The antihypertensive efficacy of losartan and amlodipine assessed with office and ambulatory blood pressure monitoring

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Abstract

Background: Losartan potassium is a recently marketed angiotensin II receptor antagonist. Previous studies have suggested that its full antihypertensive effect may be delayed for up to 12 weeks. The authors compared the antihypertensive efficacy and tolerability of losartan at 6 and 12 weeks with those of amlodipine besylate, a commonly used calcium antagonist.

Methods: This multicentre, randomized, double-blind clinical trial studied 302 patients with mild or moderate hypertension in 1995. Of the 302, 97 also underwent ambulatory blood pressure monitoring (ABPM). After a 4-week placebo run-in period, the patients were randomly assigned to group A, B or C for 12 weeks. Those in groups A and B began treatment with losartan at 50 mg/d, and those in group C began with amlodipine at 5 mg/d. If the blood pressure remained uncontrolled after 6 weeks, subjects in group A had their losartan dose doubled (to 100 mg/d), those in group B were given hydrochlorothiazide (12.5 mg/d) in addition to the losartan, which remained at 50 mg/d, and patients in group C had their amlodipine dose doubled (to 10 mg/d).

Results: At 12 weeks all 3 regimens reduced office-recorded diastolic blood pressure (DBP) with the patient sitting. The mean reduction in group A was 8.7 mm Hg (95% confidence interval [CI] 7.3 to 10.1) ($p < 0.001$), in group B 12.5 mm Hg (95% CI 11.0 to 14.0) ($p < 0.001$) and in group C 12.9 mm Hg (95% CI 11.4 to 14.5) ($p < 0.001$). Losartan alone lowered sitting DBP to a lesser degree than the other 2 treatments ($p < 0.01$). In contrast, ABPM readings, whether 24-hour, daytime or nighttime, were not different among the regimens. Comparison of the results at 6 weeks yielded similar findings. Adverse effects were uncommon and were not different among the groups, with the exception of ankle edema, which was more frequent in group C.

Interpretation: Losartan alone reduces both office and ABPM readings. The observed changes in office-recorded sitting DBP suggest that losartan is less effective than amlodipine or the combination of losartan and hydrochlorothiazide, but ABPM did not confirm this difference. Perhaps changes in office readings measure different attributes of a drug than does ABPM.

Résumé

Contexte : Le losartan potassique est un antagoniste des récepteurs de l'angiotensine II qui vient d'arriver sur le marché. Des études antérieures ont indiqué que son effet antihypertenseur total peut être retardé de jusqu'à 12 semaines. Les auteurs ont comparé l'efficacité du losartan contre l'hypertension et sa tolérabilité à 6 et 12 semaines à celles du bésylate d'amlodipine, un inhibiteur calcique répandu.

Méthodes : Cette étude clinique multicentrique randomisée à double insu réalisée en 1995 a porté sur 302 patients atteints d'hypertension bénigne ou moyenne. Sur les 302 patients, 97 ont aussi fait l'objet d'une surveillance ambulatoire de la tension artérielle (SATA). Après avoir reçu un placebo pendant une période

Evidence

Études

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See related article page 488

de rodage de quatre semaines, les patients ont été répartis au hasard pour 12 semaines en trois groupes (A, B et C). Les patients des groupes A et B ont commencé le traitement par le losartan à 50 mg/j, et ceux du groupe C, par l'amlodipine à 5 mg/j. Si la tension artérielle n'était toujours pas contrôlée après les six premières semaines, on doublait la dose de losartan administrée aux sujets du groupe A (à 100 mg/j), on administrait de l'hydrochlorothiazide (12,5 mg/j) aux patients du groupe B en plus du losartan (toujours à 50 mg/j), et on doublait la dose d'amlopidine administrée aux patients du groupe C (à 10 mg/j).

Résultats : À 12 semaines, les trois traitements ont réduit la tension artérielle diastolique (TAD) du patient en position assise, prise au cabinet des médecins. La réduction moyenne a été de 8,7 mm Hg (intervalle de confiance [IC] à 95 % de 7,3 à 10,1) ($p < 0,001$) chez les sujets du groupe A, de 12,5 mm Hg (IC à 95 % de 11,0 à 14,0) ($p < 0,001$) chez ceux du groupe B et de 12,9 mm Hg (IC à 95 % de 11,4 à 14,5) ($p < 0,001$) chez ceux du groupe C. Le losartan seul a réduit la TAD en position assise dans une proportion moindre que les deux autres traitements ($p < 0,01$). Par ailleurs, les lectures SATA de 24 heures, le jour ou la nuit, n'étaient pas différentes entre les traitements. La comparaison des résultats à six semaines a produit des constatations semblables. Les effets indésirables ont été rares et n'ont pas différé entre les groupes, sauf dans le cas de l'œdème de la cheville, plus fréquent chez les sujets du groupe C.

