AJH 1992; 5:154-160

An Evaluation of Self-Measured Blood Pressure in a Study With a Calcium-Channel Antagonist Versus a β-Blocker

Thomas Mengden, Benedikt Binswanger, Burkhard Weisser, and Wilhelm Vetter

In recent years self-measurement of blood pressure at home has gained increasing importance but there have been only a few studies comparing casual, ambulatory, and self-measured blood pressure determinations during a single clinical trial. We therefore compared treatment-induced blood pressure-reductions in a double-blind, placebo-controlled, parallel study design with a single morning dose of either 10 mg bisoprolol (n = 26) or 20 mg nitrendipine (n = 27) with casual blood pressure readings in the morning before the dose, ambulatory 24-h monitoring, and self-recorded measurements in the morning before the dose and in the evening.

Mean reductions for systolic and diastolic blood pressure after 4 weeks of therapy were significantly greater for bisoprolol than for nitrendipine. The treatment-induced blood pressure reductions were most pronounced as assessed by casual readings but showed good agreement between casual, ambulatory, and self-measured blood pressure for group comparisons. In some patients, however, marked individual differences between the three methods were observed. Correlation coefficients between ambulatory and self-measured blood pressure were 0.4 for systolic blood pressure ($P < .05$) and 0.6 for diastolic blood pressure ($P < .0005$). Under the conditions of this parallel study design and the usual statistical risks, a difference of 5 mm Hg in diastolic blood pressure can be detected in 118 patients at the clinic, in 70 patients if ambulatory blood pressure is used, or in 56 patients if self-measured blood pressure is used.

In conclusion, bisoprolol was more effective over 24 h than nitrendipine at the doses studied. Furthermore, self-measured blood pressure was suitable for monitoring 24-h efficacy of the two antihypertensive drugs under investigation. Finally, self-measured blood pressure can substantially improve the sensitivity of hypertension trials in comparison to casual readings and therefore reduce the number of patients included. Am J Hypertens 1992;5:154-160

KEY WORDS: **Casual blood pressure, ambulatory blood pressure, self-measured blood pressure, bisoprolol, nitrendipine.**

Accurate blood pressure measurement is essential for the reliable assessment of antihypertensive drugs. In clinical trials of antihypertensive drugs, casual or clinic blood pressure measurement has been routinely used. In recent years alternative methods of blood pressure determination, such as ambulatory 24-h monitoring and self-measurement at home, have gained increasing importance for the practical management of hypertension as well as for clinical trials.[1-3] The reliability of casual blood pressure measurements in determining the effect and duration of antihypertensive therapy may be limited by factors such as blood pressure variability and observer bias.[4-6] In recent years there has been growing awareness that different methods of determining blood

From the Department of Internal Medicine, University Hospital, Zurich, Switzerland.

This article based on data presented at the American Society of Hypertension's annual meeting, May 15 to 18, 1991.

Address correspondence and reprint requests to Prof. W. Vetter, MD, Department of Internal Medicine, University Hospital, Raemistrasse 100 CH-8091 Zurich, Switzerland.

0895-7061/92/$5.00

pressure, such as physician's measurement, ambulatory readings or self-measurement at home, may provide different information regarding blood pressure reduction.[7-8] Some suggested that, by the greater number of readings, ambulatory or self-recorded blood pressure measurements reduced the inherent blood pressure variability and improved the precision and sensitivity of hypertension trials.[9-11] Ménard et al in a recent trial demonstrated that self-measurement can reduce the number of subjects needed to detect a clinically relevant difference in diastolic blood pressure as compared to casual readings.[10]

The value of noninvasive ambulatory blood pressure monitoring in pharmacological studies now seems well established, but there are only limited data available on the usefulness of self-recorded blood pressure measurements during drug trials.[2,4,8-10,13] To our knowledge there have been no published comparisons of the three different noninvasive techniques for measuring blood pressure during a clinical trial.

