

Discrepancy between clinic and ambulatory blood pressure measurement in the evaluation of two antihypertensive agents

Eoin O'Brien, John P. Cox, Desmond J. Fitzgerald, and Kevin O'Malley

The Blood Pressure Unit, Beaumont Hospital, Dublin 9 and the Department of Clinical Pharmacology, Royal College of Surgeons in Ireland, Dublin 2, Ireland

Summary: Discrepancies between clinic and ambulatory BP measurements may be important in the assessment of antihypertensive drug efficacy. Trimazosin (50–200 mg twice daily) and propranolol (40–160 mg twice daily) were compared in 22 hypertensive subjects in a randomised double-blind cross-over study. Daytime ambulatory BP was measured with a non-invasive portable recorder (Remler M2000). Clinic BP measurements were made with a random zero sphygmomanometer. While both drugs reduced clinic supine BP (trimazosin by 16/10 mmHg, $P < 0.01/P < 0.001$; propranolol by 25/14 mmHg, $P < 0.001/P < 0.001$), equivalent decreases on ambulatory measurement occurred with propranolol (28/11 mmHg, $P < 0.001/P < 0.001$) but not trimazosin (8/3 mmHg, $P < 0.05/NS$). This difference in drug efficacy persisted throughout the 12-hour dosing interval.

We conclude that clinic BP measurements alone cannot be relied upon to reflect accurately changes in BP induced by antihypertensive drugs. Moreover this study confirms the necessity for ambulatory BP measurement in the evaluation of antihypertensive drugs.

Introduction

There is now evidence that BP measured in the clinic is a poor reflection of prevailing pressure throughout the day.^{1–4} Furthermore, ambulatory BP measurements may be superior to clinic measurements both in terms of correlation with target organ damage⁵ and long-term prognosis.⁶ Ambulatory monitoring may also be a better guide to titration of antihypertensive therapy than casual office determinations.⁷ However, in the individual subject, cuff BP measured in the clinic differs unpredictably from ambulatory recordings obtained invasively² and non-invasively in both normotensive subjects⁸ and treated hypertensive patients⁹ in part due to the pressor effect of the physician's presence in the clinic.¹⁰ We felt it would be of interest to examine differences in antihypertensive effect on clinic and ambulatory BP measurement in a randomised double-blind cross-over study of two drugs with different BP lowering mechanisms, namely the prazosin derivative, trimazosin¹¹ and propranolol.

Patients and methods

Twenty-four patients (14 female, mean \pm SEM age 47 ± 1.7 years) with clinic DBP 90–115 mmHg entered the study. Five patients on antihypertensive therapy were included following a period of four weeks off treatment. One patient was continued on bendrofluazide 2.5 mg daily throughout the study. Patients with serum creatinine greater than 140 micromol/l, previous myocardial infarction, stroke, or cardiac failure were excluded. The study protocol was approved by the hospital ethics committee and informed consent was obtained.

Study design

At the end of a four-week run-in placebo phase patients entered a randomised double-blind cross-over phase where they were treated with trimazosin 50 mg twice daily or propranolol 40 mg twice daily. The dose of each drug was increased at two-weekly intervals to a maximum of trimazosin 200 mg twice daily or propranolol 160 mg twice daily, or until clinic DBP was decreased to less than 85 mmHg. Each treatment period lasted 12 weeks and was separated by a four-week washout period on placebo. Patients were seen at two-

Correspondence: Dr. E. O'Brien, The Blood Pressure Unit, Beaumont Hospital, Dublin 9, Ireland
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weekly intervals for measurement of clinic BP and heart rate. Ambulatory BP measurements were carried out at the end of the run-in phase and at the end of each treatment period in the double-blind phase.

Methods

Clinic BP was measured at the same time of day and by the same observer with the Hawksley random zero sphygmomanometer. Korotkov phase V was taken for diastolic pressure. Blood pressure and heart rate recordings were made with the patient lying after 10 minutes rest and standing after two minutes with the arm supported at heart level.¹² Ambulatory BP was measured non-invasively at half-hourly intervals using a semi-automated portable recorder (Remler Corp. San Francisco). This system has been shown to be reliable and accurate.¹³ The Remler was operated by the patient from 09.00 to 23.00 hours. All Remler tapes were decoded by one operator.

Mean systolic and diastolic pressures for each patient for each day of ambulatory BP measurement and clinic readings at the end of the placebo run-in phase and each active treatment period were compared using two-way analysis of variance. For comparison of daily ambulatory BP profiles the recordings for each hour were averaged resulting in single hourly values from 09.00 to 23.00 hours. These were compared using one way analysis of variance. A probability value of less than 5% was taken to be significant.

Results

Of the 24 patients who entered two failed to complete the study (see below). Mean (\pm SEM) entry clinic supine BP was $165 \pm 4.8/105 \pm 1.1$ mmHg. There was no significant difference between clinic BPs at the end of the run-in placebo phase and washout phase, demonstrating that BP had returned to baseline levels prior to the second treatment period. The final mean (\pm SD) daily dose of trimazosin was 318 ± 26.5 mg and of propranolol 229 ± 22.5 mg given in two divided doses. Adequate ambulatory BP recordings were obtained in all but one patient (technical failure). The mean (\pm SD) number of ambulatory BP recordings made per patient was 21 ± 1.2 at the end of the run-in phase, and 21 ± 0.9 and 20 ± 1.0 at the end of the trimazosin and propranolol treatment periods, respectively.

