THE USE OF LABETALOL IN JAPAN: RESULTS OF MULTICENTRE CLINICAL TRIALS

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1 The anti-hypertensive effects and safety of labetalol have been evaluated in multicentre clinical trials in Japan based on unified study protocols. The results of three studies are reported.

2 A total of 178 patients with essential hypertension were treated with labetalol for 12 weeks, 127 of them with labetalol alone (monotherapy) and the other 51 with labetalol plus diuretics (combined therapy).

3 Satisfactory antihypertensive effects were achieved in 76 of the 119 assessable patients in the monotherapy group and 25 of the 49 in the combined therapy group. The mean daily doses of labetalol were 329 mg in the monotherapy group and 374 mg in the combined therapy group. Seven patients (six in the monotherapy group; one in the combined therapy group) were withdrawn from the trials due to side-effects.

4 Sixty-one patients with hypertension were treated with labetalol alone or combined with diuretics for 6 months or longer. In most of these patients, good blood pressure control was achieved. No patients had to discontinue the treatment due to side-effects. The mean daily doses of labetalol were stabilised in and after week 8 of the treatment at an average of 260 mg in the monotherapy and 450 mg in the combined therapy. Tolerance to the anti-hypertensive effect did not develop.

5 Thirty patients with phaeochromocytoma were treated with labetalol and good blood pressure control was achieved in 21 of them. The effects of labetalol were better in patients with predominantly adrenaline-secreting tumours, and better in patients with sustained hypertensive type than in those with paroxysmal hypertensive type.

Introduction

Labetalol is an antihypertensive drug which possesses both α - and β -adrenoceptor-blocking actions (Farmer *et al.*, 1972; Richards *et al.*, 1974). In Japan, a preliminary clinical trial on this drug, in patients with essential or secondary hypertension, was started in 1977 and indicated that labetalol had an excellent anti-hypertensive effect.

The present study was designed to investigate the clinical efficacy and safety of labetalol on a multi-

centre clinical trial basis using a similar protocol in each centre. Here we report our results in patients with essential hypertension treated with labetalol for 12 weeks and those with essential and secondary hypertension on long-term treatment with the drug. In addition, the efficacy of labetalol in patients with phaeochromocytoma has been evaluated. Data on most of these patients have been previously published in Japanese by Yoshinaga *et al.* (1981).

Methods

Study 1

A total of 178 patients with essential hypertension from 36 centres were included in this study.

Patients first received placebo in the pretreatment observation periods for 4 weeks or longer, followed by labetalol for 12 weeks. Patients with secondary hypertension were excluded based on the laboratory findings obtained during the observation period. One hundred and twenty-seven patients (77 male, 50 female; age range 22–66 yr) received labetalol alone (monotherapy group); and 51 patients (27 male, 24 female; age range 25–69 yr) who had not responded satisfactorily to the treatment with diuretics during the observation periods were treated with a diuretic plus labetalol (combined therapy group; Table 1).

The diuretics used concurrently with labetalol in the combined therapy group were: trichlormethiazide 2–6 mg daily in 43 patients, methyclothiazide 2.5–5 mg daily in two patients, hydrochlorthiazide 75 mg daily in one patient, and meticrane 300 mg daily in one patient.

The starting dose of labetalol was 150 mg daily, and if unsatisfactory anti-hypertensive effect was obtained, the daily dose was increased by 150 mg daily.

Blood pressure and pulse rate were measured every 2 weeks in the sitting position. In addition, supine and standing blood pressures were also measured before and after 12 weeks of treatment.

The anti-hypertensive effect was evaluated in patients who had received the drug for 8 weeks or more, on the basis of the difference between blood pressures before and after treatment. In addition responses were categorized on the basis of changes

in mean blood pressure. Both before and after the treatment, the following laboratory examinations were carried out: ECG, chest X-ray, haematology (erythrocyte count, leucocyte count, haemoglobin, and ESR), serum biochemistry (Na, K, Cl, total cholesterol, uric acid, urea nitrogen, creatinine, and blood glucose), liver function tests (GOT, GPT, A1-P, and LDH) and urinalysis (urinary protein, urinary glucose, and urinary sediment).

Study 2

A total of 61 patients (57 with essential hypertension and 4 with secondary hypertension) were recruited in this study. They received labetalol for 6 months or more.

