A DOUBLE-BLIND STUDY WITH ORAL LABETALOL (TRANDATE) — A NEW HYPOTENSIVE AGENT

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SYNOPSIS

A double-blind crossover study was carried out to assess the efficacy and tolerance of oral labetalol in patients with mild to moderate hypertension and also to determine a suitable dosage for achieving blood pressure control in the Malaysian population.

Results obtained from a study of 18 patients showed that:

(i) **Labetalol significantly lowered the blood pressure when compared with placebo in lying, sitting and standing positions ($p < 0.01$) for all 18 patients completing the trial.**

(ii) **The heart rate was not significantly reduced from the normal range.**

(iii) **No serious side effects were noted during the study period and within the dose range used.**

(iv) **In the treatment of mild to moderate hypertension, the dosage range of 300-600 mg labetalol was found to be adequate in bringing about satisfactory control of blood pressure, the majority of patients requiring 400 mg and above.**

INTRODUCTION

Since the first report of the antihypertensive effect of beta-blockers appeared in 1964, there are at least 10 currently available beta-blockers in Malaysia, and they are increasingly becoming very popular with many physicians. Most beta-blockers reduce cardiac output during short and long term treatment but the peripheral vascular resistance increases during short term treatment and is only gradually reduced during long term therapy, an effect which is probably related to unopposed alpha-adrenoceptor stimulation (Tarazi and Dunstan 1972, Hanson et al 1974). Therefore a drug with both alpha-and beta-adrenoceptor blocking activity can be anticipated to lower blood pressure by decreasing peripheral resistance, and at the same time inhibiting the reflex increase of heart rate and cardiac output.

Labetalol (Trandate) is a competitive adrenoceptor-blocking drug at both alpha- and beta-adrenoceptor sites in animals and man (Farmer et al 1972), and has been shown to reduce peripheral resistance without significantly reducing cardiac output and pulse rate in patients with moderately severe hypertension (Prichard et al 1975). Placebo controlled studies have shown labetalol to be superior to placebo when given orally in fixed or individually titrated doses to patients with mild to moderate and severe hypertension.

MATERIAL AND METHODS

Suitable adult male patients suffering from mild to moderate hypertension (standing diastolic pressure of 95-120mm Hg) were admitted to the trial. The majority of patients, if not all, were expected to be suffering from 'essential hypertension' and those suffering from 'secondary hypertension' were thoroughly investigated to determine the degree and seriousness of the condition. In none of the patients was there a contraindication to the use of beta-adrenoceptor blocking drugs.

The patients were studied in an outpatient clinic by means of a double-blind crossover study lasting approximately six months for each patient. The team of investigators included a trial coordinator who saw to the prescribing and dispensing of drugs and studied individual patient responses or any occurrence of side effects before a change in the treatment was done. The trial coordinator functioned independently and took no direct part in the clinical assessment of the patient. A written informed consent was obtained from each patient undergoing the trial.

Newly diagnosed patients underwent a two-week period of observation without any antihypertensive treatment. If they were still hypertensive at the end of this period they then entered the study proper. Patients who were already on antihypertensive treatment were discontinued on this medication and weekly follow-ups made. If found suitable at the end of the two weeks they were then taken into the trial.

A pretrial workup was done comprising a full history and physical examination to evaluate presenting symptoms and severity of the illness. Severity was established by five prognostic indices: basal diastolic pressure, optic fundi, cardiac, renal and cerebral complications, and patients were scored according to criteria set by the Veterans Administration Cooperative Study Group 1960. Patients with a score of 16 or more were excluded from the trial.

Patients then entered the trial and were randomly allocated into either Schedule A or Schedule B of the trial design (Fig. 1).

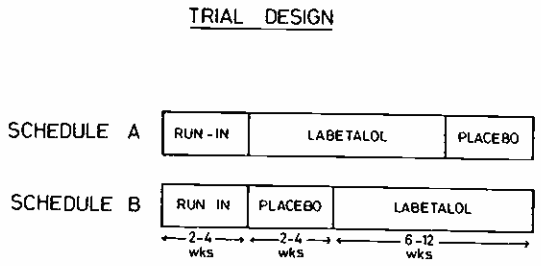


FIG. 1

The placebo and labetalol tablets (100 mg) that were used were identical in appearance. The tablets were packed in plastic strips in such a way that each strip contained 3 compartments, each compartment containing 2 tablets. Patients on both treatment schedules received 2 tablets 3 times daily, to be taken after meals.