Interprétation : Le losartan à lui seul réduit les lectures prises au cabinet du médecin et en SATA. Les changements observés de la TAD en position assise enregistrée au cabinet du médecin indiquent que le losartan est moins efficace que l'amlodipine ou que la combinaison losartan et hydrochlorothiazide, mais la SATA n'a pas confirmé cette différence. Les changements des lectures prises au cabinet du médecin mesurent peut-être des qualités des médicaments différentes de celles que mesure la SATA.

The goal of antihypertensive drug therapy is to prevent complications of hypertension. Diuretics and β-adrenergic antagonists have been shown to reduce the incidence of stroke and, to a lesser extent, myocardial infarction and renal failure.[1,2] There is a perception among both physicians and patients that these agents commonly cause adverse effects.[3,4] In particular, many physicians are concerned about "metabolic side effects" — deterioration of glycemic control and adverse changes in the lipid profile.[5,6]

Calcium antagonists enjoy a reputation for efficacy and tolerability despite recent concern regarding their efficacy in preventing myocardial infarction in patients with hypertension.[7] They can be used in patients with diabetes mellitus, hyperlipidemia, coronary artery disease, peripheral vascular disease, asthma or gout. Amlodipine besylate, a long-acting dihydropyridine calcium antagonist, is indicated for both hypertension and angina. Recent studies suggest that, unlike older, short-acting dihydropyridines, amlodipine is safe in patients with heart disease.[8] After oral dosing, peak plasma levels are achieved in 6 to 12 hours, and the terminal half-life is 35 to 50 hours.[9]

Losartan potassium is an angiotensin II type 1 receptor antagonist. After oral dosing, plasma concentrations peak at 1 hour, and the half-life of elimination is only 2 hours. Despite this, single daily doses of losartan appear to lower blood pressure throughout the day, perhaps owing to the formation of a more slowly excreted, active metabolite.[10] Currently, losartan is indicated for hypertension, although it may be useful in congestive heart failure as well.[11] In clinical trials the effect of losartan emerges slowly. In one such trial extended-release felodipine reduced blood pressure to a greater extent than losartan at 6 weeks, but by 12 weeks there was no difference in response.[12]

Adding small doses of hydrochlorothiazide to losartan increases the antihypertensive efficacy of the latter drug.[13] In many studies hydrochlorothiazide was added at 4 to 6 weeks for patients not responding to losartan alone.[13,14] It is arguable that the full effect of losartan monotherapy takes longer to occur and that adding a second drug before 12 weeks is unnecessary. In the only published comparison of losartan and amlodipine, patients who did not respond to losartan were given hydrochlorothiazide after only 4 weeks.[14]

We therefore designed a study to compare the effects, over 12 weeks, of losartan alone, losartan with hydrochlorothiazide, and amlodipine in patients with mild or moderate essential hypertension. In addition to the standard measurement of blood pressure, we performed ambulatory blood pressure monitoring (ABPM) in one-third of the patients. In ABPM a portable, automatic device is used to obtain and store blood pressure readings at predetermined times throughout a given period, usually 24 hours. The development of ABPM has provided an accurate means to as-

sess both the efficacy[15] and the duration of action[16] of antihypertensive agents. The large number of readings obtained (usually over 50) and the avoidance of time and observer bias allow accurate assessment of blood pressure throughout the day. We were therefore able to compare drug regimens using 2 complementary techniques.

We also measured changes in blood chemistry likely to reflect metabolic abnormalities of concern. Finally, we assessed drug tolerability by not only asking open-ended questions but also by administering a validated questionnaire, designed to assess quality of life in cardiovascular patients, at intervals throughout the trial.

Methods

Study design

The Canadian Cozaar Hyzaar Amlodipine Trial used a multicentre, randomized, 3-group, parallel, titration-to-goal, double-blind, double-dummy design whose main outcome variable was the change in diastolic blood pressure (DBP), with the patient sitting, after 12 weeks of therapy. The sample size of 85 patients per group was calculated to provide 95% power to detect a difference of 5 mm Hg, at a significance level (in a 2-tailed test) of 0.05, between the 3 treatment regimens, assuming a decrease of 10 mm Hg and a standard deviation of 7 mm Hg. We planned to enrol 100 patients per treatment arm, to allow for dropouts.

