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MAGNITUDE AND MECHANISMS OF THE ANTIHYPERTENSIVE ACTION OF LABETALOL, INCLUDING AMBULATORY ASSESSMENT

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1 The blood pressure (BP) effect and modes of action of a twice daily regimen of labetalol (mean 450 mg/day) were assessed in ten mild to moderate hypertensives using continuous ambulatory BP monitoring.

2 The reflex control of BP during physiological interventions was examined just prior to the next dose of medication to estimate the residual α- and β-adrenoceptor blockade.

3 Global 24 h BP was reduced by 15/9 mm Hg, and home pressures by 13/11 mm Hg. The predominant antihypertensive effect was noted during the waking hours.

4 During dynamic exercise significant inhibition of the heart rate and blood pressure rise occurred. Coupled with a reduction of the post-release BP 'overshoot' in Valsalva's manoeuvre, the response resembles that seen with β-adrenoceptor blockade.

5 A small α-adrenoceptor blocking action was evident in one patient's response to the Valsalva manoeuvre.

Keywords labetalol hypertension ambulatory blood pressure Valsalva's manoeuvre

Introduction

Attempts have been made to improve on the actions of β-adrenoceptor blocking agents by eliminating effects on bronchial muscle and peripheral vessels. Labetalol possesses both α- and β-adrenoceptor blocking properties and has the potential to reverse some unwanted peripheral side-effects of β-adrenoceptor blockers (Gilmore *et al.*, 1970) by directly lowering vascular resistance (Maxwell, 1973) and possibly by antagonising α-adrenoceptor mediated bronchoconstriction (Skinner *et al.*, 1975).

Labetalol can be expected to cause less bradycardia than other β-adrenoceptor blockers, except those with intrinsic sympathomimetic activity (Man in't Veld & Schalekamp, 1982). Because of its dual action in blocking α- and β-adrenoceptors, the drug is potentially useful in a wider spectrum of hypertensives than agents having effects only on the β-adrenoceptor.

The ratio of α- to β-adrenoceptor effect of labetalol is biased towards the latter (Richards *et al.*, 1977), and is known to change further in that direction with increasing dosage. While α-adrenoceptor blockade carries with it the potential for orthostatic blood pressure effects (Williams *et al.*, 1979), there is evidence that with labetalol this is only a problem in the presence of diuretic induced plasma volume depletion (Hunyor *et al.*, 1980).

The 24 h antihypertensive efficacy of thrice daily labetalol has been assessed in moderate to severe hypertension in a non-randomised study (Balasubramanian *et al.*, 1979a). In contrast, the present study examines the effect of a lower dose in the more common situation of mild hypertension. A twice daily regimen which most patients find practical, was used in a randomised, placebo controlled fashion.

Beside studying the 24 h blood pressure pattern, particular note was taken of the blood pressure at a time most remote from dosing, at which time the effect of contrived physiological stress (static and dynamic exercise) was also examined. The response to dynamic exercise was used as an index of β-adrenoceptor blockade (McDevitt & Shand, 1976; Jennings *et al.*, 1981). The reflex control of blood pressure during Valsalva's manoeuvre was assessed to ascertain whether the effect of labetalol is related to a significant α-adrenoceptor blocking action (Korner *et al.*, 1979).

Methods

Ten patients, of whom five were males, average age 48 years (range 30–59), gave informed consent for the study, which required that untreated diastolic blood

pressure, in duplicate, be greater than 95 mm Hg, on two separate occasions in the Hypertension Clinic. All patients were considered to have essential hypertension having had routine tests to exclude secondary causes. Serum creatinine did not exceed 0.15 mmol/l in any patient, while three showed electro-cardiographic changes of left ventricular hypertrophy.

The trial was conducted as a randomised, single blind, placebo controlled study. The patients were stabilized on labetalol, after an initial dosage adjustment period, for at least 5 weeks, and they took placebo for a similar period. Eight of the patients were on diuretic therapy throughout the trial. The average daily stable dose of labetalol during the study was 450 mg (200–800) given as twice daily regimen at 09.00 h and 21.00 h. During the last week of each treatment period the patients recorded twice daily home blood pressure at approximately 09.00 h and 17.00 h.

A continuous, ambulatory blood pressure study was performed at the end of the treatment period. The non-dominant arm brachial artery was cannulated, well up from the cubital fossa under local anaesthesia. A 3F Grandjean Teflon cannula was inserted using a Seldinger technique, and blood pressure was recorded with a modified Oxford Medilog instrument (Bevan *et al.*, 1969; Goldberg *et al.*, 1976) using the perfusion/transducer system developed at Northwick Park (Millar-Craig *et al.*, 1970). After insertion of the arterial line and calibration procedures the patients left the hospital and carried on normal activities for 24 h. They returned the following day for testing of the blood pressure effect of various contrived physiological manoeuvres, which were timed to take place between 12 and 13 h after the last dose of medication. No complications were associated with the study.

