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BLOOD PRESSURE, BODY FLUID VOLUMES AND GLOMERULAR FILTRATION RATE DURING TREATMENT WITH LABETALOL IN ESSENTIAL HYPERTENSION

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1 In a single blind study seventeen patients with mild or moderate essential hypertension and normal renal function were treated with labetalol alone in increasing doses from 300 via 600 to 1200 mg daily.

2 Average supine BP (systolic/diastolic) was reduced by 24/19 mm Hg. Seven patients attained a diastolic BP ≤ 95 mm Hg. A significant postural fall in systolic BP was recorded, but no symptomatic orthostatic hypotension occurred.

3 In twelve patients measurements of plasma volume (^{125}I-albumin), extracellular volume (^{82}Br-space) and glomerular filtration rate (^{51}Cr-EDTA clearance) on placebo and subsequently labetalol showed no systematic changes.

4 Side effects were few causing two withdrawals because of impotence and arthralgia.

5 It is concluded that monotherapy with labetalol results in clinically relevant, persistent and dose dependent reductions in BP in patients with mild or moderate essential hypertension, apparently without concomitant expansion of body fluid volumes or influence on glomerular filtration rate.

Introduction

It has repeatedly been demonstrated that treatment with most potent antihypertensive drugs including adrenoceptor blockers frequently is associated with an expansion of body fluid volumes which may account for an inadequate blood pressure reduction (e.g. Weil & Chidsey, 1968; Finnerty *et al.*, 1970; Sederberg-Olsen & Ibsen, 1972; Hansson *et al.*, 1977; Koshy *et al.*, 1977; Ibsen *et al.*, 1978; Rasmussen & Rasmussen, 1979). Addition of diuretics restore the sensitivity to treatment resulting both in a reduction in blood pressure and volumes (Rønnov-Jessen & Hansen, 1969; Finnerty *et al.*, 1970; Dustan, Tarazi & Bravo, 1972; Geyskes *et al.*, 1975; Rasmussen & Rasmussen, 1979). Further, renal function may also be reduced by antihypertensive treatment as has been reported with propranolol alone (Ibsen & Sederberg-Olsen, 1973; Bauer & Brooks, 1979) and after the addition of the α-adrenoceptor blocking agent prazosin (Ibsen *et al.*, 1979). The recently introduced antihypertensive drug labetalol, which lowers the blood pressure partly by reducing the peripheral resistance, possesses both α- and β-adrenoceptor blocking properties and may thus influence body fluid volumes and renal function. The purpose of this study was to evaluate the hypotensive efficacy of labetalol and relate this to measurements of plasma volume (PV), extra-cellular volume (ECV) and glomerular filtration rate (GFR) in patients with mild and moderate essential hypertension.

Methods

Patients studied

Nineteen patients with essential hypertension WHO stage I–II were included in the study. Two patients were withdrawn because of side-effects.

The seventeen patients who completed the study consisted of 12 men and 5 women aged 31–66 years. Four patients were untreated on entry, while the remaining 13 patients had been receiving antihypertensive therapy from 10 years to less than 1 year. One patient had criteria of ventricular hypertrophy on ECG and one patient had signs of an enlarged left ventricle on chest X-ray. The pyelographic and renographic findings were normal in all patients. One patient had an increased serum creatinine. None of the patients had accelerated hypertension, congestive heart failure, diabetes, chronic obstructive lung disease or conditions known to influence the variables investigated.

The investigational nature of the study was ex-

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plained before obtaining the patients consent to participation.

Plan of study

All investigations and clinical examinations were performed in the out-patient hypertension clinic. Antihypertensive drug therapy was withdrawn for a 4 to 8 weeks 'run-in' period. Patients with a diastolic blood pressure (DBP) between 95–115 mm Hg at the end of this period were included in the study. An initial placebo period of 4 weeks duration was followed by a treatment phase in which labetalol was administered in three daily doses increasing from 300 mg, via 600 mg to 1200 mg daily. The mean of at least two blood pressure measurements on separate visits a week apart was recorded before any changes in medication. The dose was increased until satisfactory blood pressure was obtained (i.e. DBP $\leq$ 95 mm Hg) or maximum dose was achieved or prohibitive side effects had occurred.

