Effects of combined α- and β-receptor blockade on peripheral circulation in essential hypertension

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Summary

1. Six weeks' treatment with labetalol (600 mg/day) significantly reduced systolic and diastolic blood pressures in 24 patients with essential hypertension. There was a small but not significant decrease in heart rate.

2. After 6 weeks of therapy mean digital arterial blood flow at rest and during reactive hyperaemia had increased by 26%.

3. In nine essential hypertensive patients intravenous administration of 100 mg of labetalol caused prompt and striking reductions of systolic and diastolic blood pressures without significant changes in heart rate. There was a consistent and significant increase in peripheral blood flow by 32% 5 min after administration of the drug.

4. Antagonism of α-receptors in addition to β-receptors might improve peripheral arterial blood flow while achieving antihypertensive control. Thus labetalol, owing to its favourable haemodynamic effects, may have advantages over conventional pure β-receptor-blocking agents.

Key words: adrenoceptor, labetalol, peripheral blood flow.

Introduction

Among adrenergic inhibitors β-receptor antagonists offer the most important approach to modern antihypertensive therapy. However, in some patients administration of these drugs is associated with peripheral circulatory impairment, clinically characterized by cold extremities, Raynaud's phenomenon, intermittent claudication or absent pulses [1-3]. The incidence of these haemodynamic alterations is highest with non-selective β blockers and less with cardioselective compounds [1]. The cause of these vascular problems after β-adrenoceptor blockade is probably reduction in cardiac output and blockade of β-adrenoceptor-mediated skeletal muscle vasodilatation, resulting in unopposed α-adrenoceptor vasoconstriction [4]. The orally active adrenoceptor-blocking drug, labetalol, possesses competitive adrenergic α- and β-blocking properties within the same molecule [5].

Unlike conventional β-blocking drugs, labetalol intravenously reduces peripheral vascular resistance and blood pressure and has little effect on cardiac output [6]. Thus theoretically this drug, owing to its α-blocking efficacy, has advantages over 'pure' β-blocking agents in that it may produce less deviation of haemodynamics from normal.

The aim of the present investigation was to study the short- and long-term effects of labetalol on haemodynamics in patients with essential hypertension and to assess whether antagonism of α-receptors in addition to β-receptors might affect peripheral circulation while achieving antihypertensive control.

Methods

Patient selection and study protocol

Thirty-three male patients with essential hypertension (WHO classification I–II) were enrolled in this study. They ranged in age from 21 to 52 years and had not taken antihypertensive drugs previously. Each subject signed an informed consent form after the nature of the study had been fully explained.

Two groups of patients were investigated. The effect of long-term labetalol administration on blood pressure, heart rate, digital arterial blood flow at rest and during reactive hyperaemia, and on digital arterial pressure was investigated in a
first group of 24 untreated patients with mild to moderate essential hypertension. Each patient received oral labetalol in doses of 300–900 mg/day (mean 600 mg/day) for 6 weeks.

The effect of a single intravenous dose of 100 mg of labetalol on blood pressure and on digital blood flow was studied in a second group of nine patients with moderate to severe essential hypertension. Haemodynamic measurements were performed before and 5 min after injection of the drug.

Measurements

Blood pressure was measured with a mercury sphygmomanometer, and the pretreatment blood pressure was the mean of three readings recorded at weekly clinic attendances during 3 weeks placebo period.

Digital blood flow at rest and during reactive hyperaemia was measured by means of venous occlusion strain-gauge plethysmography with the Mediamic Strain Gauge Plethysmograph SP2. Reactive hyperaemia was achieved after supersystolic blockade of digital arterial blood flow for 3 min, with subsequent release of the inflated cuff.

Data were analysed by Student’s paired t-test. Differences were considered significant at the \( P < 0.05 \) level. All results are expressed as means ± SEM.