The physiological manoeuvres employed were: (1) Dynamic exercise—sub-maximal graded treadmill exercise using three levels of the standard Bruce protocol. (2) Static exercise—isometric hand grip involving 30% of maximal voluntary contraction (MVC) for 4 min on a hand dynamometer (Stoelting Co., Chicago, Illinois, U.S.A.). (3) Valsalva manoeuvre—30 s of sustained expiratory pressure of 30 mm Hg using a mouthpiece with a small leak.

Continuous 24 h blood pressure analysis involved the use of a preprocessor (Kenny *et al.*, 1980) which derived blood pressure values over 1 min intervals from the continuous tape recording. From these results 10 and 60 min averages with standard deviations and blood pressure incidence histograms were calculated by computer (LSI-11/03) and displayed by a Hewlett-Packard HP7221 S graphics plotter. Responses during the physiological manoeuvres were analysed using direct computer digitisation of the pressure waveforms, so that beat to beat information was obtained. Statistical analysis was performed by use of a paired Student's *t*-test.

During analysis of the Valsalva manoeuvre the last ten complexes during phase 2 (just prior to release of pressure) were compared to control blood pressure values to estimate the degree of reflex vasoconstriction. The degree of blood pressure 'over-shoot' was assessed by comparing the maximum systolic pressure and the longest heart period in phase 4 with control levels.

The postural effects of labetalol were examined by extracting the lowest 1 min blood pressure values during the waking hours, and also by noting the immediate response to assumption of the upright posture after 5 min recumbency.

Results

The overall blood pressure lowering action of labetalol over 24 h was compared in the two patients not on diuretics (19/9, 11/8 mm Hg) and in the eight others taking such medication, (15/9 mm Hg). The absence of a diuretic in the regimen did not alter the 24 h pattern of labetalol effect as displayed on a pressure-time histogram, or on a diurnal pressure chart. Furthermore, at the nadir of drug action, there was no difference in relation to diuretic category (no diuretic: a.m. 21/7, p.m. 12/12 mm Hg lowering of blood pressure, whole group: a.m. 20 12, p.m. 15 12 mm Hg lowering of blood pressure). Because of this similarity of blood pressure effects, it was felt justified to consider the 10 patients' results together.

Table 1 gives a summary of the group data for 24 h direct, home and office blood pressure values. Labetalol lowered the 24 h value from 145/80 to 130/71 mm Hg, a reduction of 15/9 mm Hg ($P < 0.001$). Home blood pressures revealed a similar effect, 147/96 to 134/85 mm Hg a reduction 13/11 mm Hg ($P < 0.01$) and office readings were reduced 149/95 to 140/87 seated. 150/104 to 134/90 mm Hg standing. A pressure-time histogram (Figure 1) allows calculation of time spent between certain blood pressure limits. There is a basic difference in the shape of the curves with the placebo pressures having a wide based (approaching bimodal) distribution, which is altered by labetalol. The shift to lower pressures produced by labetalol can be readily appreciated. There were 80 min on average spent above systolic levels of 180 mm Hg in the placebo phase, compared to 6 min during active treatment. Similarly, 102 min were spent above diastolic levels of 100 mm Hg in the placebo period compared with only 7 min during labetalol treatment.

Blood pressure values in the twelfth post-dosing hour were examined. During this time of lowest drug effect, mean blood pressure was lowered by an average of a.m. 20/12, p.m. 15 12 mm Hg compared to placebo. This compares favourably with the reduction over the full 24 h of 15/9 mm Hg (NS).

The blood pressure effect of labetalol, related to time of day, is shown in Figure 2 where a treated value

Table 1 Blood pressure (mm Hg) response (mean ± s.d.) to labetalol treatment (n = 10)