The protocol and consent form were approved by the institutional review boards of each of the 21 participating centres, and each patient gave written informed consent. After a 4-week placebo run-in period, eligible patients at each centre were randomly assigned (by means of computer-generated random numbers tables) to groups A, B or C for 12 weeks. Those in groups A and B began treatment with losartan at 50 mg/d, and those in group C began with amlodipine at 5 mg/d. If the sitting DPB remained above 90 mm Hg after 6 weeks, subjects in group A had their losartan dose doubled (to 100 mg/d), those in group B were given hydrochlorothiazide (12.5 mg/d) in addition to the losartan, which remained at 50 mg/d, and patients in group C had their amlodipine dose doubled (to 10 mg/d), for the remaining 6 weeks. Losartan and hydrochlorothiazide were dispensed as tablets, and amlodipine tablets were inserted into a soft gelatin capsule. Patients were asked to take both a tablet (containing losartan, losartan plus hydrochlorothiazide, or placebo) and a capsule (containing amlodipine or placebo) after breakfast. Adherence was monitored by means of pill counts. A substantial subgroup of patients underwent 24-hour ABPM.

Secondary outcome variables included the change in systolic blood pressure (SBP) with the patient sitting, change in standing SBP and DBP, change in blood pressure after 6 weeks of treatment, clinical and laboratory adverse effects, and change in quality of life, as assessed by a questionnaire.

Patients

Men and women aged 18 to 75 years with essential hypertension were considered for entry. Exclusion criteria included recent (within 6 months) myocardial infarction or stroke, serious concomitant illness, renal or hepatic dysfunction, uncontrolled diabetes (fasting blood glucose level greater than 11.1 mmol/L) or known intolerance of any of the study medications. Women of childbearing potential were also excluded. Other drugs with measurable effects on cardiovascular function were restricted for the duration of the study.

Protocol

After giving informed consent, patients were asked to stop all current antihypertensive therapy. One to 3 weeks later they were reassessed. If the sitting DBP was 90 to 115 mm Hg, the patient was given placebo tablets and capsules and was evaluated after a further 2 and 4 weeks. If the sitting DBP was 95 to 115 mm Hg at both these visits and the difference in the reading between the visits was 7 mm Hg or less, the patient was randomly assigned to 1 of the 3 active treatment groups. Early entry was allowed for patients whose sitting DBP was 110 to 115 mm Hg, confirmed after 3 days.

Clinical and laboratory evaluations were performed at study entry and at 3, 6, 9 and 12 weeks after active treatment was started. Titration to a more potent regimen could occur, if necessary, only after the week 6 visit. At each visit, weight, pulse rate and blood pressure were measured by methods conforming to Canadian Hypertension Society guidelines.[17] The average of 3 readings obtained after 5 minutes of rest was used as the blood pressure reading for that visit. Standing blood pressure was taken as the average of 3 readings obtained at 1-minute intervals, starting 2 minutes after standing. A response to treatment was defined as a sitting DBP of 90 mm Hg or less, or a decrease of 10 mm Hg in sitting DBP.

Ambulatory blood pressure monitoring

ABPM was carried out in all patients who had been assigned to a treatment group at 7 centres (97 patients). In these centres each patient was assessed with ABPM as well as the regular protocol. Using the Spacelabs 90207 device (Spacelabs Medical Inc., Redmond, Wash.), the investigators completed 24-hour blood pressure scans, during a regular working day, following the placebo run-in

period and after 6 and 12 weeks of active drug therapy. Automatic readings were obtained at 20-minute intervals between 6 am and 10 pm (daytime) and at 30-minute intervals between 10 pm and 6 am (nighttime). The accuracy of each monitor was checked against a conventional mercury sphygmomanometer with a T tube connector. The mean of 3 conventional readings and the mean of 3 automated readings were required to be within 5 mm Hg of each other. Criteria were established before the study for acceptance of an ABPM report: there had to be at least 24 hours of recording following administration of a dose, at least 51 valid readings (80% of total possible readings) and less than 2 consecutive hours of missing data. If an ABPM report was not satisfactory, the procedure was repeated within 72 hours.