The aim of the present study was to compare the blood pressure response under the cardioselective β-blocker bisoprolol or the calcium-channel antagonist nitrendipine as observed by casual, ambulatory, and self-recorded blood pressure readings. The antihypertensive efficacy and tolerability of both drugs have been proven in comparative and noncomparative studies, most of them using conventional clinic readings.[15-18] Furthermore, we investigated whether the use of either ambulatory or self-recorded blood pressure measurement can increase the sensitivity of such a study design and reduce the number of patients needed.

METHODS

Patients Patients with mild to moderate essential hypertension were included in the study if they were between 18 and 70 years of age. Women of childbearing potential were excluded. Hypertension was defined as diastolic blood pressure ≥ 95 mm Hg on three occasions during the placebo run-in period.

There were no significant differences between the groups in age, body mass index, smoking history, or alcohol consumption at entry into the trial.

Study Design The study design was a double-blind approach with two parallel, randomized groups. If the patients still fulfilled the entry criteria at the end of the 2 week placebo run-in period, they proceeded to the active treatment phase, taking either 10 mg bisoprolol or 20 mg nitrendipine in a single morning dose for 4 weeks.

The study was approved by the ethical committee of the University of Zurich.

Blood Pressure Measurement All visits were scheduled between 8 and 10 AM and patients were asked not to take their morning medication prior to the blood pressure determination at the clinic on the consultation days. Casual blood pressure was measured after 5 min rest in a sitting position with a mercury sphygmomanometer. The same arm was always used, according to the recommendations of the American Heart Association. We used phase V of Korotkoff sounds as the diastolic blood pressure.[19] Three readings were taken at days 1, 7, and 14 of the placebo period and days 1, 14, and 28 of the active treatment phase. The mean value of the last placebo day and the last treatment day was used for group comparisons. Pulse rate was determined after casual blood pressure reading.

After the casual readings had been taken, ambulatory 24-h blood pressure monitoring was performed during an average working day (day 14 of the placebo period and day 28 of the treatment phase) using the Spacelabs 90202 (Redmond, WA) noninvasive automatic blood pressure recorder.[20,21] Blood pressure and heart rate were measured at preset 20 min intervals from 6 AM to 12 PM and at 60 min intervals at night. Systolic, diastolic blood pressure, mean arterial pressure, and heart rate were stored in the Spacelabs monitor. Artifactual readings (slow cuff inflation, measurement aborted because of low batteries, blood pressure not detected, pressure artifacts) were edited out by the Spacelabs computer program, as were readings below or above given limits (systolic blood pressure <70 or >260 mm Hg, diastolic blood pressure <40 or >150 mm Hg, pulse pressure <20 or >150 mm Hg, heart rate <20 or >200 beats/min). The data were analyzed on an IBM (Armoak, NY) computer.

After sufficient instruction in the correct self-measurement technique by the physician in charge of the trial, each patient was directed to measure blood pressure and heart rate at home in the morning before medication (6 to 8 AM) and in the evening (6 to 8 PM) and to keep a record of all readings. Self-measurement was performed during the whole study period with a previously calibrated semiautomatic, manual, aneroid device with a microphone built into the cuff and acoustic as well as visual identification of Korotkoff sounds (Sysditon, Friedrich Bosch GmbH, Juningen, Germany). In order to avoid an artificial blood pressure increase due to squeezing the sphygmomanometer bulb, each patient was instructed to place the cuff on the nondominant arm and to use the hand of the opposite arm to inflate the cuff while keeping the cuff arm relaxed.

Self-measured morning (6 to 8 AM) and evening (6 to 8 PM) blood pressures were averaged from the 2 weeks of placebo and the last 2 weeks of treatment. Means were used for group comparisons.

Since the comparisons of the treatment-induced blood pressure reductions include different numbers of measurement by each method, we have presented the results recorded by each method as group means before and after treatment. For each patient the change in blood pressure was calculated for each method of mea-

surement. These values were averaged for each method to obtain a mean reduction in blood pressure.

Results are expressed as mean ± SEM. The unpaired *t* test was used to compare the interindividual changes in blood pressure of both antihypertensive drugs. Scatter plots, paired *t* tests, and correlation coefficients were used to compare the intraindividual changes in blood pressure obtained by the different methods of measurement.

