BLOOD PRESSURE RESPONSE TO LABETALOL IN TWICE AND THREE TIMES DAILY ADMINISTRATION DURING A 24-HOUR PERIOD

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- 1 The anti-hypertensive effect of labetalol given twice or three times daily was evaluated in ambulant subjects with essential hypertension by recording blood pressure directly for 24 h before and after 15 d of labetalol administration (daily dose 600–1800 mg).
- 2 Labetalol reduced 24 h systolic and diastolic blood pressures by about 20%. The reduction was evident throughout the whole 24 h period, although it was less marked during sleep. The hypotensive effect was similar when the drug was given twice or three times daily.
- 3 The 24 h heart rate was reduced during labetalol treatment. However, this effect was less marked than the hypotensive effect and was not present in all subjects.
- 4 There was a reduction in the standard deviations of blood pressure and heart rate values. However, in neither case was the coefficient of variation altered, indicating that labetalol did not have any significant effect on the shape of the 24 h blood pressure measurements.

Introduction

Several studies that have made use of the cuff method for measuring blood pressure have shown that when administered three times daily, labetalol seems to exert a clearcut hypotensive effect (Richards & Turner, 1976).

In the present study we have performed a 24 h direct blood pressure recording (Bevan *et al.*, 1969; Goldberg *et al.*, 1976) in ambulant hypertensive inpatients before and during prolonged administration of labetalol. Our aim was to determine whether the hypotensive effect of this drug is observed throughout the day and night when patients are under relatively normal living conditions (Littler *et al.*, 1975; Goldberg *et al.*, 1978; Mancía & Zanchetti, 1980); whether the hypotension takes place not only when the drug is administered three times daily but also when only two daily administrations are used; and whether labetalol affects the features of neural cardiovascular regulation such as blood pressure variability.

Methods

Our study was performed in 12 hospital inpatients age range 31–52 yr; mean 42 ± 2 yr all of whom had essential hypertension. Patients (eight male, four female) were selected for the study if no cardiac or renal failure was present, if no signs or symptoms of coronary, cerebral or peripheral vascular insufficiency had ever occurred, if no major disease other than hypertension had been diagnosed, and if there had been no treatment with anti-hypertensive drugs during the 3 weeks preceding the time of the first direct blood pressure recording (see below). All subjects gave free consent to the procedure after its nature and purpose had been explained.

Measurements

We used the Oxford method to obtain direct and continuous blood pressure recording in our patients, as described in other studies (Bevan *et al.*, 1969; Goldberg *et al.*, 1976; Stott, 1976). In brief, a catheter was placed in a radial artery of the patient (previous local anaesthesia with 2% lidocaine) and was connected by way of a rigid-walled polyethylene tube to a plexiglass box positioned at the level of the heart. The box contained (a) a 40 ml saline reservoir and a constant flow pump which provided the catheter with a constant perfusion to keep it patent for 24 h; and (b) a blood pressure transducer con-

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nected to an amplifier and a tape recorder on which the blood pressure signal was stored during the 24 h period. The method ensured a satisfactory blood pressure recording because of the stability of the zero signal, the linearity of the transducer from 50 to 250 mmHg, and the frequency response of the whole tubing-transducer-amplifier system (optimal up to 10Hz). The small size and weight of the various parts of the device allowed the patients to be normally dressed and ambulant during the recording.

Protocol

Three to five days were allowed to elapse after a patient was hospitalized, during which period the diagnosis of essential hypertension was made and all major examinations necessary to evaluate the patient's clinical status were performed. During the

next 5 d period each patient's blood pressure was measured by the cuff method twice daily in the supine and standing positions. If the indirect measurements of blood pressure were stable, a 24 h direct blood pressure recording was performed. Thereafter, labetalol was administered orally at a dose of 200–300 mg daily.

In six patients the daily dose of labetalol was subdivided into three administrations given at 8 h intervals, whereas in the other six patients the daily dose was subdivided into only two separate administrations on a 12 h interval. The initial daily dose was increased at intervals of 3–4 d until a clearcut hypotensive effect became evident (cuff measurements). The effective dose of labetalol was then maintained for 7–10 d, after which a second 24 h blood pressure recording was performed. All direct recordings were started in the evening (between 1800 and 1900). During each recording the patient

Figure 1 Mean ($\pm$ s.e. mean) 24 h values for systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and heart rate (HR) before (●) and after labetalol (○). *P*, Difference between values before and after labetalol. $n = 12$.

was allowed to move freely within the hospital area and to engage in the social activities of the ambulant inpatients (television viewing, playing cards, visits of relatives, and so on).

