Monitoring 24-Hour Blood Pressure in a Drug Trial
Evaluation of a Noninvasive Device

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SUMMARY To test the usefulness of noninvasive ambulatory 24-hour blood pressure recording, the Del Mar Avionics system was used in a double-blind clinical trial in which 31 hypertensive patients were randomly allocated to receive placebo or pafenolol (25 mg or 50 mg), a novel, long-acting, highly selective β-blocker, once daily. The results of 24-hour blood pressure and heart rate recording after 4 weeks of treatment were compared with a previous 24-hour recording performed after a 4-week placebo run-in period using the 3-hour mean of recordings performed every 7.5 minutes both day and night. Furthermore, 24-hour means were analyzed in each patient before and after 4 weeks. The system was easy to use and, judging from two placebo periods in the same patients, the reproducibility was good. The 24-hour blood pressure and heart rate recordings showed a clear dose-response relationship for pafenolol that could not be detected by ordinary casual readings. A daily dose of 25 mg of pafenolol significantly reduced blood pressure during the 9 hours after tablet intake (p < 0.01), while 50 mg per day of pafenolol resulted in a significant reduction throughout the 24-hour period (p < 0.01). The same pattern was seen for heart rate, which indicates a greater degree of β-blockade during treatment with the higher dose. These results indicate that the tested noninvasive equipment is a useful tool for monitoring ambulatory 24-hour blood pressure. It gives important information impossible to obtain from single casual readings. This noninvasive method should be further evaluated to define its place in clinical work and as a research tool. (Hypertension 7: 688-694, 1985)

KEY WORDS • primary hypertension • ambulatory • β-blockade • pafenolol

BLOOD pressure (BP) is subject to great spontaneous variation. Continuous BP monitoring through an indwelling catheter shows this variability quite accurately. Although continuous BP recording has been used to evaluate antihypertensive drugs, it is difficult to use in large-scale studies since frequent repetition of intra-arterial monitoring in larger series of patients is not possible. The availability of a reliable, noninvasive device for monitoring ambulatory 24-hour arterial blood pressure would therefore be of great interest.

The aim of this study was to analyze the value of such a noninvasive system in a drug trial comparing the antihypertensive effect of placebo with that of two different doses of a new highly selective β-adrenergic blocker, pafenolol.

Subjects and Methods
Thirty-one patients with primary hypertension, 24 men and 7 women, 33 to 64 years of age (mean age, 51.4 years) were included. The patients were recruited from three centers in Sweden: Lund (n = 9), Danderyd (n = 11), and Göteborg (n = 11). After 5 minutes of rest in the supine position, their BP ranged from 150 to 200 mm Hg systolic and from 100 to 115 mm Hg diastolic at the end of a 4-week run-in placebo period. Satisfactory 24-hour recordings were obtained in these subjects before and after 4 weeks of treatment. Another eight patients were excluded because of the unsatisfactory quality of the 24-hour recordings (1 patient) or poor patient compliance (7 patients). All patients agreed to participate after receiving full oral and
written information about the study. The study was approved by the ethical committee of the University of Göteborg. Patients with angina pectoris, congestive heart failure, diabetes mellitus, chronic obstructive airways disease, intermittent claudication, or other serious concomitant disease were excluded. Eleven patients had never been treated, while 20 had received prior antihypertensive drug therapy. Twenty-three were classified in World Health Organization stage I and eight in stage II disease.

The treatment was started with a placebo run-in period during which one placebo tablet was given daily for 4 weeks. The patients were then randomized to double-blind treatment with either pafenolol, 25 mg or 50 mg, once daily or placebo once daily for another 4 weeks. All medications were taken in the morning. Casual BP (supine and standing) was taken 24 hours after the first dose, and 24-hour BP monitoring was done at the end of the placebo run-in period and at the end of the double-blind period 4 weeks later. In this way, all 31 patients had a 24-hour BP recording done at the end of the initial placebo period while 12 patients were re-studied after receiving 25 mg of pafenolol per day, 10 patients after receiving 50 mg of pafenolol per day, and nine patients after receiving a second course of placebo. The results from the latter nine patients, who received placebo for 8 weeks, could therefore be used to test the reproducibility of the 24-hour BP recording.

Casual BP was measured in the right arm using a 35-cm long and 12-cm wide rubber cuff connected to a mercury manometer. Measurements were obtained after 5 minutes of rest in the supine position and after 1 minute in the standing position. The disappearance of the Korotkoff sounds (phase V) was defined as the diastolic BP. Casual heart rate (HR) was also measured by pulse palpation for 30 seconds with subjects in the supine and standing positions 24 hours after the first dose.