Those on labetalol started with a dose of 300mg daily, and were reviewed every week or fortnightly until a final dose of 600mg was given, depending on individual response. When the desired blood pressure was attained on a particular dosage, that does was then maintained for a further 4 to 6 weeks.

Those on placebo received tablets of similar appearance and were followed up weekly for 2 to 4 weeks and, if found suitable, then switched over to the active drugs.

Blood pressure was taken by means of a mercury sphygmomanometer by the same observer, as far as possible, in three main positions, i.e. lying, sitting and standing after a minimum period of 3 minutes in each position. The diastolic pressure was recorded the moment the sounds changed intensity.

Heart rate was measured and recorded every time the blood pressure was taken.

The following investigations were done before commencing the trial, during the study, and at the end of the study period:

i Electrocardiogram
ii Chest X-ray
iii Urine full examination and microscopic examination
iv Full blood picture and erythrocyte sedimentation rate
v Blood urea, serum creatinine and electrolytes
vi Lactic dehydrogenase
vii Serum lipids
viii Liver function tests
ix Random blood sugar
x Antinuclear factor
xi Creatinine clearance
xii Serum proteins
xiii Urinary Vanillyl Mandelic Acid
xiv Intravenous pyelogram
xv Respiratory function tests
xvi Visual acuity, visual field and fundoscopy

The criteria used for adequate blood pressure control is a reduction to, and maintenance of, a diastolic pressure of around 90mm Hg or below.

Students' t-test was used in the analysis of the blood pressure and pulse rate data.

RESULTS

a) Blood pressure and Heart rate

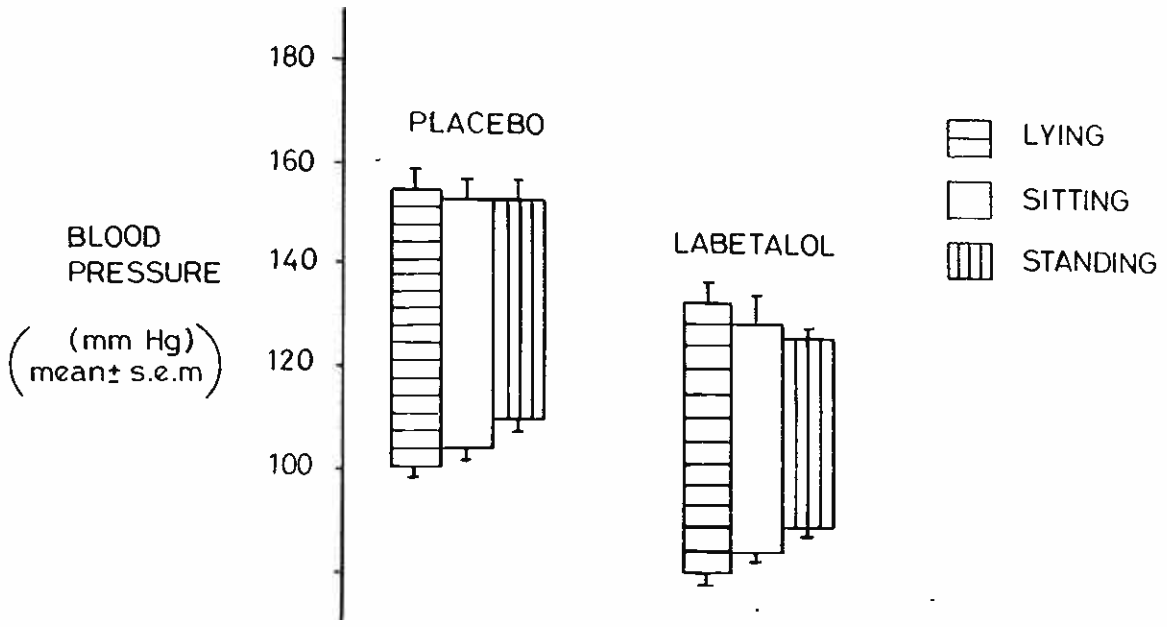
22 patients (all males) aged 31-64 (mean 46) years were admitted to the trial. 4 patients withdrew from the trial for the following reasons: one patient developed acute gout during the placebo period; one patient who was treated as a hypertensive for nearly 4 years was found to be normotensive during the run-in period as well as during the placebo period; another patient was found to be hypothyroid and was rendered normotensive by treatment with thyroxine; and the fourth patient defaulted.