Compliance Compliance with the treatment was measured by pill-counting and regarded as adequate if more than 80% of the prescribed pills had been taken. Patients with inadequate compliance were excluded from the study.

RESULTS

Trial Results Of the 53 patients who entered the study, one in each group had to be withdrawn because of intolerable side-effects. The remaining 51 patients completed the study, 25 taking bisoprolol (10 women, 15 men, mean age 50 years, range 29 to 65) and 26 taking nitrendipine (9 women, 17 men, mean age 48 years, range 22 to 70).

After 2 weeks of placebo there were no significant differences in the blood pressure values between the bisoprolol and nitrendipine groups as assessed by casual (150/100 *v* 155/102 mm Hg), ambulatory daytime blood pressure (149/96 *v* 150/97 mm Hg), ambulatory night-time blood pressure (133/82 *v* 138/86 mm Hg) and self-recorded blood pressure (146/97 *v* 146/97 mm Hg).

Changes in Blood Pressure: Bisoprolol v *Nitrendipine* Mean changes in blood pressure after 4 weeks of active treatment with bisoprolol or nitrendipine are given in Figures 1 and 2. With casual readings in the clinic the blood pressure reduction appeared to be more pronounced under bisoprolol (14 ± 2.4/13 ± 1.8 mm Hg) as compared to nitrendipine (7.3 ± 2.7/6 ± 2 mm Hg), but this difference was significant only for diastolic values ($P = .01$).

Ambulatory daytime (8AM to 8 PM) and nighttime recordings (8 PM to 8 AM) showed a greater blood pressure response under bisoprolol than under nitrendipine. The observed differences were however only significant for the nighttime period (11.6 ± 2.9/8.6 ± 1.7 mm Hg *v* 3.1 ± 2.3/1.4 ± 1.7 mm Hg). The minor blood pressure lowering effect of the calcium channel antagonist of 3/1 mm Hg 12 to 24 h after the dose was not significant as compared to the placebo period ($P > .5$).

With self-recorded measurements a reduction of 10.9 ± 2.8/10.7 ± 1.8 mm Hg was observed in the patients treated with bisoprolol. The β-blocker thus was more effective than the calcium channel antagonist, which lowered blood pressure only by 3.4 ± 1.5/3 ± 1 mm Hg.

Methodological Observations *Comparison of Casual, Ambulatory, and Self-Measured Blood Pressure Determinations* In order to investigate whether either casual or self-measured blood pressure was useful to evaluate 24-h antihypertensive efficacy of the two drugs, we compared the treatment-induced blood pressure reductions as assessed by the two techniques with those obtained by 24-h whole-day blood pressure monitoring.

A group comparison of the respective blood pressure changes demonstrated that in both treatment groups the clinical readings showed the greatest reduction, although the observed differences in comparison to ambulatory or self-recorded readings did not reach statistical significance (Table 1).

Scatter plots of the individual diastolic blood pressure changes recorded by casual, ambulatory, and self-measured readings are shown in Figure 3 and 4. Correlation coefficients were 0.6 ($P < .0005$) between ambulatory and self-measured blood pressure and 0.4 between ambulatory and casual readings ($P < .05$). The respective values for the systolic recordings were 0.4 for self-measurement and 0.48 for clinic readings ($P < .05$). However, when the statistical method discussed by Bland and Altman for assessing agreement between the different methods of blood pressure determination was used, the estimated limits of agreement were very wide.

A comparison of the blood pressure (BP) changes measured by casual and by ambulatory readings demonstrated for the systolic values a mean difference of 1.5 ± 12.7 mm Hg (casual BP − ambulatory BP, mean ± SD) with a 95% confidence interval of −2.1 to +5.2 and for the diastolic values a mean difference of 2.8 ± 9.9 mm Hg (casual BP − ambulatory BP; mean ± SD) with a 95% confidence interval of 0.001 to + 5.7.