Adverse effects

The occurrence of adverse effects was determined at each visit by asking the open-ended question: "Since we last met, has there been any change in the way you feel?" In addition, a validated 42-item questionnaire assessing 6 domains encompassing 17 symptoms[18] was completed after the initial visit, following the placebo run-in period, and at 6 and 12 weeks after the start of active drug therapy. Each question was followed by a 100-mm visual analogue scale, and the patients were asked to indicate their degree of distress for each symptom on the scale. Laboratory testing, including electrocardiography and chest roentgenography (if deemed necessary), was performed during the placebo run-in period and at intervals throughout the trial.

Statistical analyses

We compared the characteristics and responses of the 3 groups using the χ^2 statistic for dichotomous variables and the Kruskal–Wallis rank-sum test or McCullagh's method for ordered categoric variables. For efficacy analysis, we used an all-patients-treated approach (including all subjects who were assigned to a treatment group and received even 1 dose of active drug). The values obtained at the last visit while receiving active treatment were used for the remaining visits for patients who were withdrawn from the trial. Predetermined subgroup analyses stratified the patients by baseline sitting DBP, severity of hypertension (mild [sitting DBP less than 105 mm Hg] or moderate [sitting DBP 105 to 115 mm Hg]), age (under 65 years v. 65 years or more) and sex. For all variables, treatment and centre were used as main effects in 2-way analysis of variance. If the treatment effect was significant at the 0.05 level, pairwise comparisons were performed. The proportion of patients in each group reporting adverse effects was compared in pairwise fashion with the use of Fisher's exact test.

Results

Enrolment began in March 1995 and ceased on June 30, 1995; the study was completed during 1995. A total of 407 patients were screened to achieve the sample of 302 patients assigned to the treatment groups. The most common reasons for dropout before randomization were sitting DBP under 95 mm Hg or over 115 mm Hg (74 people) and abnormal laboratory test results (15 people).

The baseline characteristics of the entire cohort and of the subgroup that underwent ABPM are shown in Table 1. The groups were well balanced with regard to initial sitting DBP. Although there were a few more patients with moderate hypertension in group B than in group A or C, the difference did not reach statistical significance. In general, this was a healthy population: only 13 had had a myocardial infarction, and none had had a stroke. Most (83%) had been treated with other antihypertensive drugs. About 15% had used β-blockers, 20% diuretics, 30% angiotensin-converting enzyme inhibitors, and 30% calcium antago-

Table 1: Baseline characteristics of patients with essential hypertension randomly assigned to 1 of 3 treatment groups*

	Group A		Group B		Group C	
Characteristic	Total	ABPM	Total	ABPM	Total	ABPM
No. of patients	102	36	97	31	103	30
% male	59.8	47.2	69.1	71.0	64.1	60
Mean age (and SD), yr	54.8 (10)	52.8 (8.9)	52.9 (11)	51.1 (10.3)	54.3 (11)	49.9 (9.3)
% with mild hypertension†	82.4	88.9	72.2	71.0	84.5	90
Mean sitting DBP (and SD), mm Hg	100.9 (4.8)	99.7 (4.0)	101.9 (5.1)	102.1 (4.6)	100.7 (4.7)	100.9 (3.8)
% with prior antihypertensive treatment	81.4		83.5		85.4	
% with previous MI	5.9		1.0		1.0	
% with diabetes mellitus	5.9		6.2		3.9	

Note: ABPM = ambulatory blood pressure monitoring, SD = standard deviation, DBP = diastolic blood pressure, MI = myocardial infarction.
*Group A received losartan potassium, group B received losartan and hydrochlorothiazide, and group C received amlodipine besylate.
†Sitting DBP < 105 mm Hg.

nists (including 7% who had used amlodipine). None had taken losartan. Fifteen patients (5%) had complained of edema or swelling before assignment to a treatment group.

Of the 302 patients 284 (94%) completed the study (Fig. 1). Eighteen patients withdrew because of adverse effects (5 in group A, 4 in group B and 9 in group C). There was no difference between the groups in the proportion who completed the study.

A substantial proportion of patients in each group were given more medication at 6 weeks: 68% in group A, 57% in group B and 50% in group C. There was no difference between the groups in these proportions.

