Labetalol in hypertensive patients with angina pectoris: beneficial effect of combined α- and β-adrenoreceptor blockade

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Summary

1. Eight hypertensive patients with angina pectoris had placebo added to their existing medications for 8 weeks, then incremental doses of active labetalol with simultaneous stepwise reduction in other medicines until blood pressure was satisfactorily controlled; after that only labetalol and thiazide (8 weeks) and finally labetalol-placebo together with previous β-adrenoreceptor antagonists and thiazide for 4 weeks were administered.

2. During the labetalol plus thiazide period resting blood pressures and measurements obtained during isotonic exercise, isometric exercise and the cold pressor test were significantly lower than during the initial placebo addition period. Angina scores were significantly reduced during this period.

3. During the final treatment with placebo, β-adrenoreceptor antagonist and thiazide, blood pressures remained reduced, but angina was significantly worse.

4. Labetalol which antagonizes both α- and β-adrenoreceptors produced better relief of angina pectoris than β-adrenoreceptor antagonists during improvement in blood pressure in hypertensive patients.

Key words: α- and β-adrenoreceptor antagonism, angina pectoris, hypertension.

Introduction

Administration of β-adrenoreceptor antagonists may aggravate certain vasospastic disorders, e.g. Raynaud’s phenomenon, in hypertensive patients. Coronary arterial spasm may contribute to angina pectoris (Gensini, 1975), particularly Prinzmetal’s variant angina (Oliva, Potts & Pluss, 1973). We observed a number of hypertensive patients with angina pectoris in whom reasonable control of hypertension with agents including β-adrenoreceptor antagonists was accompanied by disappointing relief of angina and who persistently required independent management for angina pectoris.

We therefore used labetalol, which has both α- and β-adrenoreceptor antagonist activity, to assess whether antagonism of α-receptors in addition to β-receptors might relieve angina pectoris while achieving antihypertensive control.

Methods

Patient selection

Ten patients with hypertension and angina pectoris were selected from a stable outpatient clinic population. Informed consent was obtained from all patients. The characteristics of the eight patients who completed the study and details of their antihypertensive therapy are shown in Table 1. One female patient had no angina during the trial and was excluded. A male patient who developed myocardial infarction, with uneventful recovery, was excluded. All patients were classed as having moderate to severe hypertension. Seven of the eight patients had an abnormal electrocardiogram and the mean cardiothoracic ratio on chest X-ray was 0.57 (SEM ± 0.17, n = 8).

All patients were on nitrates and three patients were on perhexilene. In the two patients who did not receive β-adrenoreceptor antagonists clonidine
## Table 1. Characteristics of patients who completed labetalol trial

Resting blood pressure (systolic/diastolic), pulse rate and angina score are supplied for initial period during addition of labetalol placebo and the labetalol maintenance period of 8 weeks. Code for previous medications: M = methyldopa; Cl = clonidine; MP = prazosin; R = reserpine + thiazide; T = thiazide; P = propranolol; At = Atenolol; Ac = acebutolol.

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<th>Age (years)</th>
<th>Sex</th>
<th>Fundal grade (K-W)</th>
<th>LVH on ECG</th>
<th>Q waves on ECG</th>
<th>Resting BP (mmHg)</th>
<th>Pulse rate (min⁻¹)</th>
<th>Angina score</th>
<th>Dose of labetalol (mg/day)</th>
<th>Previous medications</th>
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<td></td>
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<td>During labetalol</td>
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<tr>
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<td>216/135</td>
<td>180/117</td>
<td>68</td>
<td>70</td>
<td>(2)</td>
</tr>
</tbody>
</table>

Mean 168/112 150/100 62 64 3.8 1.6
SEM 8.5/5.2 5.5/3.8 2.3 3.6 0.6 0.4
Labetalol in hypertension with angina

was used instead. One patient had severe cardiac failure (cardiothoracic ratio 0.59) and the other patient complained of severe reduction of effort-tolerance with addition of a \( \beta \)-adrenoreceptor antagonist.

**Quantification of angina pectoris**

Score 5: severe attacks on effort > 4/day; angina at rest; severely limited (nitrate consumption > 4 tablets daily).

Score 4: angina only on effort, 1–4 attacks/day, somewhat limited (nitrate consumption 1–4 tablets daily).

Score 3: angina inconsistently on effort; minimal limitation (nitrate consumption 0–1/day).

Score 2: attacks occasionally but definable as angina (nitrate required, but sporadically).

Score 1: pain only on marked effort and not severe; no nitrates required.

Score 0: unlimited ordinary activity without chest pain.

**Study protocol**

Patients were seen every 2 weeks. A thiazide diuretic was maintained at a constant dose throughout the study.