Supine and standing blood pressure were measured with a mercury sphygmomanometer, and diastolic blood pressure was recorded at the disappearance of the Korotkoff sounds (phase V). Mean blood pressure was calculated as the diastolic blood pressure plus one third of the pulse pressure. Blood pressure measurements were performed by a nurse unaware of the patient's drug therapy. Side effects were recorded both on placebo and at each visit during treatment with labetalol.

In twelve patients body fluid volumes and glomerular filtration rate were measured on placebo and after at least 4 weeks on an individual maximum dose of labetalol. Plasma volume (PV) was determined by i.v. injection of ^{125}I-labelled human albumin 6–8 μCi and collection of blood samples after 10, 15, 20, 30, 40, 50 and 60 min. PV was calculated from the radioactivity at time zero determined by linear regression from the semilog radioactivity-time graph and the amount of tracer injected (Parving & Gyntelberg, 1973). Extracellular fluid volume (ECV) was measured as the ^{82}Br-distribution space (Leth & Binder, 1970). About 15 μCi NH_4 ^{82}Br was injected i.v., and following an equilibration period of 3.5 h, blood samples and urine were collected. Individual correction of loss to erythrocytes and urine was done. Glomerular filtrations rate (GFR) was determined by ^{51}Cr-EDTA, using the single injection technique as decribed by Brøchner-Mortensen (1972). All examinations were carried out at 08.00 h. The patients had had nothing to eat or drink for at least 8 h. They were kept in the supine position from at least half an hour before injection of the isotopes and during the investigation which lasted 6 h (Rasmussen & Rasmussen, 1979).

Statistical analysis was performed using the Wilcoxon's test for matched pairs. Values of $P < 0.05$ were considered statistically significant.

Results

Blood pressure and heart rate

Changes in average supine and standing blood pressure as well as heart rates obtained on an individual maximum dose of labetalol in the seventeen patients who completed the study are shown in Table 1. The mean dose for the patients as a whole was 970 mg/day.

On the average supine and standing blood pressure

Table 1 Changes in blood pressures and heart rates (mean ± 1 s.e. mean) in 17 patients with essential hypertension on an individual maximum dose of labetalol compared to placebo.

	Placebo	*Labetalol*	P *value*
Supine blood pressure (mm Hg)			
Systolic	177 ± 4	153 ± 5	< 0.01
Diastolic	114 ± 1	95 ± 2	< 0.01
Standing blood pressure (mm Hg)			
Systolic	172 ± 4	142 ± 4	< 0.01
Diastolic	117 ± 2	95 ± 1	< 0.01
Systolic postural change (mm Hg)	−5 ± 1	−11 ± 1	< 0.01
Diastolic postural change (mm Hg)	+3 ± 1	0 ± 1	NS
Pulse rate (beats/min)			
Supine	78 ± 3	72 ± 3	< 0.05
Standing	82 ±	80 ± 2	NS