18 patients completed the double-blind, crossover with placebo study. Table I summarises the patients' characteristics and their mean blood pressures and heart rates in the standing positions. Table II shows the comparison of mean heart rates and blood pressures in the supine, sitting and standing positions. Figure 2 shows diagrammatically the mean blood pressures when on placebo and labetalol.

TABLE I

PT. NO.	RACE	AGE (Yrs)	WT (Kg)	HYP. SCORE	FINAL DOSE OF LABETALOL (mg/dly)	STANDING PULSE RATE AND BLOOD PRESSURE						
						PLACEBO-PERIOD MEAN SYSTOLIC	MEAN DIASTOLIC	P.R.	LABETALOL PERIOD MEAN SYSTOLIC	MEAN DIASTOLIC	P.R.	
1	IND	41	91	6	600	175	120	90	140	97	75	
2	MAL	35	94	10	600	180	120	86	125	85	85	
3	IND	58	50	8	400	165	100	90	146	87	76	
4	IND	31	74	4	600	150	100	80	125	95	67	
5	MAL	45	76	8	300	145	107	74	122	89	80	
6	MAL	37	76	8	600	153	120	79	111	88	63	
7	CHI	42	71	8	400	170	110	80	132	82	81	
8	CHI	41	66	4	300	140	108	86	122	88	77	
9	CHI	48	65	10	500	158	118	86	130	92	80	
10	MAL	49	57	7	400	170	105	97	143	88	78	
11	MAL	57	86	10	600	165	115	83	137	90	80	
12	MAL	47	69	6	400	140	108	80	120	83	74	
13	MAL	54	73	7	400	145	105	80	113	83	77	
14	MAL	48	62	8	300	140	100	80	130	90	76	
15	MAL	52	73	8	600	190	105	72	148	90	70	
16	CHI	35	55	4	300	130	100	72	116	87	73	
17	MAL	48	91	6	300	140	105	83	122	85	81	
18	IND	64	69	8	400	180	110	67	160	95	69	
		46.2 ±9	72 ±12	7.2	444	154 ±17	109 ±7	81 ±7	127 ±10	89 ±4	76 ±6	MEA ±S.D.

The mean blood pressure during treatment with labetalol in the 3 positions viz. lying, sitting and standing was significantly lower than when on placebo, the difference being 23±3.0 s.e., 25±2.5 s.e. and 27±2.5 s.e. mm Hg systolic and 19±2.0 s.e., 20±3.0 s.e. and 20±2.0 s.e. mm Hg diastolic in the lying, sitting and standing positions respectively (Table II). There was no demonstrable postural drop in the systolic pressure i.e. more than 20 mm Hg, from the lying to the standing position. A small rise in the diastolic pressure from the lying to the standing position was also seen (Fig. 2). Even though labetalol reduced the heart rate significantly when compared with placebo, none of them fell below 63 (Table II).



MEAN BLOOD PRESSURE IN 18 PATIENTS DURING PLACEBO AND LABETALOL TREATMENTS

FIG. II

TABLE II

Mean values for blood pressure and heart rate in the 18 patients during placebo and labetalol treatment