A comparison of the respective blood pressure changes as assessed by self-measured and ambulatory readings showed for the systolic values a mean difference of −1.8 ± 12.2 mm Hg (self-measured BP − ambulatory BP; mean ± SD) with a 95% confidence interval of −5.6 to +2.0 and for the diastolic values a mean difference of 0.5 ± 7.1 mm Hg (self-measured BP − ambulatory BP, mean ± SD) with a 95% confidence interval of −1.7 to +2.7.

Sensitivity of the Trial The sensitivity of the study design is described by the statistical power achieved with a given number of patients or by the number of patients needed to detect with a given statistical power a clinically significant blood pressure difference.[23] At a two-sided α risk of 5% and a statistical power of 80%, a diastolic difference of 5 mm Hg would require 118 patients with the use of casual readings, 70 with ambulatory monitoring, or 56 with self-measurement (Table 2). Similarly, the number of patients needed to detect a systolic difference of 10 mm Hg can be nearly halved by

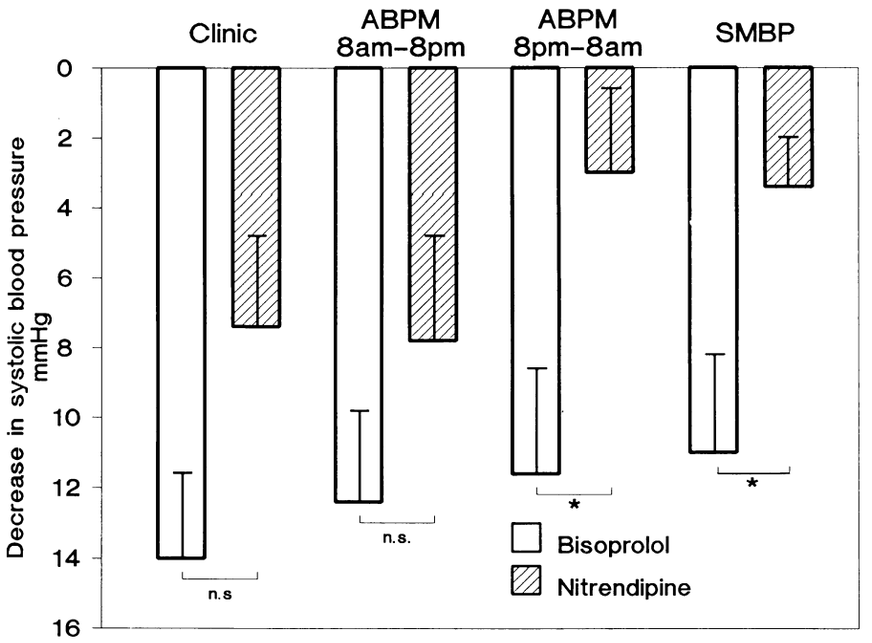

FIGURE 1. *Mean change (±SEM) in systolic blood pressure after 4 weeks of treatment with either bisoprolol or nitrendipine as assessed by casual, ambulatory (ABPM), and self-measured blood pressure (SMBP).* * $P < .05$.

the use of self-measurement rather than clinic readings (Table 2).

DISCUSSION

In the present study the antihypertensive efficacy of nitrendipine *v* bisoprolol after a single morning dose were compared, using three different methods of blood pressure determination. Recent studies comparing continuous ambulatory recordings of blood pressure with casual or self-measured readings have drawn attention to the fact that different methods of measuring blood pressure can provide different results. These observations have renewed interest in the methodological aspects of antihypertensive trials, which were a major focus of the present study.

Casual blood pressures were taken in the morning before medication in order to assess antihypertensive effect 24 h postdosage. Both drugs induced significant reductions in casual systolic and diastolic blood pressure after 4 weeks of treatment as described in other

