Comparison of propranolol and propranolol LA in hypertension using 24-hr non-invasive blood pressure monitoring

M. H. A. RUSTIN*  
B.Sc., M.R.C.P.  

E. N. COOMES  
M.D., F.R.C.P.  

St Stephen’s Hospital, Fulham Road, Chelsea, London SW10 9TH

Summary
The technique of non-invasive blood pressure monitoring was used to compare the 24-hr control of blood pressure in 10 patients with essential hypertension taking either twice daily propranolol or a once daily long-acting formulation of propranolol (propranolol LA). Both drug regimes produced smooth control of blood pressure and heart rate through the 24 hours and significantly reduced blood pressure and heart rate on bicycle ergometry tests. There was no significant difference between the two treatments. The non-invasive oscillometric method of measuring 24-hr control of blood pressure provides an alternative to ambulatory intra-arterial monitoring.

KEY WORDS: propranolol, hypertension, non-invasive blood pressure recording.

Introduction
Propranolol LA is a recently developed long-acting formulation of propranolol which gives therapeutic levels and clinical effect from a single daily dose (Leahey et al., 1980a; McAinsh et al., 1978). In contrast with single daily administration of conventional propranolol, it does not cause the excessively high plasma levels shortly after ingestion that may produce adverse effects. Moreover it maintains beta-blockade throughout a 24-hr period (Mann et al., 1980). This latter effect and the 24-hr control of blood pressure have been studied by the technique of ambulatory intra-arterial monitoring (Millar-Craig, 1979). We feel that this method is unacceptably invasive and therefore have evaluated the Dinamap automatic arterial blood pressure monitor. This machine is non-invasive and easy to use. It operates on an oscillometric principle measuring pressure fluctuation within a cuff. Blood pressure recordings from the Dinamap 845 correspond closely with direct measurements of intra-arterial pressures and with systolic and phase 5 diastolic pressures obtained with a Hawksley random zero sphygmomanometer (Silas et al., 1980; Ramsey, 1979). We report an open within-patient study comparing the 24-hr control of blood pressure and heart rate in hypertensive patients taking either once daily propranolol LA or twice daily propranolol.

Methods
Recording device
The Dinamap 845 measures and digitally displays the systolic, diastolic, mean arterial pressures and heart rate and the Dinamap 950 produces a graphic record of these measurements. The Dinamap was connected to a timer set to switch on for 30 min and off for 90 min and automatic measurements were made at 3-min intervals. Blood pressure alarm limits were set to a low of 20 mmHg and a high of 200 mmHg. The operation of the Dinamap has been fully described elsewhere (Silas et al., 1980).

Patients
Patients from a hospital clinic with essential hypertension were asked to participate in this trial if their clinic blood pressures were in excess of 155/90 mmHg after having stopped all antihypertensive drugs for 14 days. Five males with a mean age of 53 years (range 41–65 years) and weight 75.2 kg and five females with a mean age of 51 years (range 43–59 years) and weight 62.6 kg were recruited. Three patients had previously taken antihypertensive therapy. Patients were excluded if they had had a recent myocardial infarction, if there was evidence of cardiac failure or if there was ECG evidence of ischaemic changes or heart block. Those with obstructive airways disease, diabetes mellitus or severe hypertensive retinopathy were also excluded.

Procedure
Each patient was admitted to a single-bedded room during their first and all subsequent admis-
FIG. 1. Circadian curves of systolic and diastolic pressures in 10 hypertensive patients before treatment (■), during treatment with twice daily propranolol (■) and during treatment with an equivalent dose of propranolol LA taken once daily each morning (○). Lines joined pooled mean values.

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was added. At each out patient appointment, compliance was assessed by tablet counts. When adequate blood pressure control had been achieved, patients were continued on the same medications for 4 weeks and then were admitted for the second time. Twenty-four hour monitoring of their heart rate and blood pressure was performed and their standard exercise test repeated. The patients left hospital taking the nearest equivalent dose of propranolol in the long-acting formulation (propranolol LA capsule contains 160 mg propranolol) and the other antihypertensive drugs were continued at the same dosage. After 4 weeks of treatment with propranolol LA, patients were admitted for the last time for 24-hr monitoring and their standard exercise tests were repeated.

Data analysis

After each patient’s admission, there were twelve sets of recordings at 2-hourly intervals. The mean values of heart rate, systolic and diastolic pressures were calculated for each period and these means were pooled according to the stage and time of the study. Circadian curves were constructed to demonstrate trends over the three 24-hr periods, before treatment, during treatment with twice daily propranolol and with once daily propranolol LA (Figs. 1 and 2). Differences between therapies were assessed by Student’s paired t-test.

Results

All patients completed the trial and no side effects
were reported. There was no significant difference in patient compliance between the two regimes of propranolol. At the crossover from propranolol to propranolol LA, five patients maintained equivalent doses (160 mg daily in four and 320 mg daily in one) and five patients increased the total propranolol dose (80–160 mg daily in three patients and 240–320 mg daily in two).

Following conventional propranolol therapy, the systolic blood pressures were significantly lowered throughout the day \((P<0.01)\) except at 13.00, 5.00 and 7.00 when the level of significance reached \(P<0.05\). Similarly, the diastolic pressures were reduced throughout the 24 hours \((P<0.01)\) except at times 17.00, 23.00, 5.00, 7.00 and 9.00 when the degree of statistical significance was \(P<0.05\). Compared to pretreatment values, propranolol LA therapy lowered systolic pressures throughout the day \((P<0.01)\) except at 9.00, 23.00, 5.00 and 7.00 when the statistical difference was \(P<0.05\). The diastolic pressures were also reduced \((P<0.01)\) apart from times 9.00, 1.00, 5.00 and 7.00 \((P<0.05)\). There was no significant difference in the control of blood pressure between the two treatments.