Forty-one patients (22 male, 19 female; age range 23–69 yr; 38 with essential hypertension and three with secondary hypertension) received labetalol alone (monotherapy group); and 20 patients (12 male, 8 female; age range 27–62 yr; 19 with essential hypertension and one with secondary hypertension) who had not responded well to the diuretic treatment, received labetalol concurrently with diuretics (19 with trichlormethiazide 2–6 mg daily and one with hydrochlorthiazide 75 mg daily; combined therapy group; Table 1). Thirty-five patients in the monotherapy group and 18 patients in the combined therapy group received the treatment for a further year, and the remaining eight patients were withdrawn for reasons not related to labetalol treatment.

The following examinations were performed, before, and after 3 months, 6 months and 1 year of treatment: ECG, chest X-ray, haematological examinations, serum biochemistry, and urinalysis. Antinuclear antibodies were determined before and after the treatment in some of the patients.

Table 1 Details of the patients in studies 1 and 2

Treatment period Group		Study 1 12 weeks		Study 2 6 months or more	
		Monotherapy	Combined therapy	Monotherapy	Combined therapy
Number of patients		127	51	41	20
Diagnosis					
Essential hypertension		127	51	38	19
Secondary hypertension				3	1
Sex					
Male		77	27	22	12
Female		50	24	19	8
Age (yr)		46.6±0.9 (22–66)	50.3±1.5 (25–69)	47.0±1.6 (23–69)	47.5±2.4 (27–62)
Severity (WHO standards)					
I		58	23	21	9
II		61	21	14	9
III		3	5	1	0
Unknown		5	2	5	2

Table 2 Background factors of patients with a phaeochromocytoma

Number of cases	30
Sex	
Male	14
Female	16
Age (yr)	35.7±2.4 (13-60)
Site of tumour	
Adrenal gland	24
Right	13
Left	9
Bilateral	2
Ectopic	6
Type	
Paroxysmal hypertensive type	12
Sustained hypertensive type	18
Noradrenaline type	19
Adrenaline type	10
Unknown	1

Study 3

A total of 30 patients each with a phaeochromocytoma were treated with labetalol for periods ranging from 1 week to 4 months (Table 2). The diagnosis was made on the basis of endocrine studies, including the urinary excretion of catecholamines. The site of the tumour was determined radiologically, and 27 patients were subsequently operated on.

Results*Study 1*

Changes in sitting blood pressure, pulse rate and the daily dose of labetalol in 106 patients in the labetalol monotherapy group are shown in Figure 1. Blood pressure was significantly decreased, and at the end of the 12 week treatment period, the mean was $149 \pm 2/94 \pm 1$ mmHg.

Changes in sitting blood pressure, pulse rate and the daily dose of labetalol in 44 patients in the combined therapy group are shown in Figure 2. The blood pressure was significantly decreased, and at

Figure 1 Changes in sitting blood pressure and pulse rate in patients treated with labetalol for 12 weeks (monotherapy group). Data are shown as mean $\pm$ s.e. mean. Statistical significance: *** $P < 0.001$

Figure 2 Changes in sitting blood pressure and pulse rate in patients treated with labetalol plus diuretics for 12 weeks (combined therapy group). Data are shown as mean $\pm$ s.e. mean. Statistical significance: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

the end of the 12 week treatment the mean pressure was $158 \pm 3/97 \pm 2$ mmHg.

Mean pulse rates significantly decreased in both the monotherapy and combined therapy groups (Figures 1 and 2).

Average doses of labetalol at the end of the 12 week treatment were 329 ± 3 (150–900) mg daily in the monotherapy group, and 374 ± 27 (150–1, 200) mg daily in the combined therapy group.

A general assessment of the anti-hypertensive effect was made on the 119 patients in the monotherapy group and 49 patients in the combined

therapy group, all of whom had received labetalol for 8 weeks or longer. The results are presented in Table 3, which shows that treatment was regarded as effective in the majority of patients.

Table 4 shows the anti-hypertensive effects in the patients in the monotherapy group, classified in relation to their final daily doses of labetalol.

Side-effects were noted in 17 patients (27 instances) in the monotherapy group and in eight patients (14 instances) in the combined therapy group (Table 5). Drug administration had to be discontinued in six patients in the monotherapy

Table 3 Results of assessment of anti-hypertensive effect

Therapy group	Number of cases	Change in blood pressure					
		Remarkably decreased (>20 mmHg)	Moderately decreased (13–19 mmHg)	Slightly decreased (7–12 mmHg)	No change (± 6 mmHg)	Slightly elevated (7–12 mmHg)	Elevated (>13 mmHg)
Monotherapy	119	37 (31%)	39 (33%)	22 (18%)	18 (15%)	3 (3%)	0 (0%)
Combined therapy	49	11 (22%)	14 (29%)	14 (29%)	9 (18%)	1 (2%)	0 (0%)

Table 4 Assessment of antihypertensive effect in patients classified by their final dose of labetalol (monotherapy group)