The 24-hour BP and HR were recorded using the Del Mar Avionics (Irvine, CA, USA) Model 1978 Pressurometer III and analyzed on Model 1981 Blood Pressure Analysis System. The Pressurometer III is a portable, noninvasive device that measures BP at preset intervals by automatic sphygmomanometry throughout a 24-hour period. Data are stored in solid-state memory and are transferred by direct cable to the Del Mar Avionics Model 1981 Blood Pressurometer Data Analysis System, which consists of a control/computer module, a video terminal with keyboard, and a printer/plotter. The printouts are automatically edited to delete data that are obviously erroneous according to certain criteria.

Since we initially thought that the criteria developed for definition of erroneous data by Del Mar Avionics (hereafter referred to as “Avionics”) were not sufficient, much time was devoted to improving these criteria. For this purpose the Box-Jenkins model was applied.10 In this model (hereafter referred to as “Arima”) an observation at a given time was modeled as a function of its current and past values. Parameters in the model were estimated from raw data from the noninvasive recordings. The parameters were then used to forecast the time series of values. Observations were considered as outliers when the deviation between observed and predicted value exceeded three standard deviations in the effect variable.

When the two methods (Avionics and Arima) for exclusion of outliers were compared, no significant differences were observed. Both methods deleted 1.7% of the measured BPs. Correlation coefficients between 3-hour means for systolic and diastolic BP and HR calculated with the Avionics and Arima definition of outliers gave r values between 0.98 and 1.0 with no difference between baseline and values after 4 weeks of treatment. The standard Avionics criteria for outliers have therefore been used in the present study.

We conclude that these seem to be satisfactory for both group and individual analysis.

The Pressurometer III allows repetitive measurements of BP and HR achieved at time intervals of 7.5 minutes or multiples of 7.5 minutes. During operation of the equipment, a special microphone is taped over the brachial artery beneath a conventional cuff that is automatically inflated by a built-in pneumatic pump. Three chest electrocardiographic electrodes are applied to the patient. As the cuff deflates, the microphone detects sounds that are accepted as Korotkoff sounds only if the built-in computer identifies these in a well-defined time relationship to the preceding QRS complex (product information supplied by Del Mar Avionics). Systolic and diastolic BP and HR are stored in memory. Mean arterial blood pressure was calculated as diastolic BP plus one-third of the pulse pressure.

During the day the compact pressure monitor (weight, 2 kg) was carried with a shoulder strap, and it was usually placed on the night table during sleep. With few exceptions, the subjects were able to pursue their normal daily activities. During the night, however, six of 31 patients (19%) complained of sleep disturbance of varying severity.

To test the validity of the equipment, comparisons between the automatic and the conventional auscultatory measurement of systolic BP were made before and during exercise on a bicycle ergometer on 53 occasions in 11 patients (performed in one center only, Göteborg). The results of this comparison gave very good agreement between individual systolic (Figure 1) and diastolic BP values and almost identical means for the two methods.

The original measurement values of the effect variables from the 24-hour noninvasive measurements were aggregated into 3-hour and wider periods (day, night, and 24 hours). Since the noninvasive monitoring offers fewer measurements of BP than do invasive recordings, 3-hour or longer average periods were chosen instead of the much shorter average times used in invasive studies. The aggregation was also performed to diminish the number of statistical tests and to increase the reliability of the estimates of BP levels. The analysis was carried out on the assumption that there would be a normal distribution for the average values in the different treatment periods. The equality of means was
Results

Casual Blood Pressure

Nine patients had two placebo treatment periods. Statistically there was no difference between the two placebo periods in casual systolic or diastolic BP or HR (Table 1). In the group of 12 patients randomized to receive 25 mg of pafenolol daily, casual diastolic BP (supine, \(p < 0.05\); standing, \(p < 0.01\)) and HR (supine, \(p < 0.01\); standing, \(p < 0.05\)) 24 hours after dose intake were significantly lower during the active treatment than during placebo. Ten patients were given 50 mg of pafenolol daily. During active treatment casual systolic and diastolic BP (\(p < 0.01\), supine and standing) and HR (supine, \(p < 0.01\); standing, \(p < 0.05\)) in this group were significantly lower than during placebo treatment. No significant differences in blood pressure reduction between the two pafenolol treatment groups were recorded.

24-Hour Blood Pressure Measurements

The results of the group analysis of 3-hour means for systolic and diastolic BP and HR are illustrated in Figures 2, 3, and 4.

