COMPARISON OF LABETALOL WITH OTHER ANTI-HYPERTENSIVE DRUGS

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1 The anti-hypertensive effects of labetalol have been compared and contrasted with other groups of anti-hypertensive drugs in this review of the published literature.

2 The data show that the pharmacological and haemodynamic profile of labetalol in man is distinctly different from that of other specific anti-hypertensive agents; namely the properties of competitive α- and β-adrenoceptor blockade leading to haemodynamic effects of reduced blood pressure and peripheral vascular resistance with little accompanying changes in resting heart rate or cardiac output.

3 The anti-hypertensive effects of labetalol are dose related. In fixed dose comparative studies equivalent anti-hypertensive effects to those of labetalol have been shown for individual drugs of the β-adrenoceptor-blocking and diuretic groups. In dose titration studies, equivalent anti-hypertensive effects at given doses of labetalol have been demonstrated for drugs of the following types: β-adrenoceptor blockers, β-blockers plus diuretics, methyldopa, adrenergic neurone blockers and the combination of β-blockers plus a peripheral vasodilator.

4 Comparing side-effect liabilities, it is clear that quantitatively labetalol produces no greater burden of side-effects than drugs of the β-adrenoceptor-blocking group. Qualitative differences, however, do exist; in particular, symptomatic postural hypotension is dose related and is more likely to occur when excessive doses (> 2 g daily) are used.

Introduction

Since its earliest evaluation in clinical trials in the early 1970s, labetalol has now been directly compared with individual representatives of all the different groups of anti-hypertensive drugs. A number of comparative studies have helped to define the profile of anti-hypertensive efficacy possessed by labetalol. The pharmacological and haemodynamic profile can readily be seen as the basis of the anti-hypertensive effect of labetalol.

Clinical pharmacology and haemodynamics

Labetalol competitively antagonizes endogenous and exogenous stimulation at both β-and α-adrenoceptors in man, as demonstrated using pharmacological and physiological methods (Richards & Prichard, 1979). The degree of α- in relation to the β-blocking effect calculated from the inhibition of phenylephrine-induced systolic blood pressure increase and isoprenaline-induced heart rate increase, varies between a ratio of 1:3 and 1:7 depending on the dose and the route of administration. The β-adrenoceptor blocking activity is non-selective, whereas animal experiments indicate that its α-blocking effect is exclusively postsynaptic (Drew, 1978).

The dual α- and β-adrenoceptor-blocking properties of labetalol in normal subjects and hypertensive patients lead to a similar pattern of circulatory effects. Following acute intravenous administration in the supine position, significant reductions in blood pressure occur without a fall in heart rate or cardiac output (Richards *et al.*, 1979; Prichard *et al.* 1975). After continuous oral administration to patients, small reductions in resting heart rate are usually found (Lund-Johansen, 1979), although individual changes are influenced by the degree of resting sympathetic drive. Marked reductions in resting heart rate after labetalol may follow intravenous administration (Cumming *et al.*, 1979; Marx & Reid, 1979).

Cardiac output at rest does not usually change much after labetalol treatment (Koch, 1976; Edwards & Raftery, 1976; Mehta & Cohn, 1977). On the other hand at high levels of exercise there is some reduction in exercise-induced increases in cardiac output caused by the β-blocking effects of

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labetalol (Edwards & Raftery, 1976). Long-term continuous oral administration to hypertensive patients has confirmed the original findings (Lund-Johansen, 1979; Koch, 1979). Thus the lack of significant reduction in resting cardiac output after labetalol distinguishes it from that after treatment with simple β-adrenoceptor-blocking drugs but resembles the pattern seen with the combination of β-blockade plus prazosin (Lund-Johanssen, 1979).

The work of McNeil and Louis (1979) indicates that for an equivalent hypotensive effect there is a greater reduction in resting heart rate and exercise tachycardia with atenolol or metoprolol compared with labetalol. This is expected, as the hypotensive effect of labetalol results from its combined properties, in particular the α-adrenoceptor-blocking effect being responsible for acutely lowering peripheral resistance (Bahlmann *et al.*, 1979). Consequently for equivalent hypotensive effect the dose of labetalol which achieves this will have a lesser degree of β-adrenoceptor blockade than any comparative simple β-adrenoceptor blocker. McNeill and Louis (1979) have also put forward the explanation that the weak pA2 for the β-receptor for labetalol may account for this difference.