Sitting diastolic blood pressure

The change in sitting DBP over the course of the trial is shown in Fig. 2. All treatments reduced sitting DBP. The degree of blood pressure reduction at 12 weeks with losartan and hydrochlorothiazide (group B) (12.5 mm Hg [95% confidence interval (CI) 11.0 to 14.0]) ($p < 0.001$) and with amlodipine (group C) (12.9 mm Hg [95% CI 11.4 to 14.5]) ($p < 0.001$) was significantly greater ($p < 0.01$) than that with losartan (group A) (8.7 mm Hg [95% CI 7.3 to 10.1]) ($p < 0.001$). Although significantly different, the absolute variation in reduction in sitting DBP between group A and the 2 other groups was only 3.7 mm Hg (95% CI 1.7 to 5.8 mm Hg) and 3.9 mm Hg (95% CI 2.0 to 5.9 mm Hg). There was no difference between groups B and C (95% CI of the difference in change in sitting DBP −1.8 to 2.3). The centre-by-treatment interaction test did not yield significant differences.

A higher proportion of patients in group C (76%) than in group B (65%) or A (53%) responded to treatment (sitting DPB was 90 mm Hg or less, or decreased 10 mm Hg or more) (both $p < 0.01$).

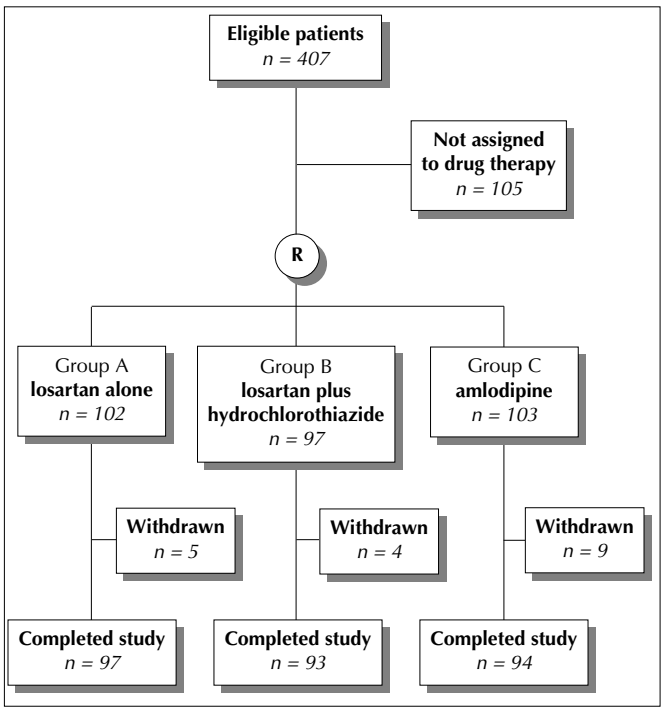

Fig. 1: Numbers of patients at various stages of the Canadian Cozaar Hyzaar Amlodipine Trial. R = randomization.

Other outcome measures

Sitting DBP fell in all groups after 3 weeks of treatment, then stabilized until 6 weeks (Fig. 2). In groups B and C, there was a further decrease between 6 and 12 weeks, likely reflecting the increased medication given to some patients at the titration step. Increasing the dosage of losartan to 100 mg/d in group A produced only a small additional decrease in sitting DBP.

Changes in sitting SBP were similar to those in sitting DBP in all the groups. The reductions in group B (16.7 mm Hg [95% CI 13.8 to 19.6]) and group C (15.1 mm Hg [95% CI 12.5 to 17.8]) were greater than that in group A (11.4 mm Hg [95% CI 9.1 to 13.6]) but were not different from each other.

There was a substantial reduction in standing blood pressure in all groups, but groups B and C showed larger reductions than group A: from baseline values of about 152/102 mm Hg, patients in group A reached 142/94 mm Hg, those in group B reached 136/92 mm Hg, and those in group C reached 138/91 mm Hg.

Changes in body weight over the period of the trial were minor (less than 1 kg) and did not differ between the groups. Likewise, heart rate differed by less than 2 beats/min in all the groups over the course of the study.