Placebo Versus Placebo

To validate the reproducibility of the method, the two 24-hour BP recordings done in the nine patients undergoing two placebo treatment periods were compared (Figure 2). No significant differences between the two placebo periods were noted for any 3-hour average of systolic or diastolic BP or for HR, except for one systolic BP reading (0–3 hr after intake; \(p < 0.05\)) and one diastolic BP reading (12–15 hr after intake). The \(r\) value between the mean value of the two recordings of diastolic BP was 0.64 (\(p < 0.001\)).

Pafenolol Versus Placebo

After 4 weeks of 25 mg of pafenolol daily the 24-hour recording showed a significantly lower 3-hour average systolic and diastolic BP than during placebo period up to 6 to 9 hours after tablet intake (\(p < 0.05\); Figure 3). In the last 3 hours before the next tablet

Table 1. Mean Casual Systolic (SBP) and Diastolic (DBP) Blood Pressure and Heart Rate (HR) After Placebo Run-in (Baseline) and After 4 Weeks of Double-blind Treatment with Placebo, 25 mg of Pafenolol, or 50 mg of Pafenolol Measured 24 Hours After Dose Intake

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n = 9)</th>
<th>25 mg Pafenolol (n = 12)</th>
<th>50 mg Pafenolol (n = 10)</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 4</td>
<td>Baseline</td>
</tr>
<tr>
<td>Supine (5 min)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>164 ± 12.3</td>
<td>160 ± 17.7</td>
<td>172 ± 9.8</td>
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<td></td>
<td></td>
<td></td>
<td>105 ± 5.1</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>67 ± 12.7</td>
</tr>
<tr>
<td>Standing (1 min)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>156 ± 18.4</td>
<td>151 ± 18.3</td>
<td>163 ± 7.7</td>
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<tr>
<td></td>
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<td>109 ± 9.2</td>
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<td></td>
<td>72 ± 15.7</td>
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<td></td>
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<td>72 ± 15.7</td>
</tr>
</tbody>
</table>

Values are means ± sd.

*p < 0.05, †p < 0.01, compared with baseline.
intake (0600–0900 hr) systolic and diastolic BP were also significantly lower on 25 mg of pafenolol than on placebo ($p < 0.05$). Heart rate tended to be lower on 25 mg of pafenolol than on placebo for a considerable part of the 24 hours, but significantly only 0 to 3 hours and 12 to 15 hours after dose intake ($p < 0.01$). When 50 mg of pafenolol was taken daily, the 3-hour average systolic and diastolic BP and HR were significantly lower than on placebo for all periods during the 24 hours (Figure 4). The only exception was an insignificant difference in systolic BP between 12 and 18 hours.

Daytime and Nighttime Mean Blood Pressure

To study separately the effect of the different doses of pafenolol on BP and HR during day and night, the 24-hour period was arbitrarily divided into daytime (0900–2100 hr) and nighttime (0100–0500 hr). The hours when most people go to bed (2100–2400 hr) and wake up (0500–0900 hr) were excluded from this analysis (Table 2). There was no difference between the two placebo periods for mean BP and HR day or night or during the 24-hour period.

In subjects receiving 25 mg of pafenolol daytime systolic and diastolic BP were both significantly lower than in those on placebo ($p < 0.001$). During the sleeping hours diastolic BP was significantly lower in subjects on 25 mg of pafenolol than in those on placebo ($p < 0.05$), while systolic BP and HR tended to change in the same direction, although neither reached statistical significance. The mean of all systolic and diastolic BPs during the 24-hour period was significantly decreased by administration of 25 mg of pafenolol daily ($p < 0.001$). With a dose of 50 mg of pafenolol daily systolic (day, $p < 0.05$; night, $p < 0.001$) and diastolic (day and night, $p < 0.001$) BP and HR (day, $p < 0.001$; night, $p < 0.01$) were significantly decreased compared with placebo during both day and night.

Dose-Response Relationship

To get an estimate of the dose-response relationship for pafenolol, daytime and nighttime averages for BP and HR on the two dose levels were compared. This analysis revealed a significantly better reduction in mean arterial BP ($p < 0.05$) and HR ($p < 0.01$ and $p < 0.05$) both day and night for 50 mg compared with 25.
mg of pafenolol. Spearman's rank correlation test showed a significant linear relationship between dose and effect (reduction in mean arterial BP and HR) for both daytime ($r_1 = 0.53$ and $0.54, p < 0.01$), nighttime ($r_2 = 0.53$ and $0.56, p < 0.01$) and for the 24-hour period ($r_3 = 0.64$ and $0.69, p < 0.001$).

Means for Individual Patients

The results of the individual 24-hour means of mean arterial BP and HR are given in Table 3. The data from patients undergoing two placebo treatment periods showed that the levels of mean arterial pressure and HR seemed to be fairly constant for an individual patient. In some patients, however, the 24-hour averages were significantly different. On 25 mg of pafenolol one patient had significantly higher mean arterial pressure and HR than on placebo, and two patients had no decrease in mean arterial pressure. In all patients receiving 50 mg of pafenolol daily, the mean arterial pressure and HR values were significantly lower than on placebo.