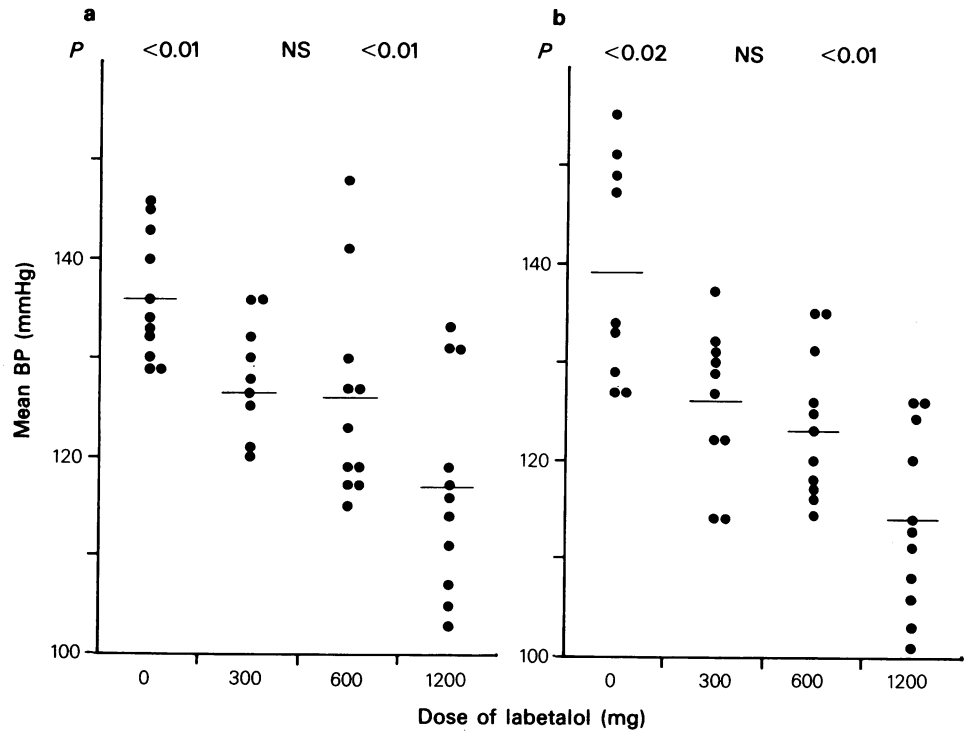

Figure 1 Individual changes in supine (a) and standing (b) mean blood pressures in 11 patients who were given all three dose levels of labetalol (i.e. 300, 600 and 1200 mg/day).

decreased significantly by 16% and 18%, respectively ($P < 0.01$). Seven patients (41%) obtained a supine diastolic blood pressure < 95 mm Hg. In one patient DBP decreased by only 4 mm Hg, while the rest had a fall from 10–32 mm Hg. On maximum treatment with labetalol alone there was a significant fall in standing systolic blood pressure as opposed to the placebo period ($P < 0.01$). Changes in diastolic blood pressure were similar in both situations (Table 1). Supine pulse rate decreased significantly by 8%, while standing pulse rate was unchanged.

In Figure 1 is shown the dose-related decrease in mean blood pressure in the eleven patients who were given all three dose levels (300 mg, 600 mg and 1200 mg daily). It should be noted that the increase in dose from 300 to 600 mg did not cause a further reduction in blood pressure.

Body fluid volumes and renal function

In seven men and four women aged 31–66 years measurements of PV, ECV and GFR were performed in the placebo period and after an individual maximum dose of labetalol (mean 875 mg/day) had been given for 4–15 weeks (mean 6 weeks). There was an insignificant increase in PV and ECV by about 5%

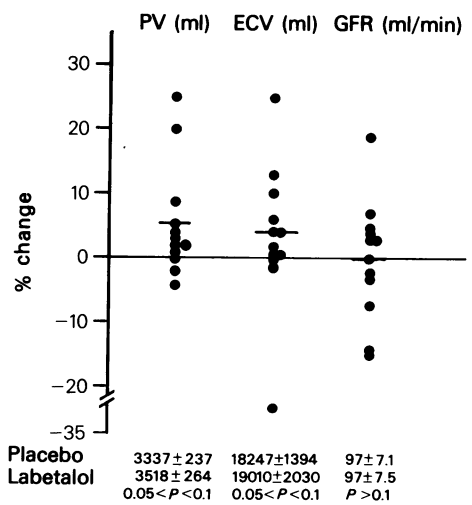

Figure 2 Individual changes in percentage of pre-treatment levels of plasma volume (PV), extracellular volume (ECV) and glomerular filtration rate (GFR) in 12 patients on an individual maximum dose of labetalol. Indicated are group mean values (± 1 s.e. mean) in the placebo phase and during labetalol treatment.

and 4%, respectively (Figure 2). There was no correlation between changes in blood pressure and body fluid volumes or dose of labetalol.

Glomerular filtration rate did not change on labetalol, being on average 97 ml/min both before and during treatment (Figure 2).