Subgroup analyses

Subgroup analyses based on baseline blood pressure, age and sex mirrored those of the main trial. Older pa-

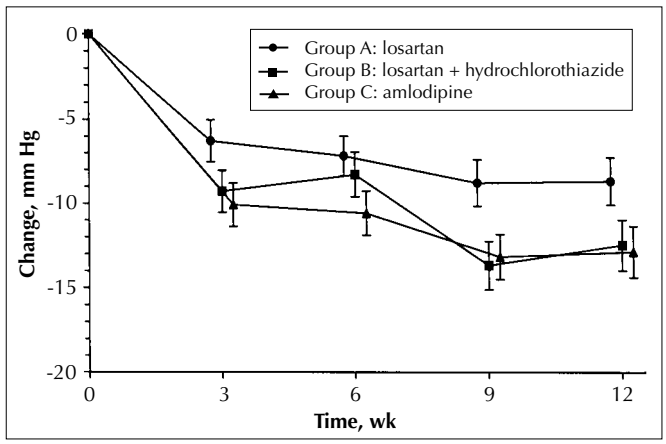

Fig. 2: Change from baseline in sitting diastolic blood pressure over time. Error bars represent 95% confidence interval.

tients and those with higher baseline sitting DBP had greater reductions in sitting DBP. However, adjustment for these did not affect the conclusions: patients in groups B and C had slightly greater reductions in sitting DBP than those in group A.

Ambulatory blood pressure monitoring

The 97 patients assessed with ABPM were representative of the group as a whole (Table 1). As in the main study, the changes in office-recorded sitting DBP after 12 weeks were greater in groups B and C than in group A (Table 2); there was no difference between groups B and C. Sitting SBP was reduced by about the same extent in all 3 groups. The SBP and DBP recorded by ABPM decreased significantly in all 3 groups. In group A the reduction in SBP was numerically greater than the reduction recorded in the office. Significant ($p < 0.001$) and similar reductions were observed in both SBP and DBP obtained during 24-hour monitoring, for all groups (Fig. 3). The ABPM results suggest that the antihypertensive response to the 3 regimens was comparable at 12 weeks.

At the 6-week visit, when 50 mg/d of losartan was being compared with 5 mg/d of amlodipine, ABPM confirmed the antihypertensive effect of both drugs. With losartan alone the reductions in SBP and DBP (and standard deviation [SD]) were 8.8 (SD 8.3) / 5.7 (SD 5.4) mm Hg (n = 67), and with amlodipine 11.3 (SD 9.6) / 6.4 (SD 5.6) mm Hg (n = 30). All of these decreases were statistically significant ($p < 0.001$), but there was no difference between the groups.

Clinical adverse effects

Of the 302 patients 123 (41%) reported an adverse effect before starting active therapy. Headache (40 patients), asthenia and fatigue (16 patients) and upper respiratory tract infection (14 patients) were most common. A total of 199 patients (66%) reported at least one adverse effect while receiving active treatment. They were fairly evenly divided among the groups: 68% of the patients in group A, 62% of those in group B and 68% of those in group C. The adverse effect was determined by the investigator to be possibly, probably or definitely related to the study drug in 96 cases (48%). The proportion of patients experiencing such drug-

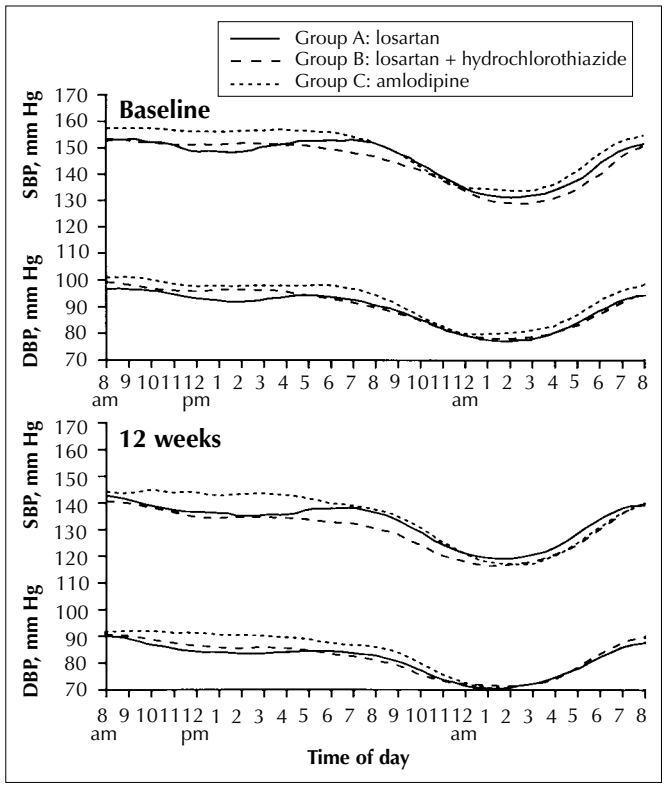

Fig. 3: Mean values of systolic (SBP) and diastolic (DBP) blood pressure recorded over 24 hours by ambulatory blood pressure monitoring at baseline (upper graph) and after 12 weeks of treatment (lower graph).