Comparison of anti-hypertensive drugs

Clear pharmacological differences, for example, the possession or not of α-receptor-blocking activity, is likely to lead to differing therapeutic response, in particular leading to swifter reduction of raised blood pressure. On the other hand comparison between anti-hypertensive drugs is often difficult. Dosage of various agents usually vary, and for a meaningful therapeutic comparison of drugs it is important that the drugs being compared are each given in their optimum dosage. Labetalol is a drug that needs to be given in variable dosage, as do most specific anti-hypertensive drugs; fixed dose comparisons therefore give limited information.

Acute use of labetalol

In contrast to β-adrenoceptor-blocking drugs that do not possess α-blocking activity, labetalol abruptly lowers raised blood pressure given either intravenously or orally, and has been shown to control the blood pressure of severely hypertensive patients in phaechromocytoma and hypertensive reactions after clonidine withdrawal, and to operate as an adjunct in the production of hypotensive anaesthesia.

Trust *et al.* (1976) reported on 20 severe hypertensive patients given labetalol 1–2 mg/kg intravenous, in four as a rapid bolus injection, in the remaining 16 slowly over 10 min. All patients showed a fall in blood pressure within 5 min of the end of the injection. The largest fall seen was from 188/142 mmHg to a trough of 90/64 mmHg, 10 min after labetalol 100 mg. Two other patients complained of nausea and faintness even while remaining recumbent. The pressures of these three patients before labetalol averaged 229/140 mmHg, heart rate 99 beats/min, and 100/77 mmHg, heart rate 60 beats/min after labetalol. Another approach by the same group of investigators has been to give graded infusions of labetalol in order to improve the smoothness of the fall of blood pressure.

The infusion was commenced at 20 mg for the first hour, 40 mg for the second hour, 80 mg for the third hour and 160 mg during the fourth hour. This resulted in a smooth reduction from a diastolic blood pressure level of 160–170 mmHg to those between 90 and 100 mmHg (Brown *et al.*, 1977).

The use of repeated bolus injections of labetalol, usually 1 mg/kg, followed by 50 mg at 10-min intervals, seemed to be less effective in controlling the blood pressure and more likely to cause side-effects (Cumming *et al.*, 1979). Less impressive results were obtained in 17 patients by McGrath *et al.* (1978). Seven patients did not respond to intravenous labetalol 1 mg/kg, repeated after 45 min; however, they were all already receiving anti-hypertensive drugs, and five of the seven a combination of prazosin and a β-blocking drug. The amount of fall of blood pressure did not seem to be affected by the rate of injection, whether 150 mg was given over 1 or 15 min (Pearson & Havard, 1978).

In a study comparing intravenous labetalol 150 mg and diazoxide 300 mg falls in blood pressure were similar. In addition diazoxide significantly reduced cerebral blood flow, although changes with labetalol were not significant (Pearson *et al.*, 1979).

Rosei *et al.* (1976) have reported one case where labetalol 150 mg intravenously was used to control blood pressure after a hypertensive crisis from clonidine withdrawal, and in a patient with aortic dissection it was used as a continous infusion to control the blood pressure (Cumming & Davis, 1979). Rosei *et al.* (1976) found that in four of five patients, labetalol successfully controlled the blood pressure in patients with a phaechromocytoma. In the other patient, intravenous labetalol lowered blood pressure but subsequent oral administration up to 400 mg four times daily failed to control hypertensive attacks. Dosage could not be further increased because of nausea, but attacks were controlled by a mixture of propranolol and phenoxybenzamine.

Labetalol has been used in single oral doses to

control blood pressure in nine patients whose diastolic blood pressures were persistently in excess of 130 mmHg (Ghose & Sampson, 1977), using 200 mg (two patients), 300 mg (four patients) and 400 mg (three patients). Two of these patients required additional doses 2–4 hs later because of inadequate response, but otherwise significant reduction in blood pressure occurred without symptoms or complications. Although a considerable fall in blood pressure is seen by 2 h, maximum effect may be in 3 h (Serlin *et al.*, 1979).

Labetalol is used in combination with halothane anaesthesia to produce controlled hypotension. A synergistic effect was observed between the labetalol and halothane with good circulatory and operating conditions. Blood pressure rose to near normal when halothane was withdrawn producing good post operative circulatory conditions (Scott *et al.*, 1976; Kaufman & Richards, unpublished observations).

