LABETALOL IN GENERAL PRACTICE: A REVIEW

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- 1 The results of the treatment of 8573 hypertensive patients with labetalol in general practice, for periods between 1 month and 5 yr, are reviewed.
- 2 The data reviewed were obtained from the published literature together with our own published (Kane *et al.*, 1976; Kane *et al.*, 1979) and more recent (unpublished) work.
- 3 Between 60% and 80% of severe (diastolic blood pressure > 120 mmHg) and previously uncontrolled hypertensives responded satisfactorily to the drug, as did up to 88% of mild to moderate hypertensives.
- 4 The anti-hypertensive effect of labetalol was not dependent on the frequency of administration, twice and three times daily treatment regimes being equally effective.
- 5 The withdrawal rate attributable to side-effects was between 6% and 13%. Tiredness, dizziness, headache and upper gastro-intestinal symptoms were the four principal side-effects, but they were usually transient when labetalol treatment was continued.
- 6 No drug interactions or adverse haematological or biochemical changes were seen.

Introduction

Eleven different studies of the use of labetalol in general practice have been reported. They provide data on a total of 8,573 patients. These studies have involved patients with all grades of hypertension, including those who could not be controlled on previous treatment regimes. Two comparative studies have been undertaken. In the first, labetalol in a dose between 50 mg twice daily and 100 mg three times daily was compared, in 66 patients, with bendrofluazide 5–10 mg daily, in a double-blind cross-over trial lasting 4 months (General Practice Research Group 1980). In the second, a single-blind study, oxprenolol was compared in a dose up to 160 mg twice daily with labetalol up to 600 mg twice daily, all 71 patients being given bendrofluazide during the run-in period (Forsell *et al.* 1979). In only one study was placebo controlled (Kane *et al.*, 1976), with the remainder being open evaluations, of which three were multicentred.

This review examines the results of treatment with labetalol: dose range, its effect on heart rate, and the frequency with which additional anti-hypertensive medication was required.

Methods

Most studies used either a twice of three times daily dosage regimen and evaluation of these regimes was made by comparing their percentage withdrawal

and success rates, the latter being defined as lowering of diastolic blood pressure below 95 mmHg.

The incidence of reported side-effects due to labetalol was compared with that of other anti-hypertensive agents but only the four most commonly reported side-effects were examined in detail.

Interactions reported between labetalol and the drugs most commonly prescribed in general practice were examined.

Results

Blood pressure control

The most marked decrease in blood pressure on labetalol was seen within the first 4 weeks of commencing treatment, shown in Figure 1 (Harris, 1978). A statistically significant dose-response relationship was seen when labetalol 400 mg daily was compared with 800 mg daily in a double-blind cross-over trial ($P < 0.05$) (Kane *et al.*, 1976).

In an open study of mild to moderately hypertensive patients, a systolic blood pressure of less than 140 mmHg was achieved in 82% and a diastolic blood pressure of less than 90 mmHg in 88% of subjects (Kane *et al.*, 1979).

Of 580 severe hypertensives (WHO grade IV) who entered on open survey in general practice, 386

Figure 1 Mean blood pressures in 53 difficult hypertensives treated with labetalol over 9 months (Harris, 1978).

(67%) had a diastolic blood pressure below 120 mmHg after 2 weeks' treatment with labetalol 201-300 mg daily. When the same dose was added to other anti-hypertensive treatments in 688 severe hypertensives in the same study, 411 (60%) had a diastolic blood pressure below 120 mmHg after 2 weeks' treatment (General Practitioner Survey, 1978).

In three other studies a total of 108 previously "difficult" or uncontrolled hypertensives were treated with labetalol. In the first, 60.5% of 23 patients responded to treatment with a significant decrease in mean blood pressure of 25.5/13.5 mmHg (Altman, 1978).

In the second, all 53 patients showed some improvement in blood pressure; 82% had a systolic blood pressure below 160 mmHg and 78% had a diastolic blood pressure below 95 mmHg (Harris, 1978). In the third study, 89% of 32 patients had a diastolic blood pressure below 95 mmHg after 6 months' treatment with labetalol (Douglas-Jones, 1980).