Table 2: Changes in office-recorded and ambulatory blood pressure (APB)* at 12 weeks

Variable	Change (and SD), mm Hg Group A *n = 36*	Group B *n = 31*	Group C *n = 30*	*p* value†
Systolic				
Office-recorded sitting SBP	−10.0 (9.2)	−16.0 (11.6)	−15.2 (10.9)	0.039
24-hour ABP	−13.1 (9.7)	−14.6 (10.5)	−14.3 (11.3)	NS
Daytime ABP	−13.7 (10.8)	−15.3 (11.6)	−14.3 (10.9)	NS
Nighttime ABP	−11.4 (9.7)	−12.7 (9.5)	−13.9 (12.0)	NS
Diastolic				
Office-recorded sitting DBP	−8.4 (5.9)	−11.9 (5.4)	−12.0 (5.7)	0.021
24-hour ABP	−8.2 (6.1)	−8.5 (6.2)	−8.6 (6.6)	NS
Daytime ABP	−8.9 (7.4)	−9.1 (6.4)	−8.8 (6.3)	NS
Nighttime ABP	−6.3 (6.3)	−7.5 (7.4)	−7.5 (7.5)	NS

Note: SBP = systolic blood pressure, NS = not significant.
*Daytime = 6 am to 10 pm, nighttime = 10 pm to 6 am.
†Comparisons between groups (analysis of variance). In all groups the change from baseline was significant ($p < 0.001$).

related adverse effects was higher in group C (41/103 [40%]) than in group B (23/97 [24%]) ($p = 0.016$); the proportion in group A was 31% (32/102). Nine patients in group C withdrew because of adverse effects, as compared with 4 in group B and 5 in group A. Edema was a complaint of 25% of the subjects reporting adverse effects in group C, substantially higher than the 2% in groups A and B. No other single complaint was more common in any group.

Only 3 serious adverse effects were recorded during the trial: 1 episode of chest pain and 2 myocardial infarctions. All 3 subjects were in group B. None of the events was considered by the investigator to be probably or definitely related to the study drug. The myocardial infarctions occurred after 1 day of therapy, whereas the chest pain episode occurred after 44 days of therapy.

Laboratory adverse effects

Changes in laboratory test results to values outside reference ranges were uncommon considering the large number of patients (302), laboratory visits (5) and tests performed (about 20 per visit). Seven patients in group A, 2 in group B and 6 in group C had such abnormalities. None was serious, and none required withdrawal of the patient from the study. There were no differences in the change in any laboratory test results between the groups.

Symptom questionnaire

Changes from baseline in the severity of symptoms in the various domains were, in general, minor. For example, the questions assessing emotional distress indicated mean values of 18.8 to 20.1 mm during the baseline period and changed by less than 2 mm on the visual analogue scale over the 12-week active-treatment period. In concordance with the open-ended questioning strategy, the questionnaire did reveal a higher rate of complaint due to "swollen ankles" in group C (increase of 19 mm) than in groups A (decrease of 0.18 mm) ($p < 0.01$) and B (decrease of 2.41 mm) ($p < 0.001$). No other changes in symptoms or domains approached statistical significance (Fig. 4).

Interpretation

We found that losartan and amlodipine both reduced sitting DBP and sitting SBP after 6 weeks of therapy. The absolute reduction in sitting DBP was slightly, but significantly, larger with amlodipine. Adding low-dose hydrochlorothiazide to the regimen of patients who did not respond to losartan enhanced the blood-pressure-lowering effect. On the other hand, increasing the dosage of losartan from 50 to 100 mg/d caused little, if any, change in blood pressure over the next 6 weeks. This suggests that, in most patients, 50 mg/d of losartan is the maximally effective dosage. Adding hydrochlorothiazide to losartan produced no deterioration of laboratory measures or untoward change in the quality of life. In general, all regimens were well tolerated. The well-recognized dihydropyridine adverse effect of edema occurred in almost one-quarter of patients receiving amlodipine and led to withdrawal from the study in some cases.