Final daily dose (mg)	Number of cases	Change in blood pressure						Cumulative number of effective cases
		Remarkably decreased (>20 mmHg)	Moderately decreased (13-19 mmHg)	Slightly decreased (7-12 mmHg)	No change (± 6 mmHg)	Slightly elevated (7-12 mmHg)	Elevated (>13 mmHg)	
150	38	12	16	7	3	0	0	28 (24%)
300	46	14	15	8	8	1	0	57 (48%)
450	5	3	1	1	0	0	0	61 (51%)
600	27	8	7	5	5	2	0	76 (64%)
900	3	0	0	1	2	0	0	76 (64%)
Total	119	37	39	22	18	3	0	76 (64%)

Table 5 Incidence of side-effects during 12 weeks of treatment

Symptoms	Number of cases	
	Monotherapy	Combined therapy
Light-headedness	9	6
Headache, dull headache	2	2
Gastrointestinal symptoms	3	0
Shoulder stiffness	1	
Insomnia	2	1
Numbness	1	
Constipation	2	
Malaise		1
Sleepiness	1	
Oedema	1	1
Asthma	1	
Goose skin	1	
Impotence	1	
Bradycardia	1	
Nightmare	1	
Oppressive sensation in the chest		1
Cold sensation at the limbs		1

group (three with light-headedness, and one with oedema, asthma, and abnormal sensation of the skin, respectively) and in one in the combined therapy group (facial oedema). In all of the other patients, side-effects were either mild or transient, and the administration of the test drug could be continued.

Examination of the mean values in the laboratory examinations performed before and after the treatment showed that in the monotherapy group, the erythrocyte count and haemoglobin concentration significantly decreased, whereas serum potassium significantly increased. On average, no signi-

ficant change was found in the values in the other examination items. In the combined therapy group, no significant change was found in any parameter.

Study 2

Changes in the sitting blood pressure in 35 patients in the labetalol monotherapy group treated for 1 year or more are shown in Figure 3. Blood pressures fell gradually until week 16; thereafter they were stable in the range 142–146/89–91 mmHg.

Changes in the sitting blood pressure in 18 patients in the combined therapy group treated for 1 year or more are shown in Figure 4. Blood pressures gradually fell until week 16; thereafter they remained stable in the range 140–153/90–94 mmHg.

Pulse rate significantly decreased throughout the periods in the monotherapy group, and at weeks 2, 8, 12 and 40, respectively, in the combined therapy group.

Average daily dose of labetalol after 8 weeks of therapy was 260 mg daily in the monotherapy group and 450 mg daily in the combined therapy group.

Side-effects occurred in five patients (six instances) out of 41 patients in the monotherapy group, and in three patients (seven instances) out of 20 patients in the combined therapy group (Table 6). All of these side-effects were mild or transient, and most of them occurred during the early stage of the treatment.

In both the monotherapy and the combined therapy groups, there was a slight decrease—within the normal range—in the erythrocyte count and haemoglobin concentration during the early stage of the drug treatment. There was, however, no further decrease thereafter. Mean serum potassium increased slightly in the monotherapy group from 3.99 ± 0.06 mEq/l to 4.18 ± 0.09 mEq/l. Any other parameters in the haematology, serum biochemistry, or urinalysis were not affected by long-term administration.

Figure 3 Changes in sitting blood pressure and pulse rate in patients treated with labetalol for one year or more (monotherapy group). Data are shown as mean $\pm$ s.e. mean. Statistical significance: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Table 6 Incidence of side-effects in the long-term treatment group

Symptom	Number of cases	
	Monotherapy	Combined therapy
Light-headedness	3	2
Sleepiness	1	0
Dry mouth	1	0
Constipation	1	0
Headache	0	1
Nausea	0	1
Chest distress	0	1
Cold sensation of the body	0	1
Fatigue	0	1

Study 3

Effects of labetalol in achieving control of the blood pressure, including the effects in preventing attacks, are presented in Table 7. Effective control of blood pressure was obtained in 21 out of the 30 patients.

As to side-effects, light-headedness was noted in three patients; chest pain, gastric discomfort, chilliness and aggravation of attacks in one patient, respectively.

Discussion

Until recently, the anti-hypertensive drugs of the first choice in Japan for the treatment of hyper-

Table 7 Efficacy rate of labetalol in the patients with a pheochromocytoma

	Noradrenaline type	Adrenaline type	Unknown	Total
Paroxysmal type	1/6	5/6	0/0	6/12
Sustained type	10/13	4/4	1/1	15/18
Total	11/19	9/10	1/1	21/30

Figure 4 Changes in sitting blood pressure and pulse rate in patients treated with labetalol plus diuretics for one year or more (combined therapy group). Data are shown as mean $\pm$ s.e. mean. Statistical significance: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

tension have been thiazide diuretics. This may be a wise choice because the Japanese are said to ingest more salt than people in Europe or the United States.

