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RATE OF ONSET OF HYPOTENSIVE EFFECT OF ORAL LABETALOL

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1 Labetalol caused a fall in blood pressure within 2 h of oral doses of 100, 200 and 400 mg in six hypertensive patients.

2 This fall which was dose-related was maximal by 3 h and was sustained when the drug was given in doses of 100 mg 8 hourly, 200 mg 8 hourly and 400 mg 8 hourly.

3 This rapid fall in pressure when labetalol is given by mouth which contrasts to that seen on administration of pure β-adrenoceptor blocking agents is a valuable therapeutic property.

Introduction

β-adrenoceptor blocking drugs are widely used to treat patients with mild and moderate hypertension; immediate effects of their administration include a fall in cardiac output, and a rise in systemic vascular resistance but no rapid fall in blood pressure (Ulryck, Frohlich, Dustan & Page, 1968). It has been suggested that a combination of α- and β-adrenoceptor blockade may form a logical basis for antihypertensive treatment, since β-adrenoceptor blockade would antagonize the reflex tachycardia caused by α-adrenoceptor blockade which in turn would lead to a decrease in peripheral vascular resistance. Early studies, however, showed that the combination of propranolol with phenoxybenzamine was of little clinical value largely due to the high incidence of unacceptable side effects, such as postural hypotension (Beilin & Juel-Jensen, 1972).

Labetalol is a unique drug in that it combines the properties of α- and β-adrenoceptor blockade in one molecule, (Farmer, Kennedy, Levy & Marshall, 1972). It has been shown to be effective in the treatment of hypertension in man, both in the short and long term, in hospital and general medical practice, (Prichard & Boakes, 1976; Kane, Gregg & Richards, 1976).

The aim of the study reported here was to investigate the rate of onset of the antihypertensive effect of labetalol given by mouth to a group of patients with mild to moderate hypertension who had not previously been given other drug therapy. Since the purpose was to look at the rate of onset of the effect, a definite decision was made not to use a double-blind technique nor to randomize drug orders or dosage regimes, all of which were considered inappropriate. Blood pressure was, however, measured throughout using apparatus designed to minimize observer bias.

Methods

Patients studied

Six patients, two male and four female, aged between 46 and 64 years were studied. Their pre-treatment (lying) blood pressure ranged from 164/98 to 217/114 mm Hg; (mean of at least six measurements) and blood urea was less than 8 mmol/l. No patient had accelerated hypertension, cardiac failure or bronchial asthma. All patients had a chest X-ray, ECG, urinalysis, and full blood count carried out and plasma electrolytes and 24 h vanillyl mandelic acid excretion measured prior to drug administration.

Plan of study

Patients were admitted to hospital for the duration of the study. During the first two or three days the initial investigations were performed. The design of the study is shown in the accompanying table (Table 1). The

Table 1 Design of study

Days	*Treatment period*
1–3	Matching Placebo 100 mg 8 hourly
4	Labetalol 100 mg 8 hourly
5	Labetalol 200 mg 8 hourly
6	Labetalol 400 mg 8 hourly
7 onwards	Placebo 100 mg 8 hourly until BP returned to pre-treatment level
For 3 days (Days A, B, C)	Labetalol 100 mg 8 hourly Placebo, 200 mg 8 hourly until BP returned to pre-treatment level
For 3 days (Days D, E, F)	Labetalol 200 mg 8 hourly

purpose of the 3 day periods A, B, C and D, E, F when labetalol 100 mg 8 hourly and 200 mg 8 hourly respectively was given was to determine if an initial hypotensive response was sustained or if continued therapy produced an increase in the hypotensive response.

During the study, blood pressure was measured in the lying position, after 5 min rest and after 30 s standing, using a Hawksley Random Zero Mercury Sphygmomanometer. Blood pressures were taken by observers fully accustomed to using the sphygmomanometer, 1, 2, 3 and 6 h after the initial dose of labetalol on days 4, 5 and 6 and then at 4 hourly intervals throughout the study. Diastolic blood pressure was taken as Phase 4 Korotkoff sounds. Pulse rate was measured at the same time as blood pressure. Peak expiratory flow (Wright Peak Flow Meter) was also measured three times daily throughout the study, 2 h after drug administration.

Blood was taken on days 3–6 for measurement of plasma renin activity, 2–3 h after the morning dose of labetalol and when the patient had been standing for 4 h. Plasma renin activity was measured by the generation of angiotensin I using the method of Sealey & Laragh (1973).