Clinic supine BP was reduced from $173 \pm 5.2/104 \pm 1.7$ mmHg on placebo to $157 \pm 4.8/$

94 ± 2.5 mmHg ($P < 0.01/P < 0.001$) on trimazosin and to $148 \pm 6.1/90 \pm 3.1$ mmHg ($P < 0.001/P < 0.001$) on propranolol (Figure 1). Standing BP was also reduced to a similar extent from $167 \pm 4.7/106 \pm 1.7$ mmHg on placebo to $153 \pm 4.2/95 \pm 2.9$ mmHg ($P < 0.01/P < 0.001$) on trimazosin and to $146 \pm 4.2/93 \pm 2.5$ mmHg ($P < 0.001/P < 0.001$) on propranolol. Propranolol reduced lying (86 ± 2.7 to 63 ± 2.0 beats per minute, $P < 0.001$) and standing heart rate (91 ± 2.9 to 64.7 ± 1.7 beats per minute, $P < 0.001$) whereas heart rate was unchanged on trimazosin. Blood pressure differences between drugs were not significant although the difference in heart rate was ($P < 0.001$).

While mean ambulatory SBP was significantly reduced on treatment with trimazosin (from 160 ± 3.1 mmHg on placebo to 152 ± 3.5 mmHg; $P < 0.05$) the diastolic reduction (from 103 ± 2.2 to 100 ± 2.2 mmHg) was not significant. On the other hand propranolol reduced BP to $132 \pm 3.4/92 \pm 1.8$ mmHg ($P < 0.001/P < 0.001$). Blood pressure differences on ambulatory measurement between drugs were also significant ($19/8$ mmHg, $P < 0.001/P < 0.01$).

The 14-hour pressure profiles, plotted from consecutive mean hourly BPs on placebo and on treatment with trimazosin and propranolol, are shown in Figure 2. Propranolol significantly reduced SBP and DBP throughout the 12-hour dosing interval, while with trimazosin the effect was less marked and not statistically significant.

Both patients who did not complete the study were on placebo (one had multiple symptoms and the other patient's BP fell to normal levels).

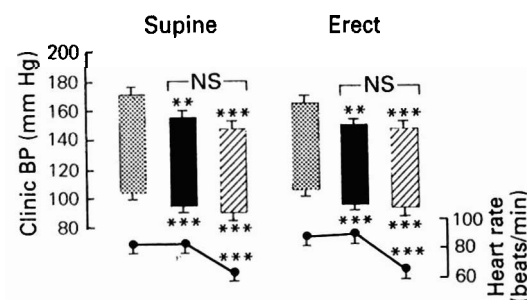


Figure 1 The effects of propranolol (▨) and trimazosin (■) on BP and heart rate measured in the clinic compared with placebo (□). Values are mean \pm SEM, $n = 22$. (** $P < 0.01$, *** $P < 0.001$).

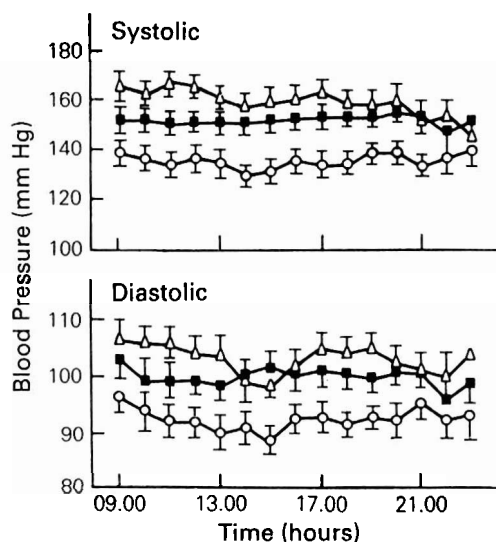


Figure 2 Fourteen-hour ambulatory BP profiles, plotted from consecutive mean hourly pressures on placebo (Δ) and after 12 weeks on treatment with trimazosin (\blacksquare) and propranolol (\circ). Values are mean \pm SEM, $n=21$.

Discussion

This study highlights important discrepancies between clinic and ambulatory BP measurement in the assessment of two antihypertensive agents, trimazosin and propranolol, in that while both drugs produced similar significant reductions in clinic BP measurement, equivalent decreases in ambulatory measurement occurred only with propranolol. Moreover the results with propranolol are in agreement with observations made in studies using different beta-blocking agents where ambulatory BP was recorded outside the clinic either by direct^{14,15} or indirect^{16,17} methods. The results with respect to trimazosin are difficult to explain. One possibility is that the clinic recordings, which were made in the morning, coincided with the period when trimazosin was exerting its

maximum effect which has been shown to occur between one and four hours and to persist for 6 to 8 hours after dosing.^{18,19} However, this is unlikely, because although the ambulatory BP profile for diastolic pressure suggests loss of antihypertensive effect after 13.00 hours, no such effect is apparent for systolic pressure.

Another explanation is that the physiological basis of BP elevation in the clinic may be different to that outside the clinic and that the dose of trimazosin effective in lowering clinic BP might not be effective in reducing ambulatory pressure. By way of support for this hypothesis is the fact that nitrendipine has been shown to reduce BP effectively in the clinic but this effect is blunted during work periods on ambulatory measurement,²⁰ probably due to increased adrenergic activity associated with work. Similarly, comparison of the beta-blocker timolol with methyldopa showed similar significant reductions in clinic measurement, but ambulatory BP was significantly lower on timolol only.²¹ Likewise, both the beta-blocker, betaxolol, and verapamil, significantly reduced clinic BP, but only betaxolol significantly reduced ambulatory BP.²² These studies are in agreement with ours and suggest that beta-blocking drugs have a sustained effect on ambulatory BP not shared by drugs with other modes of action.

In conclusion, this study raises the possibility that a reduction in casual BP readings without a similar lowering of ambulatory pressure may be due to alteration of the pressor response in the clinic which is not manifest in the ambulatory setting. More studies are needed to examine this phenomenon. The present study confirms the importance of ambulatory BP measurement in the evaluation of antihypertensive drugs.

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