Labetalol and diuretics

Labetalol has been used in combination with diuretics since the earliest clinical studies (Prichard & Boakes, 1976; Bolli *et al.*, 1976).

Horvarth *et al.* (1979) have performed a randomized double-blind trial of bendrofluazide 2.5 mg twice daily, a fixed dose of labetalol 200 mg twice daily and placebo, with results analysed in 13 cases. It was only from labetalol that a significant fall in blood pressure was obtained, although standing readings only were obtained. The authors themselves found varying blood levels from labetalol with falls in pressure being proportional to plasma concentration. This would support the suggestion that the fixed dose approach, though simplifying design, does not ensure maximum benefit is obtained from the drug.

In another fixed dose trial in mild hypertension, labetalol 200 mg three times daily was similar in effect to bendrofluazide 10mg, with the combination producing the larger fall in blood pressure. It was noted that labetalol produced a small increase in plasma renin, similar to other β-blocking drugs (Prichard & Owens, 1980). Renin was raised also by the diuretic, so that although renin effects are opposed, blood pressure responses show an additive effect (Dawson *et al.*, 1979).

Labetalol and β-adrenenoceptor-blocking drugs

Prichard and Boakes (1976) have included in their report four patients whose blood pressure previously being treated with β-blocking drugs, was better controlled when labetalol was given. In a randomized double-blind trial completed by 11 patients with mild hypertension, propranolol (average dose 480 mg; range 30–96 mg daily) gave similar degree of control to labetalol 1180 mg (range 75–2400 mg) (Pugsley *et al.*, 1979).

Pugsley *et al.* (1976*b*) have performed a formal between patient double-blind trial of labetalol and propranolol in 18 severe hypertensive patients, with all patients receiving hydrochlorothiazide 100 mg and amiloride 10 mg daily (Moduretic, two tablets). Blood pressures were reduced to a similar degree by labetalol (137/87 mmHg, average dose 763 mg) and propranolol (138/87 mmHg, average dose 532 mg), in the supine position. Blood pressures on standing (121/84 mmHg) and after exercise (117/78 mmHg) tended to fall after labetalol but the difference from propranolol, 132/93 and 133/94 mmHg, respectively, only reached statistical significance for the post-exercise diastolic blood pressure. The ratio of doses of labetalol to propranolol in this study was 1.44:1, a lower ratio than that seen in mild hypertension (Pugsley *et al.*, 1976*a*). When patients whose blood pressure control had been inadequate on β-blocking drugs were transferred to labetalol, adequate control was achieved in all patients (Dent & Kellaway, 1977).

In another study in patients with mild hypertension, although the final blood pressure reached by patients receiving labetalol 400 mg daily for the first month (average 585 mg daily, second month) was similar to propranolol 160 mg daily for the first month (average 234 mg daily, second month), the fall in pressure on labetalol was greater as pretreatment blood pressures were higher in the labetalol patients, no postural effect was observed with labetalol in this study (Hunyor *et al.*, 1980). Their investigators found that labetalol produced a significant increase in plasma volume (average 294 ml) in contrast to propranolol (98 ml, increase, not significant).

Labetalol has been compared with other β-adrenoceptor-blocking drugs. Thirty patients with mild and moderate hypertension completed a within-patient randomized trial of pindolol (average 14.5 mg daily) and labetalol (average 533 mg daily). Blood pressure control was similar. Overall the incidence of side-effects was similar. Seven other patients did not complete the study, three for drug-related reasons on pindolol, one because of dyspnoea and two because of a failure to control blood pressure (Romo *et al.*, 1979).

In a further within-patient study 18 patients received fixed doses of pindolol 10 mg daily and labetalol 400 mg daily. Control of supine and standing blood pressures was similar during exercise. A

greater inhibition of the increase in systolic blood pressure and in heart rate was seen with pindolol, whereas diastolic pressure was significantly lower during exercise after labetalol (Bjerle *et al.*, 1980).

McNeil and Louis (1979) also reported a variable-dose comparative trial. First, 29 patients received atenolol 138 ± 13 mg daily) and pindolol (24 ± 2 mg) in random order. Labetalol 308 ± 34 mg daily and metoprolol 234 ± 22 mg were compared in all but three of these patients ($n = 26$).