Results

Six weeks’ treatment with labetalol significantly reduced mean systolic and diastolic pressures to the same extent in both supine and standing positions. After 3 weeks of therapy average supine blood pressure was reduced from 159/100 to 137/87 mmHg (\( P < 0.01 \)). These values were slightly but not significantly lower than those observed after 6 weeks of therapy (Fig. 1). The small decrease in heart rate from 80 to 76 beats/min observed after 3 and 6 weeks of treatment was not statistically significant.

Despite the significant reduction of systolic and diastolic blood pressures there was a small but consistent rise in mean arterial digital blood flow from 5.6 to 6.9 ml min\(^{-1}\) 100 ml\(^{-1}\) of tissue after 3 weeks of treatment (\( P < 0.05 \)). The increase in peripheral blood flow was even more pronounced under conditions of reactive hyperaemia. As can be seen from Fig. 1, 3 weeks’ treatment with labetalol resulted in a rise of digital blood flow from 9.8 to 12.6 ml min\(^{-1}\) 100 ml\(^{-1}\) of tissue, indicating that peripheral vascular resistance had not increased with therapy.

The lower part of Fig. 1 demonstrates blood pressure and pulse rate responses after acute administration of a single intravenous (100 mg) dose of labetalol. Five minutes after injection of labetalol prompt and striking reductions of both systolic and diastolic blood pressure occurred in all patients. The decrease in pressure was associated with a small but not significant reduction in pulse rate.

After intravenous administration of labetalol, digital arterial blood flow rose significantly by 30% from a mean of 11.8 to 15.6 ml min\(^{-1}\) 100 ml\(^{-1}\) of tissue. The increase in digital blood flow at rest was observed 5 min after administration of the drug and occurred in the presence of a significant reduction of digital artery pressure. The data simultaneously obtained on the middle finger of the left and right hand were comparable (lower part of Fig. 1).

Discussion

This study demonstrates that labetalol is an effective antihypertensive agent both under short- and long-term conditions. In almost all of the patients treated, satisfactory blood pressure responses were achieved in the supine as well as in the standing position without significant orthostatic reactions or side effects. The minimal influence of labetalol on heart rate in the supine resting hypertensive patients may result from its blockade of postsynaptic \( \alpha \)-adrenoceptors, thus resembling prazosin. As with conventional \( \beta \)-adrenoceptor-blocking drugs, the patients did not become tolerant to the hypotensive effect of labetalol: thus blood pressure control was well maintained without need to increase dosage. Unlike ‘pure’ \( \beta \) blockers, labetalol apparently did not increase peripheral vascular resistance. On the contrary, in the face of striking reductions of both systolic and diastolic blood pressure as well as of digital artery pressures, peripheral blood flow at rest and under conditions of reactive hyperaemia significantly increased with labetalol, indicating a decrease in peripheral vascular resistance. The finding that intravenous labetalol caused an immediate change in digital arterial blood flow suggests that the raised peripheral blood flow after long-term labetalol also can be ascribed to a direct action of the drug on vascular tone. The observation that chronic administration of labetalol resulted in a consistent rise in peripheral blood flow may indicate that the \( \alpha \)-receptor-blocking effect of the drug mainly contributed to the hypotensive effect during long-term oral therapy.

Our data have some clinical implications. As labetalol apparently has a favourable effect on
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Peripheral blood flow it may be particularly useful in patients who experience Raynaud's phenomenon on conventional $\beta$-adrenoceptor-blocking drugs, or in patients with pre-existing peripheral circulatory impairment. Also, by its $\alpha$-adrenoceptor-blocking effects, labetalol would oppose the increase in coronary vascular resistance that occurs during $\beta$-adrenoceptor antagonism [7] and may prove effective in producing antihypertensive control as well as improvement in angina pectoris [8].

Thus, from a pathophysiological point of view, labetalol, because of its favourable haemodynamic actions, i.e. decrease in blood pressure, rise in peripheral blood flow and reduction in peripheral vascular resistance with little effect on cardiac output, may have some advantages over conventional pure $\beta$-receptor-blocking agents in the treatment of hypertension. However, further studies are necessary to analyse the effects of labetalol on haemodynamics, particularly on peripheral blood flow, under conditions of physical exercise.

References


