Br. J. clin. Pharmac. (1979), **8**, 167S–170S

A LONG-TERM STUDY OF LABETALOL IN GENERAL PRACTICE

J. KANE & I. GREGG

Department of Clinical Epidemiology in General Practice, Cardiothoracic Institute, Brompton Hospital, London SW3, UK

M.D.B. STEPHENS

Glaxo Group Research Limited, Ware, Hertfordshire SG12 ODJ, UK

1 Forty-one patients with mild to moderate hypertension have been treated with labetalol for up to 5 years.

2 Mean BP before treatment was 180/107 mmHg, after 2–3 yr treatment was 136/81 mmHg and after 5 yr was 136/74 mmHg.

3 One patient developed a licheniform rash and two patients have died of myocardial infarction. No other side-effects, not already observed in a previously reported double-blind trial, have emerged.

Methods

PATIENTS were admitted to the trial if they had a pretreatment diastolic BP greater than 95 mmHg (Korotkoff, 4th phase) on two or more occasions, provided they had essential hypertension and no disease in which the use of β-adrenoceptor-blocking agents was contraindicated. The nature of the trial was explained to each patient and their consent obtained.

A total of 41 patients (20 male, 21 female; aged 41–70 yr) were recruited from the routine clinics of our general practice. Twenty-four of these patients had completed a double-blind cross-over trial comparing labetalol with placebo (Kane *et al.*, 1976) and continued to take labetalol thereafter in a dosage based on their responses to the drug during that trial.

A further 17 patients entered the study, 10 of whom were not receiving any treatment when initially screened. Seven patients were taking other antihypertensive agents, and were changed to labetalol either because their BPs were not controlled satisfactorily or because they had unacceptable side effects due to their previous therapy. Substitution with labetalol took place without a wash-out period; their previous drugs were slowly reduced, and labetalol was gradually increased.

A starting dose of 100 mg twice or three times daily was used for all 17 patients, and increments of 200–300 mg daily were made at 2-week intervals until control of BP was achieved. Subsequently they were seen at 2–3 month intervals provided their BP was stable; this was measured throughout by a single observer (J.K.) in both the sitting and standing positions, using a conventional mercury sphygmomanometer. Whenever possible each patient attended for follow-up at the same time of day on each occasion.

The following routine tests were carried out both before and during the trial; haemoglobin, WBC, urea, electrolytes, liver function and urinalysis. An ECG was also carried out. Antinuclear antibody (ANA) titres were estimated before and during the trial in all patients. Titres were compared with those of a control group who were matched for age and sex and who had been taking comparable doses of either propranolol or oxprenolol for a similar length of time.

For the assessment of side-effects, patients were asked to volunteer any changes in their well-being at each visit to the surgery.

Results were analyzed at two randomly chosen points in time, one when most patients had been taking labetalol for up to 3 yr and the other after a maximum of 5 yr treatment. BP data analyzed refer to the last recording to be entered on the record sheet of each patient at these two different times.

Fundoscopy was carried out, and visual acuity and colour vision tested in all patients both at an early stage in the trial and again 2–3 yr later. Sixteen patients were randomly selected for estimation of tear lysosyme concentrations.

In six male patients taking higher doses of labetalol than the others, urinary catecholamines were estimated by fluorimetry and high pressure liquid chromatography.

Results

After 3 yr there were seven withdrawals from the trial. The remaining 34 patients fell into five groups

0306–5251/79/170167–04 $01.00

on the basis of the treatment which they were taking during this period (Table 1).

In group 1, two of the patients omitted to take their drugs on holiday and on their return their BPs were found to be within normal limits and labetalol treatment was not recommenced. BPs of the other two patients were found to be decreasing without any dosage change, and remained stable after a gradual reduction in dose. Finally labetalol was stopped when no increase in BP was observed on the lowest dose of the drug. All four patients were followed closely for up to 22 months; they remained normotensive without any further treatment.

Overall, in 28 out of 34 patients systolic Bps were reduced to 140 mmHg or less, while in the other six patients it was reduced to less than 170 mmHg. Diastolic BPs were reduced to 90 mmHg or less in 30 of the 34 patients and in the other four patients to between 90 and 100 mmHg. No statistically significant difference was found between BP measurements made in the sitting and standing positions.

After 5 yr treatment a further seven patients had left the study and the data of the remainder were analyzed together. Mean sitting BP for these 27 patients was 136/74 mmHg compared with that of 133/83 mmHg at the end of the double blind trial and 136/81 mmHg after 2–3 yr treatment. Their mean pulse rate after 5 yr was 76 beats/min compared with 72 beats/min at the end of the double-blind trial.