	Placebo	*Mean BP*	*Labetalol*	*Mean BP*	*P <*
24 h value	145/80 ± 14/7	107 ± 3	130/71 ± 11/6	95 ± 3	0.001
Home value	147/96 ± 15/9	113 ± 3	134/85 ± 10/9	102 ± 8	0.01
Office value					
seated	149/95 ± 23/11	113 ± 10	140/87 ± 35/15	105 ± 21	NS
standing	150/104 ± 19/11	119 ± 12	134/90 ± 27/17	105 ± 20	0.05

has been subtracted from the corresponding placebo figure at each hourly interval. In 16 of the 24 h the labetalol effect was highly significant ($P < 0.01$), but it was either absent or very small ($P < 0.05$) during the sleeping hours (23.00 h–05.00 h). To investigate the occurrence of low blood pressure levels which may result in hypotensive symptoms, the time spent at systolic pressure less than 85 mm Hg and between 85 and 95 mm Hg was calculated. During labetalol therapy there were no 1 min values lower than 85 mm Hg systolic, and only 43 min were spent between 85 and 95 mm Hg. On further analysis it was found that all these low pressures occurred during sleep. Assumption of the erect posture did cause a blood pressure fall in some patients, but this did not produce symptoms, nor did the systolic pressure stay so low as to bring the 1 min average below 100 mm Hg. Non-weight bearing 30° head up tilt for 5 min also failed to produce symptomatic hypotension.

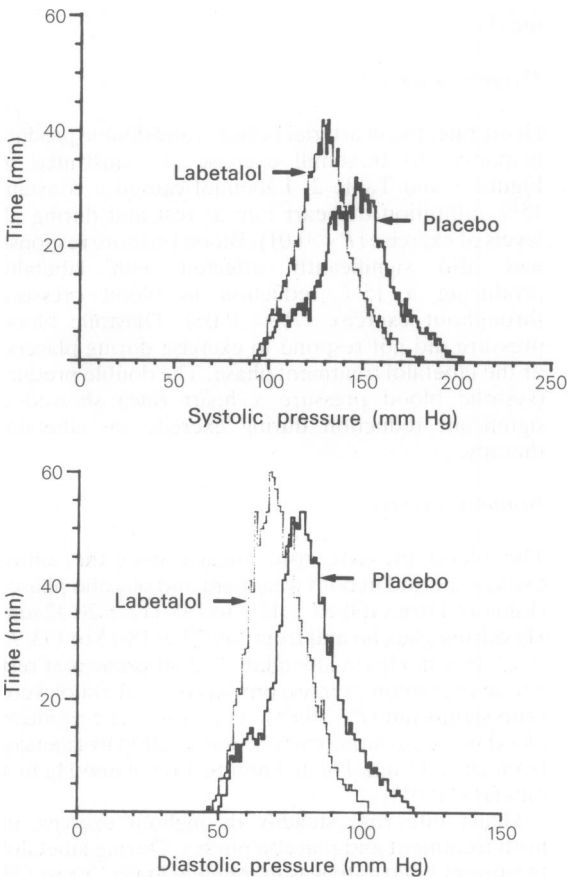

Figure 1 Pressure-time histogram showing time spent at different blood pressure levels over a 24 h period according to treatment category (n = 10).

The Valsalva manoeuvre

Blood pressure fluctuations resulting from the Valsalva manoeuvre during placebo therapy closely followed previously described changes (Korner *et al.*, 1979) (Figure 3a). At the start of forced expiration there was a small rise in blood pressure (Phase 1) and then a rapid fall for the first 5–6 s (Phase 2). The pressure then rose steadily for 10–15 s (late Phase 2). On release of pressure (Phase 3) a blood pressure 'over-

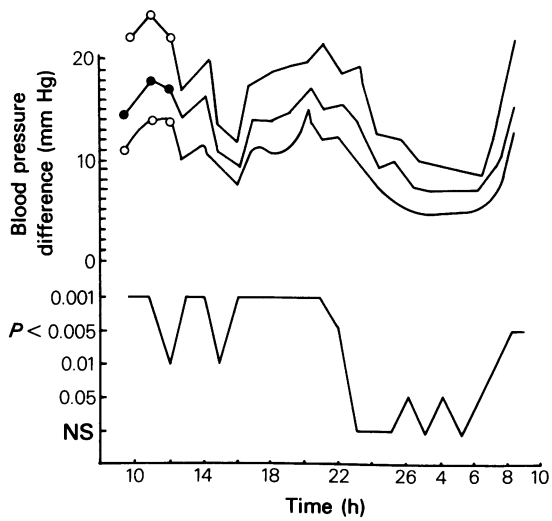

Figure 2 The time-related effect of labetalol on continuous blood pressure, derived by subtracting treated from placebo values at hourly intervals over 24 h. Systolic and diastolic pressure (○), mean pressure (●) (n = 10).