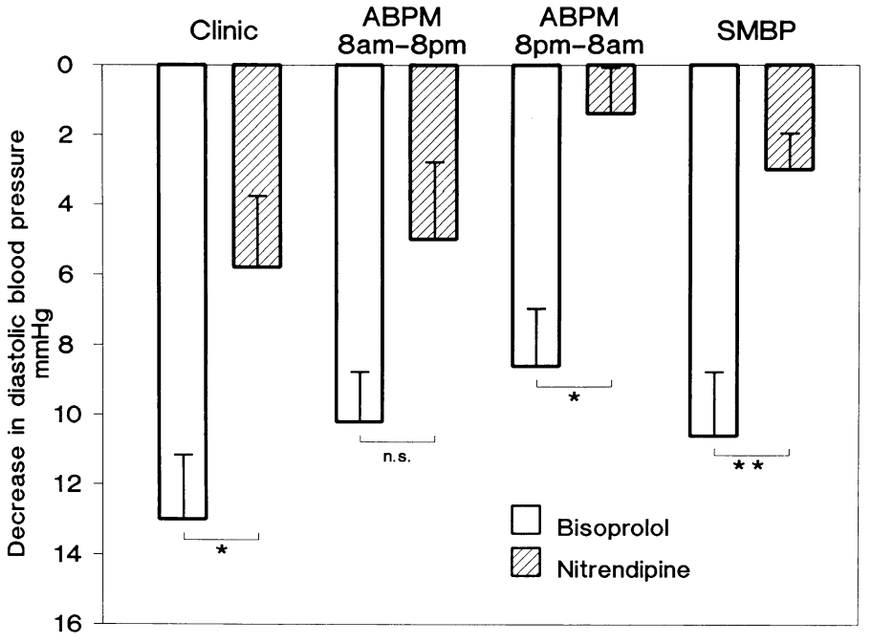

FIGURE 2. *Mean change (±SEM) in diastolic blood pressure after 4 weeks treatment with either bisoprolol or nitrendipine as assessed by casual, ambulatory (ABPM), and self-measured (SMBP) blood pressure.* * $P < .05$; ** $P < .005$.

TABLE 1. CHANGE IN SYSTOLIC (SBP) AND DIASTOLIC BLOOD PRESSURE (DBP) AND COMPARISON OF CHANGES RECORDED BY CASUAL, AMBULATORY (ABPM), OR SELF-MEASUREMENT (SMBP) AFTER 4 WEEKS TREATMENT WITH BISOPROLOL OR NITRENDIPINE

BP Reduction	Casual		ABPM		SMBP
Bisoprolol					
SBP	14.0 ± 2.4	NS	11.8 ± 2.5	NS	10.9 ± 2.8
DBP	13.0 ± 1.8	NS	9.2 ± 1.2	NS	10.7 ± 1.8
Nitrendipine					
SBP	7.3 ± 2.7	NS	5.6 ± 2.3	NS	3.4 ± 1.5
DBP	6.0 ± 2.0	NS	3.4 ± 1.7	NS	3.0 ± 1.0

Values are mean ± SEM. The mean change in blood pressure, as recorded by each method of measurement in each patient, was compared using a two-tailed Student's paired t test.

studies.[15–18] Although the casual blood pressure values achieved with bisoprolol were lower than those achieved with nitrendipine, this difference was significant only for the diastolic blood pressure reductions. Similarly, the ambulatory daytime (8 AM to 8 PM) blood pressure values demonstrated significant systolic and diastolic reductions induced by both drugs. The blood pressure response with the β-blocker was more pronounced than the response with the calcium-channel antagonist but did not reach statistical significance.

The ambulatory nighttime (8 PM to 8 AM) monitoring, however, showed that bisoprolol was significantly more effective than nitrendipine, which did not appear to be effective over 24 h after a single morning dose. Thus our results confirm the findings of recent trials with nitrendipine using ambulatory blood pressure monitoring. In these studies no significant effect on the early morning blood pressure rise was demonstrated.[17,18] The self-measured blood pressure values, obtained near the end of the dosing interval, followed a similar trend, documenting a significantly more pronounced fall in systolic and diastolic blood pressure with the β-blocker.

In addition our results suggest that the analysis of two different time periods of whole-day ambulatory blood pressure monitoring, ie, daytime and nighttime values, as well as that of the self-measured blood pressure values, may be superior to casual measurements in evaluating the 24-h blood pressure control of two antihypertensive agents with different durations of action.