Comparative studies

In studies in which labetalol was compared with bendrofluazide, 11 patients on labetalol (17%) and six patients on bendrofluazide (10%) achieved a blood pressure of less than 150/95 mmHg (not significant) (General Practitioner Research Group,

1980). However, labetalol was significantly more effective than bendrofluazide in reducing systolic blood pressure ($P < 0.02$, Wilcoxon test) in the whole group of patients. In a study comparing labetalol with oxprenolol the mean decrease in blood pressure with oxprenolol was 19/7 mmHg, whereas with labetalol it was 24/13 mmHg (Forsell *et al.*, 1979). Five patients (7%) withdrew from each treatment group, one in each due to failure to control blood pressure, the rest due to side-effects. The mean dose of oxprenolol was 117 mg daily and of labetalol 680 mg daily.

Heart rate

In most reports, resting heart rate was not altered significantly (Gomez & Phillips, 1980; Harris, 1978; Douglas-Jones, 1980). However, two studies reported a significant reduction in resting heart rate. In one, a decrease of 11 beats/min after 2 weeks was measured ($P < 0.001$) but this was not sustained thereafter (Tuomilehto, 1980). In the other a decrease of 10 beats/min after 4 weeks occurred ($P < 0.001$), but there was no dose-response relationship (Kane *et al.*, 1976).

Dosage

Daily doses of labetalol varied between 100 mg (Van Schoor, 1979; General Practice Research Group, 1980) and 2400 mg (Douglas-Jones, 1980). In the General Practice Survey more than 85% of patients took less than 600 mg labetalol daily (General Practitioner Survey, 1978). However, in a study involving patients whose blood pressure was uncontrolled on previous therapy, 96% of them required more than 800 mg daily, the mean daily dose in this study being 1107 mg (Douglas-Jones, 1980).

In only one trial was labetalol given once daily ($n=20$), the mean decrease in diastolic blood pressure being 20 mmHg (Van Schoor, 1979). In all the other studies tablets were given twice or three times daily. The mean percentage withdrawal rate due to treatment failure and/or unacceptable side-effects in 8.2% compared with 6.5% for those on a three times daily regime. The mean percentage "success" rates were 79.9% and 80.0%, respectively.

Additional anti-hypertensives

Additional anti-hypertensive agents, principally diuretics, were required by 60% of patients in the General Practitioner Survey. In a retrospective assessment of patients' anti-hypertensive therapy in one practice (Kane, unpublished) 41% of 25 patients taking labetalol required the addition of a diuretic,

Figure 2 Effect on blood pressures of adding a thiazide diuretic to labetalol in six patients (Kane *et al.*, 1979). ○, labetalol; ●, labetalol plus diuretic.

compared with 55% of 30 patients taking other anti-hypertensive agents, which were usually β -blockers.

A group of six patients already stabilized on labetalol were given a thiazide diuretic (cyclopentiazide 0.5 mg), their blood pressure decreasing significantly ($P < 0.01$, systolic; $P < 0.001$, diastolic) (Figure 2) (Kane *et al.*, 1979).

In one study of labetalol in 41 patients which has spanned 5 yr (Kane *et al.*, 1979) tolerance to the anti-hypertensive effect has not developed, the average daily dose being 550 mg after 3 yr and 450 mg at the end of the trial.

Investigations

Routine haematological and biochemical indices did not alter significantly during treatment with labetalol.

In one study (Kane *et al.*, 1979) eight out of 26 patients developed a positive anti-nuclear antibody (ANA) test during treatment with labetalol, but when their ANAs were compared with age- and sex-matched patients taking other β -blockers, positive ANA titres were evenly distributed between the two groups.