Data analysis

Blood pressure recordings were analysed using a computer (PDP-11/34, digital equipment) as previously described (Mancia *et al.*, 1980; Cioffi & Di

Rienzo, 1980). In brief, for each recording mean arterial pressure was obtained by taking a large number of points (one every 50 ms) along the blood pressure signal and averaging them over periods of 3 s, average 3 s values being obtained also for systolic blood pressure, diastolic blood pressure and heart rate. From the 3 s values averages were obtained for each half-hour, for periods of 2 and 6 h and for the whole 24 h period. In addition, each recording was evaluated in terms of variability of mean arterial

Figure 2 Twenty-four hour values for mean arterial pressure (MAP) before (●) and after labetalol (○) twice daily (upper panel) or three times daily (lower panel). Administration at arrows. $n = 6$.

Figure 3 Mean ($\pm$ s.e. mean) values for mean arterial pressure (MAP) expressed in 6 periods before (●) and after labetalol (○) given twice daily to six patients. Periods 19–1 and 7–13 where those closest to the drug administration. B, Values before treatment; D, values during treatment. *P*, Difference between values.

pressure. Variability was assessed (a) by calculating the standard deviation and the coefficient of variation (standard deviation as percentage of mean value) for each of the 48 half-hours and averaging them (in this way a measure was obtained of a relatively short term variability); and (b) by evaluating the standard deviation and the coefficient of variation that resulted from the average of the mean blood pressure values of each half-hour (in this way a longer term blood pressure variability, that is, a variability among half-hour periods, was obtained). A similar assessment of variability was done for heart rate.

To simplify presentation of the data, values obtained in each patient have been summed to obtain mean values for the whole group of patients or for the subgroups that were given labetalol twice or three times daily. Comparison of the data before and during treatment with labetalol have been made using Student's *t* test for paired observations, taking a $P < 0.05$ as the minimal level of statistical significance. Throughout the text the symbol $\pm$ refers to s.e. mean.

Results

Blood pressure

The 24 h blood pressure values obtained before and during administration of labetalol are shown in Table 1 and Figure 1. Labetalol induced a reduction

in 24 h mean arterial pressure that was significant in each patient and in the group as a whole. The average magnitude of the reduction was 19%. As shown in Figure 1 the reduction involved both systolic and diastolic pressures (reductions of 19% and 20%, respectively).

Figure 2 shows mean arterial pressure data for patients who were given labetalol twice or three times daily. Data refer to each half-hour period within the 24 h. Blood pressure values observed during labetalol treatment were always below those observed in the control period. This occurred both when labetalol was given three times daily and when two daily administrations of the drug were used. Thus, the hypotensive effect of labetalol was evident throughout the 24 h of the recording. Both at three and at two daily administrations of labetalol there was no tendency for the hypotension to become progressively less in the intervals between administrations of the drug. This is illustrated in Figure 3, based data from patients in whom two doses of labetalol per day were used. The hypotensive effect was similar when average values of the first and second 6 h periods after each administration of the drug were separately considered. A further feature of the effect of labetalol on arterial blood pressure is shown in Figure 4 in which three different 2 h periods were evaluated during the 24 h period: a morning period (from about 0830 to 1030), an afternoon period (from about 1500 to 1700) and a sleep period (from about 0100 to 0300). During all three periods there was a significant hypotensive effect compared with pretreatment values. The

Table 1 Effects of labetalol at twice and three daily administrations on mean arterial pressure and heart rate in 12 subjects with essential hypertension

Patients	Sex	Age (yr)	Labetalol (mg x times daily)	Mean arterial pressure (mmHg)			Heart rate (beats/min)		
				B	D	P	B	D	P
1	M	42	400 x 2	112	86	0.01	67	57	0.01
2	M	33	600 x 2	106	76	0.01	83	66	0.01
3	F	50	400 x 2	107	103	0.01	76	61	0.01
4	M	48	300 x 2	107	98	0.01	75	62	0.01
5	M	36	400 x 2	81	77	0.01	64	65	NS
6	M	39	400 x 2	113	83	0.01	74	71	0.02
7	M	31	200 x 3	100	88	0.01	92	86	0.01
8	F	45	600 x 3	116	108	0.01	81	85	NS
9	M	37	600 x 3	161	118	0.01	88	72	0.01
10	M	52	300 x 3	144	101	0.01	94	68	0.01
11	F	48	300 x 3	109	77	0.01	74	70	0.05
12	F	44	300 x 3	130	100	0.01	79	77	0.05