Discussion

The noninvasive equipment used for ambulatory 24-hour BP monitoring was found to have good reproducibility judging from the analysis of two recordings from subjects receiving only placebo. The diurnal changes followed the pattern seen in invasive recordings: highest BP and HR were seen during the day and very low values were seen at night followed by an early morning rise,\textsuperscript{1-3} which indicates that the noninvasive recordings probably reflect the true pattern of the diurnal changes in BP and HR. The good validity of the measurements is also clear from the analysis presented in Figure 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo ($n = 9$)</th>
<th>25 mg Pafenolol ($n = 12$)</th>
<th>50 mg Pafenolol ($n = 10$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 4</td>
<td>Baseline</td>
</tr>
<tr>
<td>Daytime</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>160 ± 9.5</td>
<td>155 ± 9.5</td>
<td>153 ± 12.8</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>103 ± 7.3</td>
<td>103 ± 9.8</td>
<td>102 ± 10.1</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>87 ± 10.8</td>
<td>84 ± 11.3</td>
<td>89 ± 12.1</td>
</tr>
<tr>
<td>Nighttime</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>123 ± 12.4</td>
<td>117 ± 13.5</td>
<td>129 ± 16.3</td>
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<tr>
<td>DBP (mm Hg)</td>
<td>82 ± 7.8</td>
<td>83 ± 8.4</td>
<td>85 ± 11.3</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>69 ± 13.9</td>
<td>67 ± 8.6</td>
<td>67 ± 8.4</td>
</tr>
<tr>
<td>24 Hours</td>
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<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>147 ± 9.8</td>
<td>144 ± 9.9</td>
<td>146 ± 14.6</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>95 ± 7.8</td>
<td>97 ± 10.4</td>
<td>97 ± 10.3</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>80 ± 11.8</td>
<td>79 ± 10.5</td>
<td>82 ± 10.7</td>
</tr>
</tbody>
</table>

Values are means ± SD.

Recordings were performed after 4-week placebo run-in period (baseline) and after 4 weeks of double-blind treatment with placebo, 25 mg of pafenolol, or 50 mg of pafenolol.

* $p < 0.05$, † $p < 0.01$, ‡ $p < 0.001$, compared with baseline.
The computer program that we created to delete outliers took a long time to create and requires extensive computing facilities for its execution. Even if the program somewhat increased the deletion of faulty BP data, the standard criteria for deletion included in the Del Mar Avionics Model 1981 Blood Pressure Analysis System seemed to be satisfactory. The Pressometer was quite easy for the majority of patients to use. Failures caused by technical problems occurred in one patient (2.5%), while poor patient compliance caused by the equipment was seen in seven patients (18%). Our experience with the equipment is quite similar to that of other research groups.

The trial presented here was part of a clinical evaluation of pafenolol, a novel, highly selective, \(\beta\)-blocker with more than 70 times higher affinity for \(\beta_1\) adrenergic receptors than for \(\beta_2\)-adrenergic receptors. It was designed to define the effects of different doses of pafenolol on BP and HR during a 24-hour period. The casual BP readings showed that both 50 mg and 25 mg of pafenolol reduced BP and HR significantly; however, these casual measurements were not capable of showing a definitive dose-response relationship for BP. On the other hand, casual HR did show such a relationship, with significantly lower HR on the higher dose, which indicates a greater degree of \(\beta\)-blockade showing a definitive dose-response relationship for BP and HR.
on systolic and diastolic BP of only 6 to 9 hours, while 50 mg of pafenolol decreased both systolic and diastolic BP significantly throughout the 24-hour period. The pattern was the same for HR. Pafenolol, 25 mg, showed no significant decrease in BP during the night; however, during the morning hours a significant reduction was again recorded, probably because the well-known increase in sympathetic tone during this time revealed the β-blockade. Pafenolol, 50 mg, was shown to reduce BP at night as well. Whether or not this effect is an advantage cannot be established from these data.

In conclusion, 24-hour BP monitoring seems to be better suited for the study of dose-response relationships and effect-duration relationships than casual BP readings. With the use of noninvasive equipment, this type of dose-response and effect-duration study could be performed with more precision and be a valuable tool in the clinical evaluation of new antihypertensive drugs. Furthermore, we found that responders and nonresponders could be identified more accurately by analyzing 24-hour means in individual patients, as illustrated in Table 3. This noninvasive method should be further evaluated to define its place in clinical work and as a research tool.

Acknowledgments

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