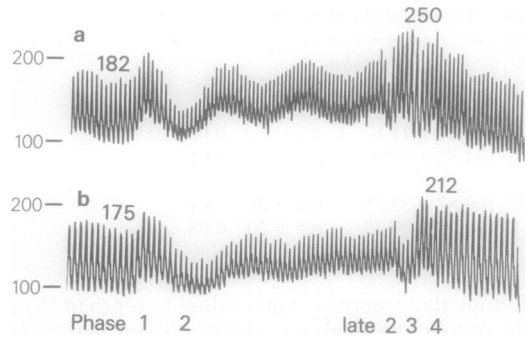

Figure 3 Direct arterial pressure during Valsalva manoeuvre in one patient showing the usual effect of labetalol therapy on late Phase 2 rise in blood pressure and on the blood pressure 'overshoot'. a) placebo treated, b) labetalol treated. Numbers refer to systolic pressure.

shoot' occurred for 5–10 s (Phase 4) before returning to the resting level.

The mean blood pressure rose to 12% (120 ± 7 to 135 ± 18 mm Hg) above resting values during Valsalva Phase 2 in the placebo period and 9% (109 ± 11 to 118 ± 12 mm Hg) during treatment (NS). Placebo treated, post-release, 'over-shoot' blood pressure was 207/125 ± 23/13 mm Hg compared with a control value of 161/98 ± 12/7 mm Hg. The overshoot level was lowered by labetalol to 176/100 ± 20/11 mm Hg from a control of 151/88 ± 18/8 mm Hg (25/19 *vs* 46/27 mm Hg rise on placebo $P < 0.01$). As a consequence of the reduction in 'over-shoot' by labetalol the reflex bradycardia was also lessened. Resting heart period was increased from 672 to 815 ms (20% rise) by the Valsalva manoeuvre during placebo while it rose by 12% from 744 to 835 ms during labetalol ($P < 0.01$).

In one subject (DC) there was evidence of a significant α- as well as β-adrenoceptor blockade during performance of Valsalva's manoeuvre (Figure 4). During labetalol treatment the late Phase 2 blood pressure remained 17 mm Hg below the control value

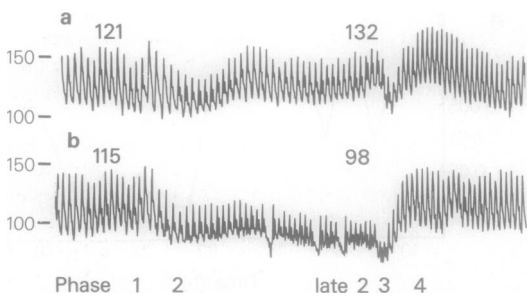

Figure 4 Valsalva response in one patient (DC) who was on the highest dose of labetalol (800 mg per day) illustrating a significant inhibition of the α-adrenoceptor mediated rise in mean blood pressure during late Phase 2. a) placebo treated, b) labetalol treated.

Table 2 Mean ± s.d. blood pressure* (BP; mm Hg) and heart rate (HR; beats/min) response during treadmill exercise (Bruce Protocol)

Stage of exercise		*Placebo*	*Labetalol*	P <	*% Reduction*
Rest	BP	122 ± 9.6	104 ± 7.7	0.05	15
	HR	86 ± 11.7	72 ± 8.8	0.01	16
I	BP	133 ± 15.6	113 ± 11.9	0.05	15
	HR	115 ± 17.1	99 ± 20.4	0.01	14
II	BP	135 ± 15.7	114 ± 8.2	0.05	16
	HR	132 ± 23.1	112 ± 24.5	0.01	15
III	BP	135 ± 14.6	115 ± 6.7	0.05	15
	HR	142 ± 19.8	123 ± 26.2	0.01	13

*derived by electrical integration of area under pressure waveform

in contrast to the group response where it had risen 9 mm Hg above the pre-Valsalva level. This subject was taking the highest dose of labetalol (800 mg/day), was the youngest in the study and had experienced the largest treatment reduction of blood pressure (23/17 mm Hg).

Dynamic exercise

Heart rate, mean arterial pressure and double product responses to treadmill exercise are illustrated in Figure 5 and Table 2. Labetalol caused a constant 15% inhibition of heart rate at rest and during all levels of exercise ($P < 0.01$). Blood pressure response was also significantly affected with labetalol producing a 15% reduction in blood pressure throughout exercise ($P < 0.05$). Diastolic blood pressure did not respond to exercise during placebo or the labetalol treatment phase. The double product (systolic blood pressure x heart rate) showed a significant reduction during exercise on labetalol therapy.

Isometric exercise

The blood pressure rose linearly over the entire exercise period in both treatment and placebo phases (Figure 6) from 150/85 ± 12/7 to 195/112 ± 20/12 mm Hg during placebo and from 145/77 ± 18/13 to 173/96 ± 23/16 mm Hg on labetalol. The differences at rest and at maximum exercise produced by labetalol were both significant ($P < 0.05$). The rate of rise of mean blood pressure during exercise was lowered by labetalol from 26 ± 11 mm Hg in 4 min to 19 ± 9 mm Hg in 4 min ($P < 0.01$).