Data are shown for each subject as average 24 h values $\pm$ s.e. B, values before treatment; D, values during treatment. P, Difference between B and D values.

hypotensive effect of the drug was similarly well pronounced during the morning and the afternoon periods. By comparison the effect was less pronounced during the night-time, the difference being significant ($P < 0.05$).

Heart rate

Table 1 and Figure 1 show 24 h heart rate values obtained before and during labetalol. As shown in

Table 1 labetalol induced a significant (and marked) bradycardia in seven patients but in the remaining five patients the reduction in heart rate was modest (heart rate reduction less than 4 beats/min) or absent. During labetalol administration there was a significant reduction in mean heart rate, but the magnitude of the effect was almost half the magnitude of the hypotensive effect (11% compared with 20% ($P < 0.05$)). Thus during labetalol treatment heart rate showed a reduction which was not as

Figure 4 Mean ($\pm$ s.e. mean) values for mean arterial pressure (MAP) during 2 h periods taken from three segments of the day before (●) and after labetalol (○). $n = 12$. P, Difference between values.

Figure 5 Relationship between changes in resting heart rate (HR) after labetalol and resting HR values before labetalol administration. Each point refers to an average 6 h value, a total of four points per patient being shown. $r = 0.46$; $n = 48$; $P < 0.001$

consistent and marked as the reduction in blood pressure.

There was a significant inverse correlation between heart rate after labetalol treatment plotted against pretreatment heart rate (average 6 h values, four values for each patient, Figure 5). Thus, the labetalol-induced bradycardia tended to be greatest when the pretreatment heart rate was highest.

Blood pressure and heart rate variability

Data on blood pressure and heart rate variability are shown as averages for all patients in Table 2. Labetalol significantly reduced the standard deviation of mean arterial pressure within half-hour periods but it did not affect the standard deviation for mean arterial pressure among half-hour periods. More importantly, in both cases the variation coefficient was constant, indicating that the blood pressure oscillations around the mean values were similar before and after administration of the drug.

A similar result was obtained with regard to heart rate variability. The standard deviation of heart rate during labetalol treatment was significantly less than the pretreatment value, based on calculations within and among half-hour periods.

However, the variation coefficient was not significantly altered by the drug. Also, percentage oscillations of heart rate around the mean values were not reduced by administration of labetalol.

Discussion

Several studies using the cuff method for measuring arterial blood pressure have shown that administration of labetalol can effectively reduce systolic and diastolic blood pressure values in hypertensive patients. Our study in ambulant patients, in whom blood pressure was recorded directly, confirms the anti-hypertensive effect of labetalol and allows the following additional points to be made. The blood pressure reduction that can be achieved in hypertension by labetalol administration may be of considerable magnitude, as suggested by the fact that in our patients the average 24 h mean arterial pressure fell by about 20%. Such blood pressure reductions occurred not only under resting conditions but also throughout the range of activities undertaken during a subject's normal life. The reduction in blood pressure achieved by labetalol is sustained throughout the intervals between the administrations of the drug, whether or not the drug is given twice or three times daily. It is clear that labetalol can consistently reduce arterial blood pressure when administered twice daily, and such a feature may improve patients' compliance to treatment with this drug.

In many of our patients the 24 h mean arterial pressure was only slightly above 100 mmHg, which may suggest that patients with mild hypertension were preferentially selected. It should be emphasized, however, that average 24 h blood pressure values are normally lower than those obtained by selected cuff measurements because an average 24 h value includes a considerable number of sleep during which blood pressure usually falls markedly (Littler *et al.*, 1975; Littler, 1979) and the cuff measurement may be associated with an emotionally-induced increase in blood pressure (Mancia *et al.*, 1981). Furthermore, use of the radial artery is known to provide a blood pressure that is somewhat lower than that existing in the brachial artery and the aorta (Hestad *et al.*, 1968). Thus, our subjects had certainly more than a mild hypertension and the limitation we have now mentioned does not apply to our results with labetalol treatment.