In both treatment groups systolic and diastolic blood pressure reductions tended to be more pronounced with casual measurements than with either ambulatory monitoring or self-measurement, although the difference was not significant. The lack of a significant difference between the methods differs from other studies demonstrating under- as well as overestimates of the overall blood pressure decrement by conventional readings.[8,13,24] In a verapamil study, Gould et al observed a

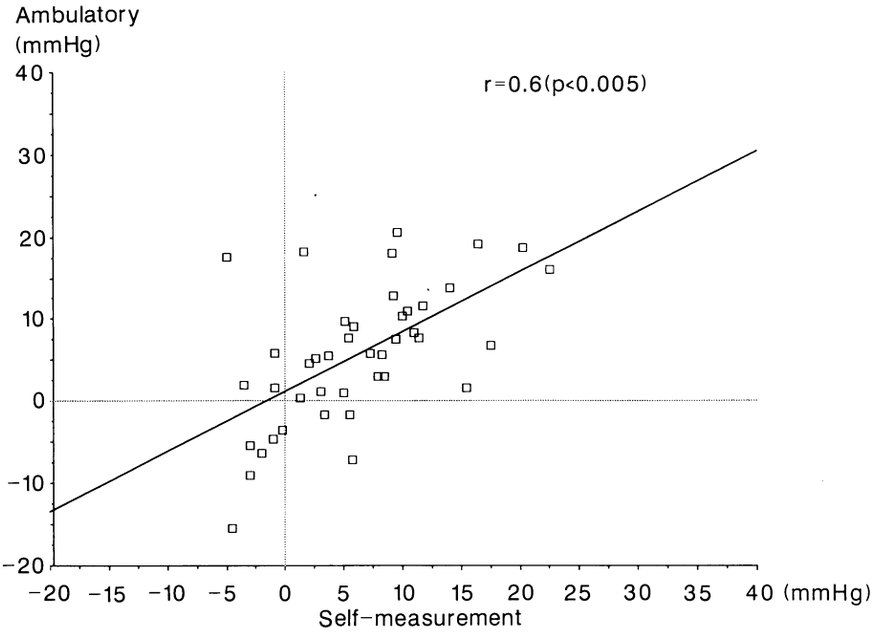

FIGURE 3. *Scatter plot of change in mean diastolic blood pressure (mm Hg) recorded by ambulatory whole-day monitoring* v *self-measured blood pressure.*

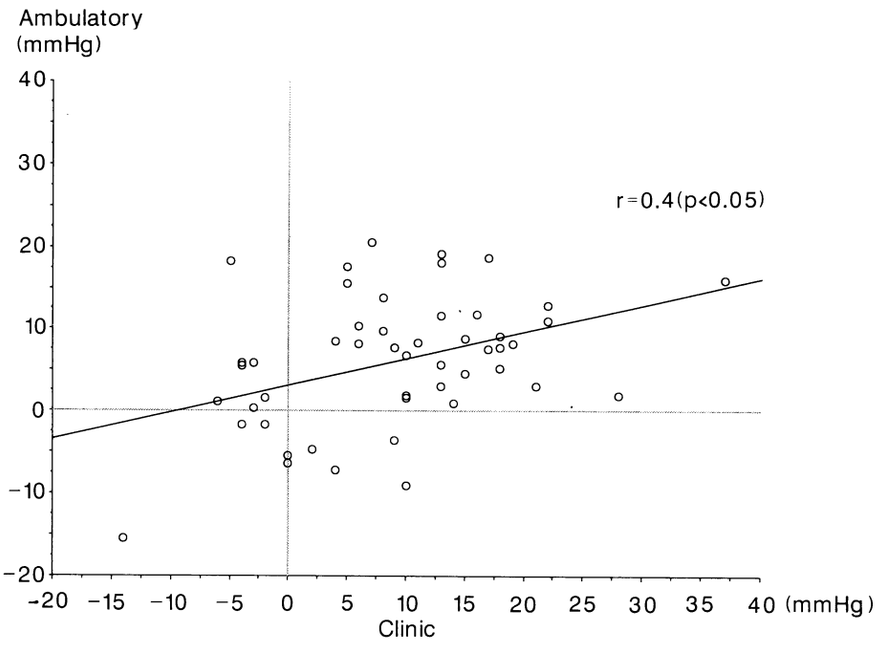

FIGURE 4. *Scatter plot of change in mean diastolic pressure (mm Hg) recorded by ambulatory whole-day monitoring* v *casual blood pressure.*