ABPM, performed in a subgroup of patients whose demographic and clinical characteristics were similar to those of the larger group, confirmed the antihypertensive efficacy of all 3 regimens. The modest but statistically significant differences between group A and the 2 other groups in office-recorded readings were not corroborated by ABPM, whether 24-hour, daytime or nighttime. Indeed, analysis of the ABPM data indicated that, after 12 weeks, the 3 regimens reduced SBP and DBP over the entire 24-hour period to an equivalent extent. Even after 6 weeks of treatment the reductions seen with 50 mg/d of losartan and 5 mg of amlodipine were substantial and were not statistically significantly different. Such differences in response to antihypertensive drugs as measured in the office and by ABPM have been reported by other investigators.[19,20] The reasons for the discrepancy are unknown. Es-

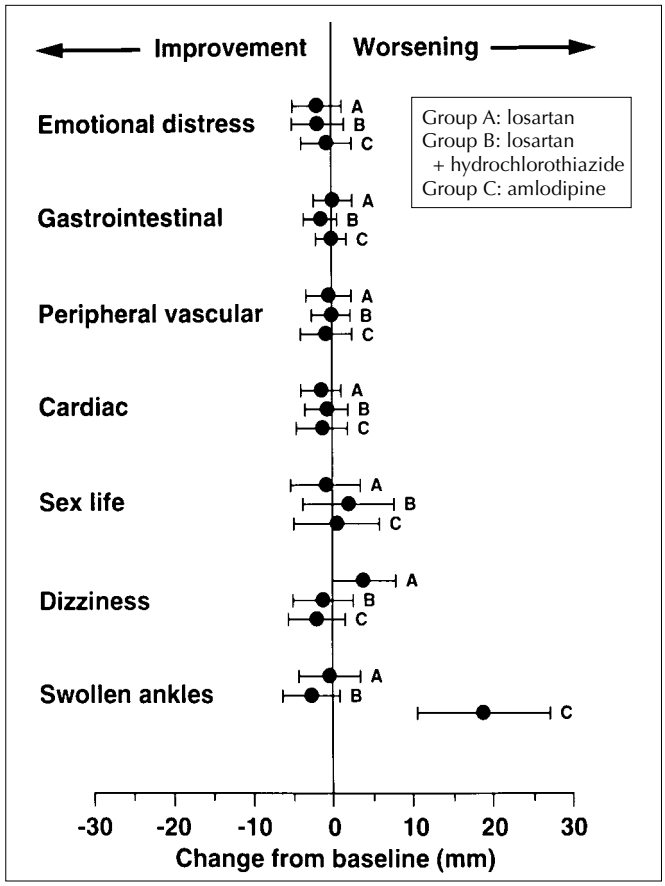

Fig. 4: Subjective change in symptoms as reported on a questionnaire with a visual analogue scale.

sentially, losartan-induced reductions in blood pressure recorded in the office and with ABPM were similar, whereas in the 2 other groups the reductions recorded in the office were greater than those obtained with ABPM. Office-recorded blood pressure readings are often higher than those recorded by ABPM,[15] a phenomenon attributed to the "alerting" response to manual blood pressure determination. The response to drug therapy recorded in the office should then consist of an effect on basal blood pressure and an effect on the alerting response. Perhaps there are differences among drug classes in their relative effects on these responses. Another possibility is a type 2, or β, error: ABPM may not be robust enough to detect a difference. We think this is unlikely. We calculate the power of our study to detect a difference of 5 mm Hg in DBP recorded with 24-hour ABPM to be greater than 80%.

In the final analysis, the relative utility of antihypertensive drugs depends not on the degree to which blood pressure is lowered but, rather, on the reduction of complications relative to the adverse effect profile. Even minor adverse effects can lead patients to stop drug therapy. In the British Medical Research Council trial almost 20% of the subjects withdrew over a 5-year period,[21] and in the more recent Treatment of Mild Hypertension Study 6.1% to 14.5% of patients assigned to receive 1 of 5 active drugs stopped therapy within 4.4 years.[22] Such dropouts increase the cost-benefit of hypertension treatment.[23] Therefore, the assessment of adverse effects, even apparently trivial ones, is of great importance. In our study the overall effect on the quality of life of each regimen was minimal. Indeed, most patients perceived no difference. Nevertheless, some patients (up to 1 in 5) taking amlodipine were troubled by edema, a well-recognized adverse effect of calcium antagonists.

In summary, losartan and amlodipine reduce both ABPM and office-recorded blood pressure while producing few subjective or laboratory adverse effects. Our finding of a discrepancy between the degrees of reduction in blood pressure measured by different techniques merits further investigation.

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