Heart rates were significantly reduced from control values whilst taking propranolol \((P<0.05)\) except at times 21.00, 23.00 and 01.00 and during propranolol LA therapy \((P<0.05)\) except time 01.00. There was no difference between the two drug regimes.

Comparison of pooled values of heart rate and blood pressure measured for 10 min before exercise and for 1 min after bicycle ergometry showed a significant reduction with both treatments \((P<0.001)\) compared to pre-treatment values (Table 1). Again, there was no significant difference between the two treatments.

**Discussion**

In most clinical trials assessing new antihypertensive drugs, patient's blood pressures are measured either by a mercury sphygmomanometer or by ambulatory intra-arterial monitoring. The former method suffers from observer bias, digit preference and variation between observers, especially when staff change (Fitzgerald, O'Malley and O'Brien, 1982; O'Brien and O'Malley, 1979). The readings obtained may not even compare with simultaneous

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**Table 1.** Blood pressure (BP mmHg) and heart rate (beats/min) before (pre) and after (post) bicycle ergometry in 10 hypertensive patients before treatment, during treatment with twice daily propranolol and during treatment with an equivalent dose of propranolol LA taken once daily each morning. Figures shown are mean levels +/− s.d. All values on both propranolol preparations were significantly different \((P<0.001)\) compared to the control value.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Conventional propranolol</th>
<th>(P) value v. control</th>
<th>Propranolol LA</th>
<th>(P) value v. control</th>
</tr>
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<tbody>
<tr>
<td>Pre</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Systolic BP</td>
<td>169±14</td>
<td>135±20</td>
<td>&lt;0.001</td>
<td>138±18</td>
<td>&lt;0.001</td>
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<td>Diastolic BP</td>
<td>101±7</td>
<td>82±13</td>
<td>&lt;0.001</td>
<td>85±8</td>
<td>&lt;0.001</td>
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<tr>
<td>Heart rate</td>
<td>77±10</td>
<td>61±7</td>
<td>&lt;0.001</td>
<td>60±6</td>
<td>&lt;0.001</td>
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<tr>
<td>Post</td>
<td></td>
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</tr>
<tr>
<td>Systolic BP</td>
<td>178±14</td>
<td>158±16</td>
<td>&lt;0.001</td>
<td>157±14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>115±12</td>
<td>94±14</td>
<td>&lt;0.001</td>
<td>89±10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate</td>
<td>111±15</td>
<td>84±14</td>
<td>&lt;0.001</td>
<td>80±10</td>
<td>&lt;0.001</td>
</tr>
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intra-arterial blood pressure recordings (Hunyor, Flynn and Cochineas, 1978). Continuous ambulatory monitoring has demonstrated the striking variation in blood pressure during normal activity but unfortunately it is invasive, is unpleasant and may cause complications (Littler, 1976). We therefore assessed the feasibility of using the Dinamap 845 for 24-hr blood pressure monitoring and were gratified to find that the circadian rhythms of blood pressure we obtained closely resemble those obtained by ambulatory monitoring in hypertensive patients (Miller Craig et al., 1978a; Miller Craig, Bishop and Raftery, 1978b).

The advantages of this method are that it is not dependent on auscultation of Korotkoff sounds, is atrumatic, enables multiple studies to be done on the same patient and eliminates motion artefact. Indeed, the Dinamap 845 has been shown to give a more accurate estimation of central aortic pressure than auscultatory methods (Borow and Newburger, 1982). The disadvantages are that the patient cannot be mobile during the monitoring, the maximum systolic pressure measurable is 210 mmHg and the blood pressure cannot be accurately determined if there is a large beat-to-beat fluctuation in systolic and diastolic pressure as in atrial fibrillation. Some patients complained of disturbed sleep during cuff inflation on their first admission but this problem resolved once blood pressure control had been achieved. We did not assess whether the position of the patient during sleep or lying on the non-dominant arm altered blood pressure readings and this should be investigated. During this preliminary study, patients were admitted to hospital but we consider that home monitoring would be feasible. This would allow recordings between normal activities and provide the advantages over self-monitoring.

Propranolol LA taken once daily is an effective treatment of mild to moderate hypertension. It produces smooth control of blood pressure and heart rate throughout the 24 hr and similar results have been reported by different authors (Leahey et al., 1980b, Petrie et al., 1980). Twice daily propranolol produced similar results and no significant difference between the regimes was detected. Propranolol LA produced a significant reduction in blood pressure and heart rate during bicycle ergometry tests. These tests were timed at between 3–4 hr after the last dose of propranolol LA and were not designed to test the efficacy of the drug beyond 24 hr.

This study was non-randomized because it was thought that if patients started on long-acting propranolol and their blood pressures were not controlled, an incremental rise of 160 mg would be too great and predispose them to side effects. We therefore started all patients on twice daily conventional propranolol and increased the daily dose by increments of 80 mg.

This had two consequences. Firstly, because the drugs were always administered in the same order, it was not possible to separate treatment from time effects. Secondly, five patients took an equivalent dose of propranolol in the long-acting formulation but five increased their overall dose. There was no significant difference in the blood pressure control between the two groups so some patients were taking an unnecessarily high dose of propranolol in the LA formulation. Although five patients do not have great statistical power, it does seem there might be a place for a smaller-dose LA tablet.

In conclusion, we have shown that both once daily propranolol LA and twice daily conventional propranolol produce an effective and similar 24-hr control of blood pressure and heart rate in hypertensive patients. We have also demonstrated that the Dinamap non-invasive blood pressure recorder can assess blood pressure control and suggest that it may play a useful role in future trials of anti-hypertensive drugs.

Acknowledgments

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M. H. A. Rustin and E. N. Coomes


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