Heart rate rose steadily throughout exercise in both treatment and placebo phases. During labetalol treatment heart rate was marginally lower at rest (78 ± 8 *vs* 82 ± 3 beats/min NS) and during each 30 s of exercise. The average heart rate rise of 14 beats/min was not altered by labetalol.

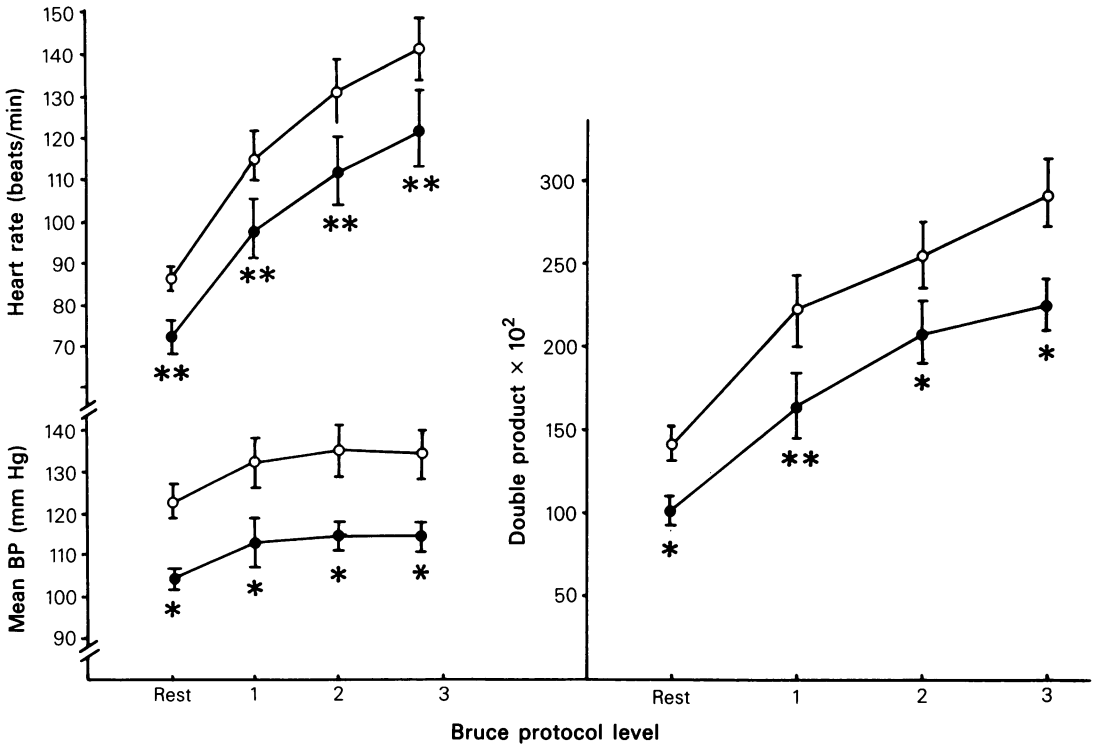

Figure 5 The treadmill exercise response of heart rate, mean blood pressure and double product (systolic pressure x heart rate) in placebo (○) and labetalol treated (●) ($n = 7$) patients. $^*P < 0.05$. $^{**}P < 0.01$.

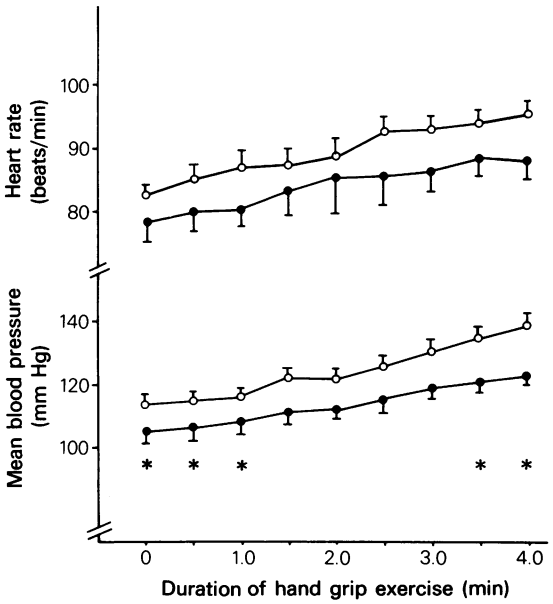

Figure 6 The effect of labetalol treatment on heart rate and blood pressure in response to isometric exercise (30% MVC) ($n = 7$). Notation as for Figure 5.