Drug dosage was adjusted to produce a standing diastolic blood pressure of 90 mmHg or less. Similar control of supine standing and post-exercise blood pressure was obtained, there was less of a reduction in the increase in heart rate during exercise after labetalol. The pattern of reported side-effects was similar, but numerically less with labetalol than atenolol or pindolol.

Labetalol and β-blockers plus hydrallazine

A double-blind comparative study in mild to moderately severe hypertensives found labetalol 600 mg twice daily was approximately equivalent to pindolol 15 m twice daily plus hydrallazine 50 mg three times daily (Barnett *et al.*, 1978).

In a further fixed-dose randomized study in 12 patients with mild hypertension, who received methylclothiazide 5 mg throughout, labetalol 300 mg twice daily, was equally effective as propranolol 80 mg twice daily, better than hydrallazine 50 mg twice daily; but although labetalol was similar to the combination of propranolol plus hydrallazine in the standing position, the combination was more effective (West *et al.*, 1980).

Lehtonen *et al.* (1979) have compared labetalol (average 960 mg daily) up to 600 mg twice daily with propranolol (average 363 mg daily) up to 240 mg twice daily plus dihydrallazine (average 113 mg daily) up to 75 mg twice daily in 17 patients.

The decreases in blood pressures were greater with propranalol plus dihydrallazine, with the exception of the standing systolic blood pressure. Supine heart rates were reduced to a similar degree by both regimens but the standing heart rate was significantly lower with propranolol plus dihydrallazine. Measurement of plasma concentrations revealed a correlation between dose of labetalol and plasma concentration but because of individual variation a correlation was not seen with propranolol. Side-effects were experienced by two patients on labetalol 400 mg twice daily; one experienced postural dizziness, one tiredness; and three patients on propranolol plus dihydrallazine experienced cold legs, limb weakness and headache. An additional patient experienced headache and nausea on the combination of propranolol plus dihydrallazine and was withdrawn from the study.

A between-patient study in 40 patients found that labetalol 400–800 mg daily was more effective than acebutolol 400–800 mg daily but the combination of acebutolol 800 mg daily plus dihydrallazine 25 or 50 mg twice daily was similar in effect to labetalol up to 800 mg twice daily. In this study a correlation between the initial renin levels and response to acebutolol was noted but there was no such correlation for the response to labetalol (Thibonnier *et al.*, 1980).

Labetalol and methyldopa or sympathetic inhibitory drugs

Prichard and Boakes (1976) have reported a long-term study largely with patients already under treatment with existing anti-hypertensive drugs. They used an average daily dose of 889 mg (range 75–3200 mg) but in the 11 patients not previously treated who were generally a more mildly affected group, the average dose was 529 mg. Blood pressure control on labetalol was similar to treatment with methyldopa or the sympathetic inhibitory drugs, bethanidine, debrisoquine and guanethidine. Long-term follow up for over 3 years in 13 patients indicated that tolerance to labetalol did not develop.

Further evidence to support the suggestion of Prichard *et al.* (1975), that labetalol was a drug that could control the blood pressure in patients previously needing large doses of methyldopa, was provided by the work of Dargie *et al.*, (1976). They treated a group of 16 very severe hypertensive patients whose outpatients supine blood pressures averaged 172/108 mmHg (standing 155/102 mmHg) while being treated with bendrofluazide 10 mg plus a mixture of other drugs; propranolol average dose 892 mg in 13 patients, methyldopa average 4560 mg in eight patients, clonidine average 2.53 mg in seven patients, bethanidine average 62 mg in seven patients, hydrallazine average 300 mg in four patients and guanethidine 70 mg in one patient. The diuretic was continued but labetalol (average 3091 mg; range 1200–8000 mg) was substituted for the other drugs; blood pressures were 150/98 mmHg supine, 131/91 mmHg standing.