Side effects

Two patients withdrew from the study, one because of impotence and one because of painful sensations in the joints of the fingers. Further, two patients complained of impotence and one of tiredness. In the placebo period two patients complained of tiredness and headache.

Discussion

In this single-blind study we found that labetalol given alone caused dose-related significant reductions in blood pressure and heart rate. These results are in agreement with the findings in other placebo-controlled trials attesting to the efficacy and safety of labetalol in the treatment of hypertension (Johnson, La Brooy & Munro-Faure, 1976; Kane, Gregg & Stephens, 1979, Frick & Pörsti, 1976; Pugsley *et al.*, 1979; Sanders *et al.*, 1979; Dawson *et al.*, 1979; McNeil & Louis, 1979). However, in a recent study (Weidmann *et al.*, 1978) it was found that labetalol given alone in increasing doses during a 6 week period caused only a transient fall in supine blood pressure. Measurements of plasma volume and blood volume in the second and fourth week of treatment showed progressive and significant increases of up to 20% and 17%, respectively. Further, a gain of 1.7% in body weight was observed. It was concluded that the sensitivity to treatment was reduced by the expansion of body fluid volumes. Addition of chlorthalidone caused a significant reduction in blood pressure and intravascular volume even though the dose of labetalol was reduced. The present study did not show significant increases in PV and ECV. Differences in the design of the two studies could explain these divergent results. Body fluid expansion during antihypertensive therapy may be a transient phenomenon (Birkenhäger & Schalekamp, 1976). We performed the second determination of PV and ECV when the patients had been on labetalol for at least 4 weeks while Weidmann *et al.* (1978) increased the dose weekly and measured volumes in the second and fourth week. However, we have not observed any relationships between fluid retention and time or magnitude of dose administered. No significant association between increases in body fluid volumes and diminished blood pressure reduction could be demonstrated. The small number of patients studied makes it difficult to reach any firm conclusions on this point. In some studies fluid retention as indicated by weight gain or development of oedema and inadequate blood pressure response has been observed especially in hypertensive patients with renal impairment (Thompson, Joekes & Hussein, 1979; Bailey, 1979), while others have not found any evidence of tolerance during long-term therapy (Prichard, Boakes & Hernandez, 1979). However, it seems most likely that fluid retention can occur during monotherapy with labetalol and that addition of diuretics is a rational approach in the event of inadequate blood pressure response (Weidmann *et al.*, 1978; Kane *et al.*, 1979; Thompson *et al.*, 1979).

Our study indicates that treatment with labetalol does not affect glomerular filtration rate. These results agree with other investigations including hypertensive patients with normal and impaired renal function (Williams, De Voss & Craswell, 1978; Thompson *et al.*, 1979; Bailey, 1979).

As expected from an α-adrenoceptor blocking drug, a fall in standing blood pressure and posture-related dizziness have been reported during labetalol treatment. It has seldom necessitated withdrawal of the drug (Brogden *et al.*, 1978; Weidmann *et al.*, 1978; Sanders *et al.*, 1978; Pugsley *et al.*, 1979; Dawson *et al.*, 1979; Kane *et al.*, 1979). Others have not observed postural or exercise hypotension (Prichard *et al.*, 1979; Thompson *et al.*, 1979). In this study there was a significant reduction in systolic standing blood pressure, but none of the patients complained of posture related dizziness. In all, side-effects were few, but due to the number of patients in the study, only large differences in side-effects would be expected to be found. Three patients complained of impotence while on active drug and one of them withdrew from this study. This is a likely side effect due to the α-adrenoceptor blocking properties of the drug, and has been reported previously (Pugsley *et al.*, 1979).

The results of the present study suggests that labetalol alone caused significant, dose-related, persistent and clinically relevant reductions in blood pressure when given to patients with mild and moderate essential hypertension. Glomerular filtration rate is not affected during treatment. Changes in body fluid volumes seem to be of the same order of magnitude as has been seen with α- and β-adrenoceptor blocking drugs.

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