Discussion

This study demonstrates the 24 h antihypertensive efficacy, even during physiological stress situations, of labetalol given as a twice daily regimen. The control of blood pressure exerted at the trough effect of the drug is evidence for the lasting 12 h action of a single dose given on a chronic basis. It appears that, at the dose employed in this study (450 mg/day) in mild to moderate essential hypertensives, labetalol acts predominantly as a β-adrenoceptor blocking drug. In this group of patients, even when combined with a diuretic, labetalol did not produce postural hypotension.

The placebo blood pressures (continuous 24 h, self-measured at home and office levels) in our study group were significantly lower than untreated levels in a previous study of labetalol (Balasubramanian *et al.*, 1979a). The apparent difference is due partly to use of diuretics in eight of our ten patients as well as to a placebo effect.

The finding of a 24 h intra-arterial value which was lower than the home pressures may be explained by the inclusion of night-time values among the ambulatory results and by the known relationship

between direct and indirect blood pressure readings (Briet & O'Rourke, 1974; Hunyor & Nyberg, 1978). In contrast, the effect of physical activity during the waking hours would tend to raise ambulatory values. Previous studies have demonstrated a circadian rhythm in blood pressure, (Millar-Craig *et al.*, 1978; Goldberg *et al.*, 1978), which was also seen in our patients who had lower values during sleep. The same general 24 h pattern was maintained during labetalol therapy, although the diurnal pattern was less noticeable. Such a predominant day-time action was also a feature of 'pure' β-adrenoceptor blocking drugs (Millar-Craig *et al.*, 1979; Mehta *et al.*, 1980). The more pronounced effect on day-time pressures is further illustrated by the change in the 24 h blood pressure frequency distribution to a lower level with a change from a broad based to a narrow pattern. This shows the movement of day-time pressures on treatment to merge with the more basal night-time values.

Symptomatic postural hypotension has previously been noted with labetalol, especially in high doses (Williams *et al.*, 1979; Prichard *et al.*, 1979). None of the patients in this study, even in the presence of diuretics, complained of postural symptoms. During the ambulant hours there were no episodes where blood pressure was sustained for more than 1 min at low levels likely to lead to postural symptoms. This finding supports the observations of Balasubramanian *et al.* (1979b) concerning postural fluctuations.

The design of this study assured that the blood pressure effects of labetalol were also thoroughly assessed between 12–13 h after drug administration. The continued efficacy of labetalol at this time, even during heightened reflex activity, would imply that a twice daily regimen is practical.

Valsalva manoeuvre

The rise in blood pressure during late Phase 2, representing reflex vasoconstriction, was minimally affected by labetalol, which is similar to that seen with cardiac adrenergic blockade (Korner *et al.*, 1979). A notable exception was the subject receiving the largest dose of labetalol (800 mg per day), who had also experienced the most marked blood pressure response (Figure 4). The effect of significant α-adrenoceptor blockade would have been to cause a sustained fall in blood pressure during late Phase 2 because of an action on efferent α-adrenergic pathways at the effector site (Korner *et al.*, 1979). It seems that with a small dose of labetalol, as used in our study (450 mg/day), there is a far greater β-adrenoceptor blocking effect indicated by the Valsalva response. The late Phase 2 rise in blood pressure was not analysed in previous ambulatory work (Balasubramanian *et al.*, 1979b) where the use of a 10 s forced expiratory period would not have allowed sufficient time for reflex vasoconstriction to reach equilibrium (Korner *et al.*, 1979).

The most marked effect of labetalol on the Valsalva response, consisting of a reduction in post-release blood pressure 'overshoot', was also noted by Balasubramanian *et al.* (1979b) using a much shorter stimulus. Such 'overshoot' inhibition is consistent with the myocardial β-adrenoceptor-blocking effect of labetalol, preventing the usual increase in stroke volume which follows the post-release enhancement of venous return.

Dynamic exercise

The dynamic exercise response to chronic labetalol treatment corresponds with findings in previous studies (Edwards & Raftery, 1976; Lund-Johansen & Bakke, 1979; Frismam *et al.*, 1981), with blood pressure effect being similar to that on β-adrenoceptor blocking agents. The lowering of peripheral resistance by the α-adrenoceptor blocking properties of labetalol (Edwards & Raftery, 1976; Lund-Johansen & Bakke, 1979), would explain the reduction in heart rate inhibition with labetalol compared with some β-adrenoceptor blockers.