Sanders *et al.* (1979) have performed a variable-dose cross-over trial using placebo, labetalol and methyldopa in 20 patients to a maximum dose of 1000 mg three times daily of each drug. Average blood pressures with labetalol (average dose 810 mg ± 166 mg daily) were 158/92 mmHg supine, 144/89 mmHg standing; with methyldopa (average dose 1183 ± 201 mg daily) they were 153/92 mmHg supine, 144/90 mmHg standing; and with placebo,

readings were 181/107 mmHg supine, 173/104 mmHg standing. Two of the patients failed to complete the methyldopa period, one because of lethargy, the other because of failure of blood pressure control within the maximum dose used in the trial. There were no significant differences in the incidence of side-effects. In a recent report on pregnancy-induced hypertension, labetalol 400 or 800 mg daily gave better control of the blood pressure in 14 patients: a fall from a mean arterial blood pressure of 112 to 91 mmHg, compared with methyldopa 750 to 1500 mg daily: a fall in mean arterial blood pressure from 111 to 101 mmHg (Lamming *et al.*, 1980).

Side-effects

Labetalol interferes with the innervation of the α_1-adrenoceptor and therefore symptoms of postural hypotension might be expected to occur. However, these are uncommon with labetalol. It is clear that the fall in blood pressure after labetalol is due to its combined α- and β-blocking properties. Symptoms associated with posture-related changes in blood pressure result from both the speed and depth of the fall in blood pressure. Active vasoconstrictor mechanisms mediated by α-adrenoceptors counteract the fall in blood pressure. As the α_1-adrenoceptor-blocking effect of labetalol is competitive, then the increased α-mediated sympathetic activity associated with the erect posture can be expected to at least partly overcome the reversible blockade. This logic is supported by the data which showed that when the non-competitive α-blocker phenoxybenzamine is added to propranolol, the additional anti-hypertensive effect was entirely postural (Beilin & Juel-Jensen, 1972) and indeed symptomatic complaints were quite numerous. Posture-related falls in blood pressure do occur more frequently with higher doses of labetalol (Dargie *et al.*, 1976; Prichard & Boakes, 1976) and postural effects occur at lower dosages when a diuretic is used in all or most of the patients (Bolli *et al.*, 1976; Pugsley *et al.*, 1976*a*). This most probably relates to the fact that diuretics produce a chronic reduction in blood volume (Prichard & Tuckman, 1977). This will in turn increase sensitivity to α-adrenoceptor inhibition under physiological stresses such as the erect posture. Postural reductions in blood pressure also occur more obviously as a result of acute elevation in plasma labetalol values (McNeill *et al.*, 1981) and this probably explains the findings reported in early clinical trials where labetalol was given abruptly in doses of 400 mg and 800 mg in a double-blind trial (Kane *et al.*, 1976).

Side-effects in general seem to be more frequent early in treatment with labetalol than later (Pugsley *et al.*, 1976*b*). This is probably a function of the reported initial effects of a lowering in blood pressure and a diminution in side-effects with time, regardless of the drug administered, when bethanidine, guanethidine and methyldopa were examined (Prichard *et al.*, 1968).

Transient tiredness in three patients and transient calf muscle pain in two patients were reported in a series of 17 patients examined by Andersson *et al.*, (1976). Urinary retention due to labetalol has been reported in one patient (Dargie *et al.*, 1976) and there has been an isolated report of one patient suffering from vivid dreams that could possibly have been due to labetalol (Hansson & Hanel, 1976). Bolli *et al.* (1976), in a series of 17 patients has reported two patients with mild constipation and one patient with angina which worsened when labetalol was substituted for metoprolol. Although labetalol does have significant anti-anginal action, it may be less effective than β-blocking agents in normotensive patients (Boakes & Prichard 1973).

Dargie *et al.* (1976) have reported that sedation and dry mouth was less common than on methyldopa and clonidine and Bolli *et al.* (1976) have found that two patients experiencing Raynaud's phenomenon on β-blocking drugs were improved on labetalol.

The two side-effects in susceptible subjects, heart failure and asthma, associated with the administration of β-adrenoceptor-blocking drugs, have been reported only occasionally with labetalol. However, we have seen one hypertensive patient develop subjective symptoms and objective signs of airways obstruction on labetalol that was reversed on dosage reduction without loss of blood pressure control (Prichard *et al.*, 1979). There have not been any reports of heart failure being precipitated by labetalol but the drug is probably best avoided in patients crucially dependent on their sympathetic drive to maintain cardiac output.

Overall, labetalol produces only modest side-effects; in some instances they have been less than on previous treatment.

Conclusions

Despite difficulties inherent in many of the studies, particularly the use of fixed dosage, it can be concluded that labetalol is probably as effective as a mixture of β-blocking drugs plus hydrallazine. Other studies have indicated that labetalol is as effective or more effective than methyldopa.

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