Retinal changes (using Keith Wagener Barker classification) were assessed subjectively in several studies. In two of them, no alteration of the fundi was seen following the use of labetalol (Douglas-Jones, 1980; Kane *et al.*, 1979). In another a stated "improvement" was seen in six of the 53 patients (Harris, 1978). A further study reported retinal

Figure 3 Time course of side-effects (Gomez & Phillips, 1980). Number of withdrawals: ●, tiredness ($n=9$); ▲, dizziness ($n=20$).

improvement in 46 and deterioration in 15 of the 1286 patients (Gomez & Phillips, 1980).

Side-effects

The side-effects most frequently reported were tiredness, dizziness, headache and upper gastrointestinal symptoms. Their incidence after 3 months' treatment with labetalol 400 mg or less in 1061 patients were respectively 3.9%, 4.5%, 1.9% and 2.6% (General Practitioner Survey, 1978). Scalp tingling at this dose occurred in 1.0% of patients after 3 months. Unacceptable side-effects accounted for a withdrawal rate of around 10%. However, for those patients who remained on therapy, symptoms diminished rapidly with time (Figure 3.). The incidence of side-effects seems to be dose dependant; for example, the incidence of tiredness was 2.3% with 400 mg, 4.3% with 400–600 mg and 4.5% with 600 mg daily (Richards & Jackson, 1980).

When the incidence of side-effects due to other anti-hypertensive agents such as methyl dopa and slow-oxprenolol was retrospectively compared these were nearly always found to be greater than during labetalol treatment. The incidence of tiredness reported with propranolol and oxprenolol was also greater than during labetalol. However, with labetalol 400–600 mg daily, headache occurred more frequently than with either of these β -blockers (Figure 4) (General Practitioner Survey, 1978).

In an open study of 54 patients with a known history of bronchospasm (Gomez & Phillips, 1980), bronchoconstriction, necessitating withdrawal from the trial, occurred in nine of them (16.6%). This compared with an overall withdrawal rate of 7.2%.

Figure 4 Incidence of side-effects with other anti-hypertensive agents compared with labetalol (Monitoring of Trandate, Allen & Hanbury's Ltd). Key to columns (in order from left to right): methyldopa; propranolol; slow oxprenolol; labetalol < 400 mg; labetalol 400-600 mg.

Drug interactions

No adverse drug interactions were observed during the course of the studies; drugs from the groups of analgesics, anti-inflammatory agents, anti-depressants, hypnotics, tranquillizers, hormones and hypoglycaemic agents were used concurrently with labetalol.

Discussion

It now seems clear that labetalol is a suitable agent for all grades of hypertension and for patients who have failed to respond to other therapy. The maximum anti-hypertensive effect is seen after 4 weeks (Harris, 1978), and this fact, coupled with the drug's wide dose range, permits accurate titration of

labetalol in the large variety of hypertensive patients seen in general practice.

The drug does not produce a dose-dependent decrease in pulse rate (Kane *et al.*, 1979) and thus the bradycardia often seen with other β -blockers, does not occur with labetalol.

The two comparative studies which have been undertaken indicate that labetalol is at least as effective as oxprenolol (Forsell *et al.*, 1979) and more effective in reducing systolic blood pressure than bendrofluzide (General Practice Research Group, 1980).

Although a trial using labetalol once daily reported a favourable anti-hypertensive effect (Van Schoor, 1979) the time interval between taking the drug and measurement of blood pressure was not specified. Furthermore in another study it was shown that a single dose of labetalol is not effective at lowering blood pressure over a 24 h period (Wilcox, 1978). On the other hand both twice and three times daily dosage regimens seem to be equally effective in reducing blood pressure.

The side-effects which occur with labetalol tend to be transient, and in many cases less common than with other anti-hypertensive agents including β -blockers. However, patients with a known history of bronchospasm are twice as likely to stop treatment than the average withdrawal rate from studies would suggest.

Although it has been shown that labetalol is taken up by the melanin pigment in the retinae of animals (Poynter, Martin, Harrison & Cook, 1976) and that there is no alteration in the colour vision or visual acuity of patients (Kane *et al.*, 1979), the general improvement in grade of hypertensive retinopathy observed in some studies is of uncertain significance.

In conclusion labetalol has proved an acceptable and effective drug for use in general practice in the treatment of hypertension.

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