		On Placebo	On Labetalol	Difference (± s.e.)	P
Blood pressure (mm of Hg)					
Lying	Systolic	155	133	23 ± 3.0	<0.001
	Diastolic	100	81	19 ± 2.0	<0.001
Sitting	Systolic	154	129	25 ± 2.5	<0.001
	Diastolic	104	84	20 ± 3.0	<0.001
Standing	Systolic	154	127	27 ± 2.5	<0.001
	Diastolic	109	89	20 ± 2.0	<0.001
Heart rates (per min.)					
Lying		78	73	5 ± 1.5	<0.01
Sitting		80	75	5 ± 1.0	<0.01
Standing		81	76	5 ± 1.5	<0.01

b) Laboratory findings

There were no significant alterations in the routine haematological and boichemical parameters during both placebo and active drug treatment periods. No changes were observed in the random blood sugar and SGOT levels. 3 of the patients had a weak positive antinuclear factor, 2 in a dilution of 1 in 100, and 1 in a dilution of 1 in 10. In the rest of the patients, ANF remained negative throughout.

c) Side effects

None of the 18 patients encountered any serious side effects that warranted their withdrawal from the trial. The side effects frequently seen in this study are listed in Table III.

TABLE III

Complaints	Frequency
Paraesthesias (scalp & upper extremities)	5
Tiredness/fatigue	2
"Swelling of the head"	2
Giddiness	1
? Sexual dysfunction	2

The most frequently met side effect was complaints of numbness and pricking sensations in the scalp and the extremities (5 patients). These complaints were prominent at the onset of treatment but waned off with time, and seemed to be aggravated by exposure to the sun, the significance of which is unknown. 2 patients complained of weakness and/or fatigue on and off when on labetalol; 1 patient (patient No. 10) complained of persistent giddiness during the run-in, placebo and active drug periods and an ENT examination done by the ENT surgeon was negative. 2 patients complained of both failure of erection and ejaculation; however these complaints did not correspond with the periods of active drug therapy.

No patient complained of any visual disturbances. Fundoscopy and perimetry by an ophthalmologist revealed no significant changes. No patient developed any symptoms of respiratory obstruction.

DISCUSSION

The results found from this study supports various other studies in finding labetalol effective in significantly reducing blood pressure (Kane et al 1976, Frick and Porsti 1976).

In our patients, labetalol significantly lowered the blood pressure when compared with identical placebo in all the three positions, viz. lying, sitting and standing. In the treatment of mild to moderate hypertension, the dosage range of 300-600mg daily was found to be adequate in bringing about satisfactory control of blood pressure, the majority of patients requiring 400mg and above. The average dose required for the 18 patients was 444mg daily, which suggests that the majority of Malaysian patients would require a starting dose of 300mg daily.

We did not monitor cardiac output and total peripheral resistance changes during the placebo and active drug periods. But certain inferences can be made from the results as to the pharmacodynamic activity of labetalol in our hypertensives. It is apparent that there was no significant postural drop in systolic pressure from the lying to the standing position, but a small rise in diastolic pressure was noted in patients on labetalol. These observations may be partially explained by the presence of a minimal alpha blockade activity at the dose range of 300-600mg daily of labetalol used in this study.

There was no significant bradycardia. However the fall in heart rate between the placebo and the active drug, concomitant with the fall in blood pressure, indicates the presence of a partial beta-blocking component. But no conclusions can be made whether alpha or beta effects are of greater importance in reducing blood pressure during continuous oral administration of labetalol in these patients. It has been shown in other studies that the ratio of the alpha to beta effect of labetalol is estimated to be 1 : 3 (Richards 1975).

No serious side effects were noted during the period of study. Those noted were found to be mild and transient and did not necessitate withdrawal of therapy. However new drugs appear to have a more favourable profile of side effects than existing drugs and therefore one must always adopt an alert attitude until one has gained a longer period of experience.

Posture related giddiness is an expected consequence of alpha blockade. One patient complained of persistent giddiness throughout the study when both on placebo and active drug, but even in this one case, no associated postural drop in blood pressure was documented when he was on active drug. The absence of this adverse effect in our group of patients may be explained by the relatively lower doses that were used.

Impotence was the other side effect that we actively pursued for in our patients. 2 of them complained of 'a deterioration' in their sexual performances. Both reported

no distrubance in sexual desire and urge but they could not maintain erection and sustain ejaculation. When they were on placebo, these problems were also present. Both were above 50 years of age. None of the younger patients and the other old ones volunteered similar problems.

No significant alterations were observed in the various laboratory investigations studied during the active drug periods. As was noted, 3 patients developed weakly positive ANF during the trial period.

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