significantly greater mean reduction of the clinic systolic blood pressure compared with either intraarterial or self-recorded pressure. They suggested that overestimates in casual measurements may result from the lack of a placebo control.[8] Other authors observed that casual blood pressure, measured near the end of the dosing interval, tends to underestimate overall drug efficacy.[24] Gordon et al measured the blood pressure reduction in response to a thiazide diuretic, using both casual and self-recorded measurements.[13] Their findings differ from ours in that the clinic systolic blood pressure determinations indicated a smaller reduction than did the self-measured blood pressures.

The correlation coefficients for the change in blood pressure between ambulatory monitoring and self-measurement were higher than recently reported by another group.[8] These discrepancies may be explained by the use of different devices for measuring ambulatory and self-recorded blood pressure. In the present study self-measurement was performed with a semiautomatic device without stethoscope, avoiding the difficulties in identifying Korotkoff phase V as diastolic blood pressure. Thus, in our hypertension trial self-recorded blood pressure measurement at home appears to give valid results when used to estimate the antihypertensive effect of drugs.

TABLE 2. SENSITIVITY OF THE STUDY DESIGN WITH CASUAL, AMBULATORY (ABPM), OR SELF-MEASURED BLOOD PRESSURE (SMBP) DETERMINATIONS

Method	Number of Patients	
	Systolic	Diastolic
Casual	55	118
ABPM	44	70
SMBP	31	56

Number of patients needed to detect at a two-sided α risk of 5% and a statistical power of 80% a systolic blood pressure difference of 10 mm Hg and a diastolic difference of 5 mm Hg.[23]

When the statistical method discussed by Bland and Altman[22] for assessing agreement between the different methods of blood pressure determination was used, a similar limit of agreement of casual and self-measured readings as compared to ambulatory readings was demonstrated for the systolic blood pressure values.

For the diastolic blood pressures the agreement between self-measurement and ambulatory monitoring was distinctly superior to the agreement between self measurement and the casual readings. However, in some patients marked intraindividual variations between the three different methods of blood pressure determination were observed.

Another interesting finding emerging from the present study was the observation that the use of self-measurement can substantially improve the sensitivity of the trial. Similarly, in a previous study Ménard et al observed that a difference of 5 mm Hg in diastolic blood pressure could be detected in 27 patients using casual blood pressure determinations or in 20 patients using self-measurement.[10] The seeming discrepancy between the data in our study and those of Ménard, in determining the number of patients required to obtain clinically relevant results using the different forms of blood pressure measurement can be explained by the use of a different study design. Thus, in the present study a par-

allel approach was chosen, whereas Ménard et al used a crossover design, which substantially improves the sensitivity of the trial.[25] This information is useful for the future planning of studies to test antihypertensive drugs. The number of patients necessary for a trial is dependent on the expected difference in blood pressure and the observed variability. Generally to halve the variability, ie, the standard deviation of the mean difference between readings, will double the precision of the trial.

In conclusion, our results indicate that bisoprolol was more effective over 24 h than nitrendipine at the doses studied. Furthermore, the analysis of ambulatory day- and nighttime values as well as that of self-measured blood pressure values were superior to casual readings for monitoring 24-h efficacy of the two antihypertensive drugs under investigation. Finally self-recorded blood pressure measurements can substantially improve the sensitivity of a parallel study design by halving the number of patients needed to detect clinically significant differences in blood pressure control.

ACKNOWLEDGEMENTS

We wish to thank Miss Buschmann-Deckels for support of the study and Mrs. L. Sahli (E. Merck AG) for excellent secretarial assistance.