Our data suggest that the labetalol-induced hypotension was less during sleep than during wakefulness (see Figure 4). This finding is probably related to the well known reduction in sympathetic tone that occurs during sleep which is largely responsible for the hypotension that characterises this condition (Mancia & Zanchetti, 1980). In these circumstances it is not surprising that the effects of labetalol, the action of which also involves a reduction in sympathetic tone, may be less pronounced.

It might be expected, from its β -adrenoceptor blocking property without intrinsic sympatho-

Table 2 Effects of treatment with Labetalol on short- and long-term 24 h blood pressure and heart rate variability

		Standard deviation (mmHg)		Variation coefficient (%)	
		Within half-hours	Among half-hours	Within half-hours	Among half-hours
Mean arterial pressure	B	8.0 ± 1.7	11.7 ± 2.9	6.9 ± 1.3	10.4 ± 3.2
	D	6.8 ± 1.8	10.5 ± 2.0	7.3 ± 1.9	11.6 ± 3.1
	P	<0.02	NS	NS	NS
Heart rate		Standard deviation (beats/min)		Variation coefficient (%)	
		Within half-hours	Among half-hours	Within half-hours	Among half-hours
	B	7.2 ± 2.8	9.8 ± 2.9	9.1 ± 3.0	12.4 ± 3.3
(n = 12)	D	6.6 ± 2.9	7.5 ± 4.3	9.4 ± 3.3	10.5 ± 4.9
	P	<0.001	<0.01	NS	NS

Data are shown as average values ± s.e. mean of the 12 subjects shown in Table 1. B, Values before treatment; D, values during treatment. P, difference between B and D values. For definition of standard deviation and variation coefficient within and among half-hours (short- and long-term 24 h variability), see Methods section. NS, Not significant.

mimetic activity, that labetalol would induce a clearcut reduction in heart rate (Koch, 1976). Indeed, several of our patients did show a bradycardia and this effect was particularly evident in those with an elevated heart rate value before drug administration. This in itself suggests the existence of a more pronounced sympathetic tone to the sino-atrial node (see Figure 5). However, in other patients the heart rate values, although they never increased, were either unchanged or only slightly reduced by labetalol. This may be the result of the combined α - and β -adrenoceptor-blocking properties of the drug. The pronounced anti-hypertensive effect that may follow α -adrenoceptor blockade reflexly induces an increase in heart rate through deactivation of arterial baroreceptors. This effect may be counteracted by the β -adrenoceptor blockade, the role of which in some instances would thus be that of preventing tachycardia rather than inducing bradycardia.

Continuous blood pressure recording has shown that in normotensive and hypertensive subjects blood pressure and heart rate are characterized by marked variability (Mancia *et al.*, 1980; Littler *et al.*, 1978; Watson *et al.*, 1979). Part of this variability is explained by the cardiovascular changes that accompany the wakefulness-sleep cycle (Littler *et al.*, 1975; Littler, 1979) and possibly by circadian influences (Millar-Graig *et al.*, 1978). Another part, however, is due to the rapid and short lasting occurrence of blood pressure and heart rate

variations sometimes associated with but sometimes independent of identifiable behavioural events (Littler *et al.*, 1978). An important factor in the production of this phenomenon may be the spontaneous variation in the influence of the autonomic nerves on heart and peripheral circulation (Mancia *et al.*, 1980; Mancia *et al.*, 1981). In our patients the standard deviations of blood pressure and heart rate showed a tendency towards a reduction following administration of labetalol. This was the case for standard deviation among and within half-hour periods.

However, the reduction paralleled the reduction in the 24 h mean values and the variation coefficients, that is, the percentage standard deviations, were in no case significantly affected by the drug. This finding suggests that labetalol did not cause a substantial alteration in long- and short-term blood pressure and heart rate variability. It further suggests that the adrenergic properties of labetalol, even when capable of inducing hypotension and bradycardia, do not decrease the ability of the autonomic nervous system to phasically modulate the heart and the blood vessels, thereby leaving this important cardiovascular control system substantially unimpaired.

This research has been supported in part by a grant from the Finalized Program of National Research Council, Subproject Hypertension.

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