Reduction in the double product at all levels of exercise by labetalol suggests a significant decrease in myocardial oxygen demand. A recent study of labetalol in patients with angina pectoris resulted in reduction in the frequency of attacks, as well as an increase in exercise time (Frishman *et al.*, 1981). The reduction in myocardial oxygen demand and possible simultaneous vasodilation produced by the α-adrenoceptor blocking properties of labetalol, may indicate a role in patients with angina pectoris who have an element of coronary artery spasm or peripheral vascular disease.

Isometric exercise

The heart rate response to static hand grip was not altered by labetalol. Absolute heart rate responses were reduced slightly but the rate of rise of heart rate during exercise was not. Ewing *et al.* (1973) described two types of response to isometric exercise in hypertensive patients, claiming that those with only a small rise in heart rate were raising blood pressure through increasing peripheral resistance, because of limited cardiac reserve. The patients who had the smaller increase in heart rate in the present trial were not necessarily those who had left ventricular hypertrophy. The reduction in the rate of rise of blood pressure during static hand grip which this study has demonstrated, was not seen in previous work (Balasubramanian *et al.*, 1979b) and has not been shown to be a feature of β-adrenoceptor blocking drugs (Hunyor & Nyberg, 1978; Taylor *et al.*, 1979). This finding in our patients would be consistent with an α-adrenoceptor blocking component of action of

labetalol. The inhibition of the rate of blood pressure rise by treatment was only small and could be due to the relatively low α/β-adrenoceptor blocking ratio (1:3) (Richards *et al.*, 1977) at the low doses of labetalol used in our study. On the other hand, it could be an indication that our patients increased their blood pressure by stroke volume mechanisms rather than by peripheral vasoconstriction.

We conclude that labetalol is an effective agent in mild to moderate hypertension and that a twice daily regimen is both convenient and adequate. The antihypertensive effect is clearly discernible even during heightened reflex activity at a time remote from the last dose. At the relatively low doses tested, postural hypotension appears not to be a problem even in the presence of diuretic therapy. Labetalol controls high levels of blood pressure encountered during daily activity mainly through its β-adrenoceptor blocking property.

References

BALASUBRAMANIAN, V., MANN, S., RAFTERY, E.B., MILLAR-CRAIG, M.W. & ALTMAN, D. (1979a). Effect of labetalol on continuous ambulatory blood pressure. *Br. J. clin. Pharmac.*, **8**, 119S–123S.

BALASUBRAMANIAN, V., MANN, S., MILLAR-CRAIG, M.W. & RAFTERY, E.B. (1979b). Effect of labetalol in hypertension during exercise and postural changes. *Br. J. clin. Pharmac.*, **8**, 95S–100S.

BEVAN, A.T., HONOUR, A.J. & STOTT, F.H. (1969). Direct arterial pressure recording in man. *Clin. Sci.*, **35**, 329–344.

BRIET, S.N. & O'ROURKE, M.F. (1974). Comparison of direct and indirect blood pressure measurements in hospitalised patients. *Aust. N.Z.J. Med.*, **4**, 485–491.

EDWARDS, R.C. & RAFTERY, E.B. (1976). Haemodynamic effects of long term oral labetalol. *Br. J. clin. Pharmac.*, **3**, 733S–736S.

EWING, D.J., IRVING, J.B., KERR, F. & KIRBY, B.J. (1973). Static exercise in untreated systemic hypertension. *Br. Heart J.*, **35**, 413–421.

FRISHMAN, W.H., STROM, J.A., KIRSCHNER, M., POLAND, M., KLEIN, N., HALPRIN, S., LeJEMTEL, T.H., KRAM, M. & SONNENBLICK, E.H. (1981). Labetalol therapy in patients with systemic hypertension and angina pectoris: Effects of combined alpha and beta adrenoceptor blockade. *Am. J. Cardiol.*, **48**, 917–928.

GILMORE, E., WEIL, J. & CHIDSEY, C. (1970). Treatment of essential hypertension with a new vasodilator in combination with beta adrenergic blockade. *New Engl. J. Med.*, **282**, 521–527.

GOLDBERG, A.D., RAFTERY, E.B. & GREEN, H.L. (1976). The Oxford continuous blood pressure recorder—technical and clinical evaluation. *Postgrad. med. J.*, **52**, 104S–109S.

GOLDBERG, A.D., RAFTERY, E.B., CASHMAN, P.M.M. & STOTT, F.D. (1978). Heart rate, blood pressure correlation in ambulant untreated hypertensive subjects. I.S.A.M. (1977). *Proceedings of the International Symposium of Ambulatory Monitoring*, eds. Stott, F.D., Sleight P. & Goulding, L., pp. 157–165. London: Academic Press.

HUNYOR, S.N., BAUER, G.E., ROSS, M. & LARKIN, H. (1980). Labetalol and propranolol in mild hypertensives: comparison of blood pressure and plasma volume effects. *Aust. N.Z.J. Med.*, **10**, 162–166.

