 AM and at 9 PM) for three weeks. If, after three weeks of placebo, the blood pressure had still not reached the level required for inclusion, the placebo period was extended by two weeks to a maximum total duration of five weeks. Patients who conformed to the admission criteria at the end of the placebo phase were randomized to receive treatment with either 2.5 mg isradipine or placebo twice daily. This was given for six weeks.

Blood Pressure Measurement Sitting pulse and blood pressure recordings were taken after the patient had been in the clinic for at least 20 min and had rested in a sitting position for at least 3 min. Systolic blood pressure (SBP) was recorded with a mercury sphygmomanometer at Korotkoff phase I and DBP was recorded at Korotkoff phase V. Throughout the study, blood pressure measurement for each patient was performed with the same cuff size (appropriate to the circumference of the arm), from the same arm and, if possible, by the same investigator.

For the examinations at the end of the placebo period and after four and six weeks of the double-blind treatment, the patient attended the clinic in the morning between 8:30 and 9:30 AM, 12 h ($\pm$30 min) after the previous evening medication at 9 PM. Blood pressure was measured (trough values), followed by administration of the morning dose of isradipine. The effect on blood pressure at peak was not recorded. If, on the days of these three visits the morning dose had inadvertently been taken before attending the clinic, or the previous evening dose had been taken more than 13 or less than 11 h before, the examination was postponed until the next day to ensure that true trough values were obtained.

Statistical Methods The null-hypothesis to be tested was: there are no differences in trough blood pressure-lowering effects between treatment with 2.5 mg isradipine twice daily and placebo twice daily after six weeks of treatment. The Wilcoxon signed-rank test was used to compare the changes from baseline within each treatment group, and the U-test according to Mann-Whitney-Wilcoxon was used to assess the changes from baseline between the two treatment groups.

In addition, a categorical analysis of the blood pressure results in evaluable patients was also conducted, using the following categories of DBP response at week 9 (six weeks of treatment) and the minimum discrimination statistic (2 $\hat{I}$ test): 1. $\leq$90 mm Hg; 2. $>$90 mm Hg, but with reduction $\geq$10 mm Hg; 3. $>$90 mm Hg, but with reduction $<$10 and $\geq$5 mm Hg; 4. $>$90 mm Hg and with reduction $<$5 mm Hg.

RESULTS

A total of 188 patients were recruited into the study. One withdrew during the placebo phase because of gastrointestinal bleeding, leaving 187 patients to be randomized. Four patients discontinued the double-blind treatment because of adverse events. The placebo group comprised 90 patients (46 men, 44 women; mean age 50 years, range 27 to 64 years), and the active treatment group included 97 patients (53 men, 44 women; mean age 49 years, range 23 to 65 years). One hundred and ten patients received isradipine in the four-week selection phase; the remaining 77 patients had already received isradipine for periods of up to 127 weeks before entering the study.

Table 1 shows the average blood pressure values for the 183 patients who completed the double-blind study. The two treatment groups were comparable for both SBP and DBP at baseline, and both groups showed a statistically significant reduction in DBP after four and six weeks of treatment. However, the isradipine-treated patients showed a further fall in blood pressure between the fourth and sixth weeks of treatment whereas, in the placebo-treated patients, there was no relevant change in blood pressure after the fourth week of treatment. The reduction in DBP from baseline was statistically significantly greater ($P = .001$) in the isradipine-treated patients after six weeks than in the placebo-treated patients.

The percentage of patients achieving a supine DBP of 90 mm Hg or less was greater (52/96, 54%) in the active-treatment group than in the placebo-treated group (30/87, 33%). Also greater was the number of patients who did not attain a DBP of 90 mm Hg or less, but did

TABLE 1. AVERAGE BLOOD PRESSURE VALUES AND NORMALIZATION RATE BEFORE, DURING, AND AFTER TREATMENT WITH 2.5 MG ISRADIPINE OR PLACEBO TWICE DAILY

	Placebo		Double-blind Phase	
	Before†	After‡	4 Weeks‡	6 Weeks‡
Systolic blood pressure (mm Hg)				
Isradipine	142 ± 12	158 ± 12	151 ± 15	148 ± 14
Placebo	144 ± 14	160 ± 14	153 ± 18	153 ± 17
Diastolic blood pressure (mm Hg)				
Isradipine	88 ± 6	102 ± 5	94 ± 9	92 ± 9
Placebo	88 ± 6	102 ± 5	96 ± 8	96 ± 9
Responder rate§				
Isradipine (n = 96)				64/96 (66%)
Placebo (n = 87)				35/87 (39%)

*** between isradipine 158 ± 12 and isradipine 151 ± 15; *** between isradipine 158 ± 12 and isradipine 148 ± 14; NS between isradipine 151 ± 15 and placebo 153 ± 18; * between isradipine 148 ± 14 and placebo 153 ± 17; *** between placebo 160 ± 14 and placebo 153 ± 18; *** between placebo 160 ± 14 and placebo 153 ± 17; *** between isradipine 102 ± 5 and isradipine 94 ± 9; *** between isradipine 102 ± 5 and isradipine 92 ± 9; NS between isradipine 94 ± 9 and placebo 96 ± 8; *** between isradipine 92 ± 9 and placebo 96 ± 9; *** between placebo 102 ± 5 and placebo 96 ± 8; *** between placebo 102 ± 5 and placebo 96 ± 9