Results

The hypotensive response to labetalol was observed within 2 h of administration of the first dose, and this response was usually maximal by 3 h. The standing blood pressure fell significantly ($P < 0.025$) from

$$\frac{190.1 \pm 11.56}{113.9 \pm 3.10} \text{ mm Hg (mean} \pm \text{s.e. mean) to}$$

$$\frac{155.0 \pm 11.80}{94.3 \pm 5.66} \text{ mm Hg at}$$

a mean time of 2.4 ± 0.21 h after the first dose of active labetalol. Figure 1 shows a typical fall in blood pressure in one patient after administration of the first dose of 100 mg labetalol.

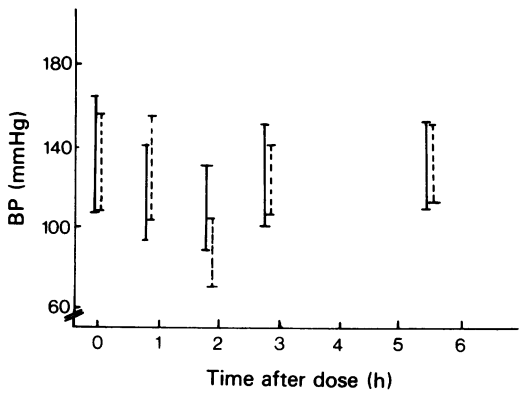

Figure 1 Blood pressure (——— lying, - - - - standing) in one patient after single oral dose of labetalol 100 mg.

Four hourly blood pressure measurements were averaged in each patient during days 1–3 and compared with those on days 4, 5 and 6 (Table 2). There was a significant ($P < 0.01$) fall of blood pressure between days 1–3 (placebo) and that on day 4 (labetalol 100 mg 8 hourly) in systolic and diastolic blood pressures, both lying and standing. The fall in blood pressure between days 4 (100 mg 8 hourly) and 5 (200 mg 8 hourly) was not significant. Similarly, there was not a significant ($P > 0.05$) fall in pressure between days 5 and 6 (400 mg 8 hourly). However, when blood pressures were compared between days 4 and 6 the difference was significant in both systolic and diastolic in both positions ($P < 0.01$).

During the second and third placebo phases, blood pressures were not significantly different from those found during days 1–3. Blood pressure took between 1 and 5 days to return to pre-treatment levels during these placebo periods.

There was a significant ($P < 0.05$) fall in blood pressure, systolic and diastolic, lying and standing, during days A, B, C (labetalol 100 mg 8 hourly) when

Table 2 Blood pressures (mean ± s.e. mean) of six patients studied

Days	*Lying systolic (mm Hg)*	*Lying diastolic (mm Hg)*	*Standing systolic (mm Hg)*	*Standing diastolic (mm Hg)*
1–3 placebo	192.9 ± 3.86	109.1 ± 1.33	192.0 ± 4.56	114.0 ± 1.33
4 (100 mg three times daily)	173.2 ± 6.12	97.6 ± 2.03	169.5 ± 6.63	99.7 ± 2.58
5 (200 mg)	165.3 ± 6.77	91.3 ± 2.58	158.7 ± 6.07	96.6 ± 2.50
6 (400 mg)	157.9 ± 6.23	88.6 ± 2.11	147.3 ± 6.31	89.2 ± 2.81
Placebo	186.4 ± 5.88	105.4 ± 1.88	177.8 ± 5.97	111.4 ± 1.63
A, B, C, 100 mg three times daily for 3 days	168.0 ± 4.28	94.8 ± 1.59	161.2 ± 4.10	98.3 ± 1.45
Placebo	188.4 ± 4.24	105.6 ± 1.74	182.9 ± 4.60	111.1 ± 1.42
D, E, F, 200 mg three times daily for 3 days	172.3 ± 4.37	97.4 ± 1.82	169.6 ± 5.62	101.2 ± 2.10

the 4 hourly averaged blood pressures were compared to those during the placebo period. The falls in pressure were not significantly different ($P > 0.05$) from those seen on day 4 (labetalol 100 mg 8 hourly for 1 day). The fall in blood pressure on days D, E, F (labetalol 200 mg 8 hourly) whilst significantly different ($P < 0.05$) from the preceding placebo phase, was no different from that during day 5 (labetalol 200 mg 8 hourly for 1 day) or during days A, B, C. These results are shown in Figure 2. No significant changes in pulse rate were seen during any of the periods of labetalol administration. Peak flow rate similarly was unchanged by labetalol (355.7 l/min on placebo, 369 l/min on labetalol 400 mg three times daily)

Plasma renin activity decreased significantly ($P < 0.01$) during labetalol treatment (Table 3) but these decreases were not dose related.