REFERENCES

1. World Hypertension League: Self-measurement of blood pressure. J Hypertens 1988;6:257–261.
2. Weisser B, Mengden T, Vetter W: Ambulatory twenty-four-hour blood pressure measurement in pharmacological studies. J Hypertens 1991;8(suppl 6):87–92.
3. Mengden T, Bättig B, Vetter W: Self-monitoring of blood pressure. J Hum Hypertens 1990;4(suppl I):47–50.
4. White BW: Methods of blood pressure determination to assess antihypertensive agents: are casual measurements enough? Clin Pharmacol Therap 1989;45:581–586.
5. Weber MA, Cheung DG, Graettinger WF, Lipson JL: Characterization of antihypertensive therapy by whole-day blood pressure monitoring. JAMA 1988;259:3281–3285.
6. Steiner A, Oertel R, Bättig B, et al: Effect of fish oil on blood pressure and serum lipids in hypertension and hyperlipidaemia. J Hypertens 1989;7(suppl 3):73–76.
7. Waeber B, Petrillo A, Scherrer U, et al: Are some hypertensive patients overtreated. A prospective study on ambulatory blood pressure recording. Lancet 1987;ii:732–734.
8. Gould BA, Hornung RS, Kieso H, et al: An evaluation of self-recorded blood pressure during drug trials. Hypertension 1986;8:267–271.
9. Cottier C, Julius S, Gajendragadkar SV, Shork A: Usefulness of home blood pressure determination in treating borderline hypertension. JAMA 1982;248:555–558.
10. Menard J, Serrurier D, Bautier P, et al: Crossover design to test antihypertensive drugs with self-recorded blood pressure. Hypertension 1988;11:153–159.
11. Conway J, Coats A, Radaelli AJS: Ambulatory blood pressure in relation to drug treatment and clinical trials. J Hypertens 1990;8(suppl 6):83–85.
12. Coats AJS: Reproducibility or variability of casual and ambulatory blood pressure data: implications for clinical trials. J Hypertens 1990;8(suppl 6):17–20.
13. Gordon RD, Pawskey GK, O'Halloran MW, et al: Use of home blood pressure measurement to compare the efficacy of two diuretics. Med J Aust 1972;2:565–570.
14. Goa KL: Nitrendipine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the treatment of hypertension. Drugs 1987;33:123–155.
15. Lancaster SG, Sorkin EM: Bisoprolol: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in hypertension and angina pectoris. Drugs 1988;36:256–285.
16. Weiner L, Fritz G: Antihypertensive effect of bisoprolol during once daily administration in patients with essential hypertension. A dose-ranging study with parallel groups. Eur J Clin Pharmacol 1986;29:517–521.
17. Heagerty AM, Swales JD: A double-blind randomized cross-over study of the efficacy and tolerability of nifedipine and nitrendipine in the treatment of mild to moderate hypertension. Br J Clin Pharmac 1989;27:411–416.
18. Groth H, Stimpel M, Edmonds D, et al: Nitrendipine, a new calcium antagonist, as first-choice treatment in essential hypertension. Schweiz Rundsch Med Prax 1985;74:503–506.
19. Kirkendall WM, Feinlieb M, Freis ED, Mark AL: Recommendation for human blood pressure determinations by sphygmomamometers. Circulation 1980;62:1146A–1155A.
20. O'Brien E, Sheridan J, Browne T, et al: An evaluation of the Spacelabs 90202 non-invasive ambulatory blood pressure recorder. J Hypertens 1989;7(suppl 6):S388–S389.
21. Graettinger WF, Lipson JL, Cheung DJ: Validation of oscillometric, auscultatory and r-wave gated auscultatory automated portable blood pressure measurements by intra-arterial line and sphygmomanometer. Am Heart J 1988;116:1155–1160.
22. Bland JM, Altman DG: Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;i:307–311.
23. Altman DG: Statistics and ethics in medical research. III. How large a sample? Br Med J 1980;281:1336–1338.
24. Weber MA, Tonkon MJ, Klein RG: Blood pressure monitoring for assessing the duration of action of antihypertensive treatment. J Clin Pharmacol 1987;27:751–755.
25. Hills M, Armitage P: The two-period cross-over clinical trial. Br J Clin Pharmacol 1979;8:7–20.