No significant change in the routine haematological or biochemical analyses was seen during the trial. However, ANAs were present in eight more patients when estimated during treatment than during the period before labetalol was started. A similar proportion of the patients taking propranolol or oxprenolol were found to possess ANAs, the titres of which were in the same range as for patients taking labetalol.

No unusual changes in visual acuity or fundoscopy were seen over the 3 yr period nor was colour vision affected in any patient. Tear lysosyme concentration was normal in all 16 patients in whom it was estimated (Mackie *et al.*, 1977).

Urinary catecholamines, when measured in the six patients using a fluorimetric method, were elevated. Values ranged from 50–615 μg/24 h for noradrenaline (normal less than 50) and from 78–410 μg/24 h for adrenaline (normal less than 50). However, values for noradrenaline and adrenaline when measured using high performance liquid chromotography fell, in most instances, within the normal range, values for noradrenaline being 28–90 μg/24 h and for adrenaline 10–62 μg/24 hours.

Side-effects and withdrawals

One patient had measurable postural hypotension with associated dizziness. Three patients complained of posture-related dizziness, one of a muzzy feeling in the head, and one of tiredness; but these symptoms were all transient. Leg cramp occurred in two patients, but lasted only 2–3 weeks. Scalp paraesthesia occurred in one patient but did not persist.

Withdrawals from the trial included six patients lost to follow-up, one patient who complained of tired aching legs, and one who had a number of non-specific complaints and just generally felt unwell.

One patient aged 57 died of myocardial infarction. He was taking labetalol 200 mg daily and his BP on his last attendance to the surgery was 110/70 mmHg. He had had angina for several years but had needed to take less glyceryl trinitrate since he had started labetalol.

One patient developed erectile impotence. He had been taking labetalol 800 mg daily for 18 months without side-effects. He first noticed impotence 1 week after addition of cyclopenthiazide 2 tablets daily. However, after withdrawal of both drugs his impotence failed to improve. It is therefore unlikely that labetalol was responsible for this symptom.

Table 1 Effect of labetalol in 34 patients treated continuously for up to 3 yr

	Group 1	*Group 2*	*Group 3*	*Group 4*	*Group 5*
Number of patients	4	11	2	6	11
Mean age	54 yr 9 mths	58 yr 6 mths	68 yr 4 mths	56 yr	58 yr 7 mths
Initial treatment	Labetalol	Labetalol plus diuretic throughout	Diuretic	Labetalol	Labetalol throughout
Final treatment	None		Labetalol plus diuretic	Labetalol plus diuretic	
Mean pre-treatment BPs	165/96	176/110	192/106	192/114	175/109
Mean BP on initial treatment	129/78		180/99	175/106	
Mean BP on final treatment	128/75	132/81	158/90	138/83	126/75
Average daily dose of labetalol	496 mg	737 mg	250 mg	736 mg	535 mg

Diuretic was always cyclopenthiazide two tablets daily.
BPs were measured in the sitting position.

One patient who had been taking labetalol 1200 mg daily for five months developed a lichenified skin eruption. There was involvement of the extremeties as well as lichen planus lesions in the mouth. The lesions failed to respond to 0.5% hydrocortisone cream over 6 weeks. However, on withdrawal of labetalol the eruption cleared completely within 2 weeks. The patient has not been rechallenged, nor has the rash returned.

Discussion

Labetalol was found to be effective in treating hypertension either alone or with a diuretic in patients with mild to moderate hypertension, and in particular the seven patients who changed from other therapy to labetalol all responded well to the drug.

It was interesting that the first group of four patients remained consistently normotensive for between 8–22 (mean 15) months after they had ceased taking labetalol. The patients in group 4 were also of interest. Labetalol in doses up to 1500 mg daily produced only a modest fall in mean BP, 17/8 mmHg. However, the addition of cyclopenthiazide 2 tablets every morning brought about a further much greater fall in mean BP, 37/23 mmHg. This suggests that labetalol and cyclopenthiazide acted in a synergistic manner for this particular group of patients, although conclusions must be drawn with care due to the small number of patients involved.

Average daily dose required for the total group of patients in this trial was 500 mg. However, BP in several patients was well controlled on much smaller doses, for example, 200 mg daily; and at the other end of the spectrum, 1800 mg daily was used without side-effects. Indeed, other investigators have used in excess of 3000 mg daily (Prichard & Boakes, 1976).