HUNYOR, S. & NYBERG, G. (1978). Comparison of intra-arterial and indirect blood pressure at rest and during isometric exercise in hypertensive patients before and after metoprolol. *Br. J. clin. Pharmac.*, **6**, 109–112.

JENNINGS, G., BOBIK, A. & KORNER, P. (1981). Influence of intrinsic sympathomimetic activity of β-adrenoceptor blockers on the heart rate and blood pressure responses to graded exercise. *Br. J. clin. Pharmac.*, **12**, 355–362.

KENNY, P., HUNYOR, S.N. & RENWICK, J.A. (1980). An appraisal of technical characteristics of the Oxford medilog ambulatory blood pressure recording system. I.S.A.M. (1979). *Proceedings of the Third International Symposium on Ambulatory Monitoring*, eds. Stott, F.D., Raftery, E.B. & Goulding, L., pp 445–448. London: Academic Press.

KORNER, P.I., TONKIN, A.M. & UTHER, J.B. (1979). Valsalva constrictor and heart rate reflexes in subjects with essential hypertension and with normal blood pressure. *Clin. exp. Pharmac. Physiol.*, **6**, 97–110.

LUND-JOHANSEN, P. & BAKKE, O.M. (1979). Haemodynamic effects and plasma concentrations of labetalol during long term treatment of essential hypertension. *Br. J. clin. Pharmac.*, **7**, 169–174.

MAN in't VELD, A.J. & SCHALEKAMP, M.A.D.H. (1982). How intrinsic sympathomimetic activity modulates the haemodynamic responses to beta-adrenoceptor antagonists. A clue to the nature of their anti-hypertensive mechanism. *Br. J. clin, Pharmac.*, **13**, 245S–247S.

MAXWELL, G.M. (1973). The effects of a new alpha and beta-adrenoceptor antagonist (AH5158) upon the general and coronary haemodynamics of intact dogs. *Br. J. Pharmac.*, **49**, 370–372.

McDEVITT, D.G. & SHAND, D.G. (1976). Plasma concentration and the time course of beta blockade due to propranolol. *Clin. Pharmac. Ther.*, **18**, 708–713.

MEHTA, S.K., WALSH, J.T., MONI, K. & GOLDBERG, A.D. (1980). Single daily dose of acebutolol in hypertensives: the effects on the circadian rhythm as measured with 24 hour blood pressure monitoring. I.S.A.M. (1979). *Proceedings of the Third International Symposium of Ambulatory Monitoring*, eds Stott, F.D., Raftery, E.B. & Goulding, L., pp 197–202. London: Academic Press.

MILLAR-CRAIG, M.W., BISHOP, C. & RAFTERY, E.B. (1978). Circadian rhythm of blood pressure in hypertension and modification by drug therapy. I.S.A.M. (1977). *Proceedings of the Second International Symposium of Ambulatory Monitoring*, eds Stott, F.D., Sleight, P. & Goulding, L., pp 133–139. London: Academic Press.

MILLAR-CRAIG, M.S., HAWES, D. & WHITTINGTON, J. (1970). New system for recording ambulatory blood pressure in man. *Med. Biol. Eng. Comp.*, **16**, 727–731.

MILLAR-CRAIG, M.W., MANN, S., KENNY, D. & RAFTERY,

E.B. (1979). The effect of once daily atenolol on ambulatory blood pressure. *Br. med. J.*, **1**, 237–238.

PRICHARD, B.N.C., BOAKES, A.J. & HERNANDEZ, R. (1979). Long term treatment of hypertension with labetalol. *Br. J. clin. Pharmac.*, **8**, 171S–177S.

RICHARDS, D.A., PRICHARD, B.N.S. BOAKES, A.J., TUCKMAN, J. & KNIGHT, E.J. (1977). Pharmacological basis for antihypertensive effects of intravenous labetalol. *Br. Heart J.*, **39**, 99–106.

SKINNER, C., GADDIE, J. & PALMER, K.N.V. (1975). Comparison of intravenous AH5158 (ibidomide) and propranolol in asthma. *Br. med. J.*, **2**, 59–61.

TAYLOR, S.H., WATT, S.H., COLDSTRAW, P.W. & TAYLOR, J.A. (1979). Effect of antihypertensive drugs on the circulatory response to dynamic and static exercise in hypertension. *Am. J. Cardiol.*, **43**, 418.

WILLIAMS, L.C., MURPHY, M.J. & PARSONS, V. (1979). Labetalol in severe and resistant hypertension. *Br. J. clin. Pharmac.*, **8**, 143S–147S.

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