† *'Office' blood-pressure measurement.*
‡ *Blood pressure measured 12 h after dosage.*
§ *Response = diastolic blood pressure ≤ 90 mm Hg or a fall of ≥ 10 mm Hg.*
* P = .034; *** P ≤ .001; *NS = not significant.*

achieve a reduction of at least 10 mm Hg in DBP [12/96 (12%) *v* 5/87 (6%)]. Thus, the total number of patients with either a normalization of blood pressure or a good blood pressure response was 64/96 (66%) in the isradipine group and 35/87 (39%) in the placebo group. The difference in categorical response between the two groups was statistically significant ($P = .003$).

The most common adverse event reported during the study in both treatment groups was headache (six occurrences with isradipine and nine with placebo). Although the percentage of all patients entering the double-blind study who reported adverse events was similar for both treatment groups (16/97, 16% with isradipine and 13/90, 14% with placebo), the total number of adverse events was greater in those receiving isradipine (n = 26) than placebo (n = 18). There were two reports of flushing and three of edema in patients receiving active treatment, but no reports of either in patients taking placebo. Four patients discontinued the double-blind treatment because of adverse events: one because of edema (isradipine) and three because of headache (placebo).

DISCUSSION

The blood pressure-lowering effect of isradipine under normal clinic conditions is well established.[1-5] In those studies, however, blood pressure was measured whenever the patient attended the clinic, and therapy was taken twice daily, once in the morning and again in the evening. Thus, the blood pressure measurements reflected the effects of the drug between its peak period and its trough. This is the blood pressure value generally used by physicians in their usual care of patients, but it does not clearly establish that the drug has a blood pressure-lowering effect that persists throughout the dosing interval. That the effect is still present at the end of the 12 h dosing interval has been shown in other studies.[6,7] Those studies were, however, either single-blind[6] or were carried out in elderly patients.[7]

The study reported here was performed to assess the 12 h duration of action using a placebo-controlled study design in younger patients. The results showed a statistically significantly greater lowering of DBP with isradipine than with placebo. In this study, therapy was given at 9 PM on the evening before the next morning's clinic visit, which was at 9 AM ± 30 min. Thus, the blood pressure values recorded were true trough values and the blood pressure-lowering effect was that at the end of the dosing interval.

It can, therefore, be concluded that the blood pressure-lowering effect of isradipine is present throughout the dosing interval and that a twice-daily regimen is appropriate. The fact that the blood pressure fell in the isradipine-treated patients between the fourth and sixth weeks of treatment while remaining stable, or even rising slightly, in the placebo-treated patients is further evidence that the reduction in blood pressure is an effect of the treatment and not a spontaneous change. This is also an indication that the effect of isradipine is not maximum at, for example, two weeks of treatment and,

therefore, conclusions as to the magnitude and duration of antihypertensive effect based on studies in which the effects are assessed after only two weeks are of limited value.

Although the study was not intended to assess the tolerability of isradipine but, rather, to examine the duration of action in patients who had already shown a response to treatment, these results also demonstrate that isradipine is well tolerated. Although the number of adverse events (but not the number of patients reporting adverse events) was higher in the isradipine-treated patients than in the placebo-treated patients, the overall safety was adjudged by the investigators to be the same for both treatments.

REFERENCES

1. Sundstedt CD, Rüegg PC, Keller A, Waite R: A multicenter evaluation of the safety, tolerability and efficacy of isradipine in the treatment of essential hypertension. Am J Med 1989;86(suppl 4A):98-102.
2. Shepherd AMM, Carr AA, Davidov M, et al: Efficacy and safety of isradipine in hypertension. J Cardiovasc Pharmacol 1989;13:580-585.
3. Simonsen K, Sundstedt CD: Dose-response relationship and incidence of adverse drug reactions with isradipine in patients with essential hypertension. Am J Med 1989; 86(suppl 4A):91-93.
4. Kirch W, Burger KJ, Weidinger G, Welzel D: Efficacy and tolerability of the new calcium antagonist isradipine in essential hypertension. J Cardiovasc Pharmacol 1990: 15(suppl 1):S55-S59.
5. Miller H: Isradipine: overall clinical experience in hypertension in the United States. J Cardiovasc Pharmacol 1990;15(suppl 1):S60-S64.
6. De Keyser P, Bouvé J, Clement D, et al: Isradipine in essential hypertension: the Belgian General Practitioners' Study. Am J Med 1989;86(suppl 4A):103-109.
7. The British Isradipine Hypertension Group: Evaluation of the safety and efficacy of isradipine in elderly patients with essential hypertension. Am J Med 1989;86(suppl 4A):110-114.