In recent years, studies have been carried out on the clinical efficacy of various β -adrenoceptor-blocking agents in the treatment of hypertension, with comparatively good results in mild to moderate hypertension. As a result of these studies, β -adrenoceptor-blocking agents are now frequently used as diuretics in Japan as anti-hypertensive drugs.

Since 1977, a preliminary clinical study has been carried out to investigate the clinical efficacy of labetalol in the treatment of hypertension, in which labetalol was shown to have an excellent anti-hypertensive effect, indicating that the appropriate initial daily dose was 150 mg, divided into three doses.

Where labetalol was administered alone for 12 weeks, a fall in the mean blood pressure by 13 mmHg or more was achieved in 64% of patients. This efficacy rate is considered to be equal to, or higher than those achieved with other β -blockers in Japan (Takeda *et al.*, 1977; Ikeda *et al.*, 1978).

The initial daily dose of 150 mg is rather small compared with doses used for European patients. However, at this dose the fall in mean blood pressure was 13 mmHg or more in 28 (24%) out of the 119 patients in the labetalol monotherapy group, thus confirming that the dose of 150 mg daily is an appropriate starting dose for Japanese patients. Furthermore, the mean daily dose (329 ± 13 mg) at the end of treatment was also low, implying that, in comparison with Europeans, Japanese people may respond well to labetalol in lower doses.

The efficacy rate was lower in the combined therapy group than that in the monotherapy group, in spite of higher mean dose of labetalol adopted in the former group. This is probably because in the combined therapy group, the subjects were comparatively severe cases who had not responded well to diuretics.

Labetalol is said to be less prone to cause or aggravate bronchial asthma because it also possesses α -adrenoceptor-blocking actions (Skinner *et al.*, 1975; Maconochie *et al.*, 1977). But in the present study, labetalol was found to induce bronchial asthma in a 39-yr-old female who had a previous history of infantile asthma. This indicates that care

should particularly be taken when labetalol is administered to patients prone to bronchial asthma.

Labetalol administration had to be discontinued in a total of seven patients (including the above case) because of side-effects. Side-effect symptoms disappeared soon after the withdrawal of the drug tending to confirm the causal association.

In the monotherapy group, mean erythrocyte count and haemoglobin concentration decreased, and serum potassium increased. The decreases in the erythrocyte count and haemoglobin might be caused by an increase in the peripheral venous volume caused by the α -adrenoceptor-blocking actions. Weidman *et al.* (1978) have reported similar changes in the haematology and serum biochemistry findings.

With long-term labetalol treatment, good control of blood pressure was achieved in most of the hypertensive patients. There was almost no change in the mean dose of labetalol after week 8 of treatment, indicating that the effect of labetalol did not decrease during the course of the continued administration.

In these studies, labetalol exerted an excellent anti-hypertensive effect, with very low incidence of side-effects; and in long-term use, it did not cause serious side-effects nor drug tolerance.

From these clinical results and in view of the effects of labetalol on haemodynamics, labetalol may be considered an appropriate drug for the treatment of essential hypertension.

The conventional practice for the treatment of pheochromocytoma has been the combined use of an α -adrenoceptor-blocking agent and β -adrenoceptor-blocking agent. Therefore, labetalol, a drug with both α - and β -adrenoceptor blocking actions, is expected to be useful in the treatment of this disease. In fact, Baily (1979) and Rosei *et al.* (1979) have reported that labetalol is effective in this condition.

We have also evaluated the clinical efficacy of labetalol in Japanese patients with a pheochromocytoma.

Good blood pressure control including prevention of attacks was obtained in 21 out of 30 patients. In patients with adrenaline type or sustained hyper-

tensive type, better blood pressure control was achieved than in those with noradrenaline type or paroxysmal hypertensive type. Nineteen patients with noradrenaline type consisted of six with paroxysmal type and 13 with sustained type. Good blood pressure control was obtained in one patient with paroxysmal type and ten with sustained type, respectively. Ten patients with adrenaline type consisted of six with paroxysmal type and four with sustained type, and good blood pressure control was obtained in five patients with paroxysmal type and all the four patients with sustained type, respectively. Thus, it seems that in patients with a predominantly noradrenaline-secreting tumour who have paroxysmal hypertension, labetalol is likely to be less effective in preventing hypertensive attacks.

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