Discussion

Oral labetalol caused a rapid fall in blood pressure. In the six patients studied, a significant fall in blood pressure was observed within 2 h of oral drug administration and this fall was usually maximal by 3 h. This contrasts with administration of a β-adrenoceptor blocking agent such as propranolol where the rate of fall of blood pressure is considerably slower and may even take weeks to be maximal (Prichard & Gillam, 1964). Presumably this rapid fall is a manifestation of the additional α-adrenoceptor blocking effect of labetalol. It is of importance that there was no change in pulse rate on drug administration, due to simultaneous β-adrenoceptor blockade. This study was designed to examine the hypotensive response to oral labetalol after single doses and sustained (3 days) treatment. Both the magnitude and rate of hypotensive response were similar during single dose administration and during the 3 day treatment period.

A dose related fall in blood pressure, both systolic and diastolic was seen as the dose of labetalol was increased daily from 100 to 400 mg 8 hourly, but the lack of change of the blood preasure when the drug was given at doses of 100 mg and 200 mg 8 hourly for 3 days (A–C and D–F) is difficult to explain and is not reflected in our general clinical experience and sustained therapy with a larger dose might have produced a significantly greater fall in blood pressure.

No significant side effects were seen during this study. Postural hypotension was a problem as had been found by Beilin & Juel-Jensen (1972) with a combination of coventional α- and β-adrenoceptor blocking drugs. Even when the drug is given in higher doses for prolonged periods, it is our experience that this side effect is not prominent, (Breckenridge, Calvey, Green, McIver, Orme & Serlin, 1977). One patient complained of transient nausea after taking labetalol 200 mg 8 hourly for 3 days, but this was minimized by administering the drug with food. Of interest is the fact that labetalol, like many other β-adrenoceptor blocking agents caused a significant fall in plasma renin activity in our study. This has been noted previously (Trust, Rosei, Brown, Fraser, Lever, Morton & Robertson, 1976).

It has been previously shown, (Richards, Maconochie, Bland, Hopkins, Woodings & Martin, 1977) that labetalol is rapidly absorbed after oral administration, peak plasma concentrations occurring within 2 h. In addition, the same workers showed that there was a rapid decline in plasma concentrations although inhibition of exercise-induced tachycardia persisted longer than 4 h. Our observations would suggest that by 6 h after a single oral dose of 100 mg, blood pressure is returning towards pre-treatment levels. After single doses of 400 mg, the duration of the hypotensive response was greater than after 100 mg.

Labetalol is a useful anti-hypertensive agent for patients with all grades of hypertension and the

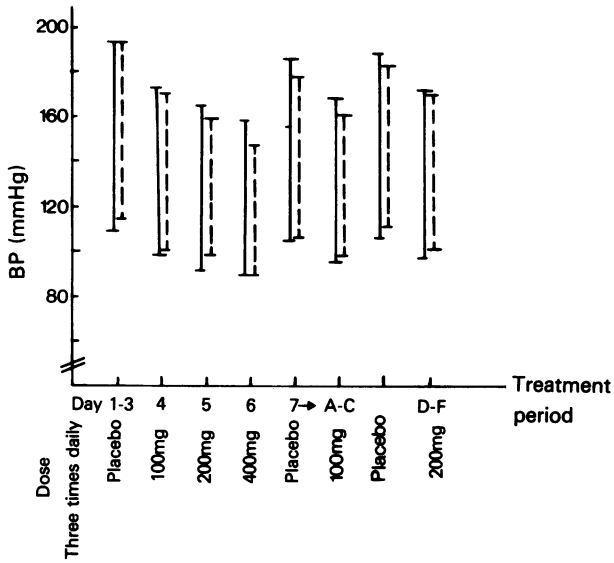

Figure 2 Averaged blood pressures (——— lying, - - - standing) of six patients during different periods of the study.

Table 3 Plasma renin activity (mean ± s.e. mean) in the six patients

	PRA (ng ml^{-1} h^{-1})
Placebo Day 3	1.04 ± 0.23
Labetalol 100 mg Day 4	0.75 ± 0.21
Labetalol 200 mg Day 5	0.73 ± 0.23
Labetalol 400 mg Day 6	0.48 ± 0.17

present study would suggest that an additional advantage is the rapid fall in blood pressure when the drug is given by mouth.

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