Both twice and three times daily treatment regimens were assessed. BP was well controlled with both, and on the basis that compliance is likely to be better if the drug is taken twice daily, it is suggested that labetalol be administered in this way.

Tolerance has not developed with labetalol over the 5-yr period of the trial. Taking the 11 patients in group 5 (labetalol only throughout the trial), for example, the average daily dose after 3 months' treatment was 660 mg and after 2 yr was 500 mg. After 5 yr, average daily dose of labetalol for the 27 patients who remained in the trial was 450 mg.

Although it was anticipated that labetalol would produce a postural fall in BP due to its α-adrenoceptor-blocking activity, we have found no difference between BPs measured in the sitting and standing positions (Kane *et al.*, 1976) with the exception of one patient. However, others have shown a greater fall in BP on standing from the supine position (Pugsley *et al.*, 1976). Three patients complained of posture-related dizziness. This symptom was overcome in one patient by changing his daily dosage from twice daily to a three times daily regimen, and in the other two, by asking them to take the drug after meals rather than before.

Although the patient with the lichenified skin reaction was not rechallenged, its quick disappearance on withdrawal of the drug is strongly suggestive of a drug eruption. Similar types of skin rashes after labetalol treatment have been reported (Gange & Wilson–Jones, 1978; Finlay & Waddington, 1978) which did recur when the patients were rechallenged.

ANAs are present in apparently normal sybjects, and the incidence is highest in elderly females. Many factors probably play a part in their prevalence and many drugs are also known to produce positive ANAs (Wilson *et al.*, 1978). However, in the practolol syndrome there was no consistent correlation between positive ANAs and the severity of the syndrome. None of our patients developed an ANA titre level normally associated with auto-immune disease. Furthermore, when ANA titres of patients who had taken labetalol for 1 yr or more were compared with those of patients, matched for age and sex, taking either oxprenolol or propranolol, plus or minus a diuretic, in comparable dosage, the results were almost identical.

Mackie *et al.* (1977) have estimated the tear lysosyme concentration in 13 patients with practolol toxicity and found it to be reduced in all of them. In one patient the abnormality preceded the symptoms of toxicity by two months. It is therefore encouraging that no such changes in tear lysosyme concentration were seen in the 16 patients taking labetalol in whom this was carried out.

Although it has been shown that labetalol is taken up by melanocytes in the retina (Poynter *et al.*, 1976), in no patient did the visual acuity alter significantly nor was colour vision affected between the two occasions.

Although seven further patients left the trial in the last 2 yr, in four this was due to moving from the district and one other patient died of a myocardial infarction. No further side-effects have emerged.

References

FINLAY, A. & WADDINGTON, E. (1978). *Br. med. J.*, **1**, 987.

GANGE, R. & WILSON JONES, E. (1978). Bullous lichen planus caused by labetalol. *Br. med. J.*, **1**, 816–817.

HAMILTON, C.A., JONES, D.H., DARGIE, H.J. & REID, J.L. (1978). Does labetalol increase excretion of urinary catecholamines. *Br. med. J.*, **2**, 800.

KANE, J., GREGG, I. & RICHARDS, D. (1976). A double

blind trial of labetalol. *Br. J. clin. Pharmac.*, **3,** suppl., 737–741.

MACKIE, I., SEAL, D. & PESCOD, J. (1977). β-Adrenergic receptor blocking drugs; tear lysosyme and immunological screening for adverse reaction. *Br. J. Ophthalmol.*, **61,** 354–359.

POYNTER, D., MARTIN, L.E., HARRISON, C. & COOK, J. (1976). Affinity of labetalol for ocular melanin. *Br. J. clin. Pharmac.*, **3,** 711–720.

PRICHARD, B. & BOAKES, A. (1976). Labetalol in long treatment of hypertension. *Br. J. clin. Pharmac.*, **3,** suppl., 743–750.

PUGSLEY, D., ARMSTRONG, M., NASSIM, M. & BEILIN, L. (1976). Controlled comparison of labetalol and propranolol in the management of severe hypertension. *Br. J. clin. Pharmac.*, **3,** suppl., 777–782.

WILSON, J.D., BULLOCK, J.Y., SUTHERLAND, D.C., MAIN, C. & O'BRIEN, K. (1978). Antinuclear antibodies in patients receiving non-practolol β-blockers. *Br. med. J.*, **1,** 14–16.