**Placebo addition.** Tablets resembling active labetalol and in identical containers were added to existing antihypertensive regimen for 2 months.

**Titration period.** Substitution of 50 mg of labetalol three times a day for placebo with gradual reduction of existing antihypertensive agents and increase of the labetalol by 50 mg three times a day every 2 weeks until 200 mg three times per day or a satisfactory level of blood pressure was reached.

**Maintenance period.** The final dose of labetalol and diuretic were continued for 2 months.

**Second placebo period.** The labetalol tablets were replaced by placebo and the previous \( \beta \)-adrenoreceptor antagonist (or clonidine in two patients) was substituted in the maximum dose used previously and the patient seen on two further occasions.

**Measurements**

Patients sat quietly for 10 min before the pulse rate and blood pressure were recorded. They then stood erect for 2 min and the blood pressure measurements were repeated. Thereafter patients walked 60 m rapidly after which the standing blood pressure was recorded. At the initial visit the maximal force exerted on a hand-grip dynamometer was determined for each patient. At each visit thereafter the patient maintained his or her half-maximal level for 60 s after which the blood pressure was recorded. Thereafter the patient’s left arm was immersed in water and ice for 1 min and the blood pressure measured.

Standard 12-lead ECG recordings, chest radiographs, and values for serum electrolytes, urea and creatinine were obtained after the first placebo period and after the labetalol maintenance period.

The angina status of the patient was assessed by direct questioning.

**Statistics**

Student’s \( t \)-tests, paired or unpaired as appropriate, were used and \( P < 0.05 \) was used to indicate statistically significant differences between mean values. Mean values ± SEM for \( n = 8 \) are supplied throughout.

**Results**

There was significantly better control of resting blood pressures during labetalol therapy (\( P < 0.01 \)) (c.f. Table 1). Erect blood pressure was reduced from 166 ± 9/114 ± 5 mmHg during the placebo addition period to 146 ± 5/101 ± 4 mmHg during the labetalol period (\( P < 0.05 \)). After walking, blood pressure was significantly lower during the labetalol period than during the initial placebo addition period (161 ± 9/107 ± 5 and 148 ± 6/97 ± 6 mmHg respectively, \( P < 0.05 \)). The responses after isometric exercise were 186 ± 10/133 ± 7 mmHg during the initial placebo addition period and 169 ± 8/118 ± 4 mmHg during the labetalol period (\( P < 0.05 \)). During the cold pressor test, the blood pressures reached were 178 ± 10/124 ± 5 mmHg during the initial placebo addition period and 165 ± 7/114 ± 6 mmHg during the labetalol period (\( P < 0.05 \)). The differences between the resting blood pressures and the responses during standing, isotonic exercise, isometric exercise and the cold pressor test were not different during the labetalol period in comparison with the placebo addition period. Pulse rates were not different during the various phases. The cardiothoracic ratios did not change (0.57 ± 0.17 during placebo addition and 0.56 ± 0.15 during the labetalol plus thiazide periods). Serum urea was 7.4 ± 0.5 mmol/l and 8.4 ± 0.6 mmol/l during the two periods respectively; these values were not different.
Discussion

This study demonstrates that labetalol is an effective antihypertensive agent and is capable of improving angina pectoris while achieving antihypertensive control. A deterioration in angina status occurred in six of eight patients when treatment was again switched to β-adrenoreceptor antagonist plus diuretic even though satisfactory blood pressure responses were maintained. Incremental blood pressures obtained during isotonic exercise, isometric exercise and cold pressor test were not reduced by labetalol in comparison with the other antihypertensive agents used even though the baseline blood pressures were lower. Pulse rates were similar during the labetalol therapy and placebo periods.

An α-adrenoreceptor-mediated increase in coronary vascular resistance, presumably related to coronary arterial spasm has been demonstrated (Mudge, Grossman, Mills, Lesch & Braunwald, 1976). In Prinzmetal's variant angina coronary arterial spasm has been shown to be the most important pathogenetic factor (Oliva et al., 1973). A reduction in myocardial blood supply, mediated by α-adrenoreceptor-mediated coronary arterial spasm, in addition to an increase in myocardial oxygen consumption, may contribute to the angina during the adrenoreceptor overactivity which accompanies an attack of angina pectoris. In hypertensive patients with increased arterial reactivity, unopposed α-receptors in the coronary vessels, may occur during β-adrenoreceptor blockade.

Labetalol, which possesses α- and β-sympathetic antagonist properties, markedly reduces the pressure–rate product in hypertensive patients and it was predicted by Mehta & Cohn (1977) that it should be effective in angina pectoris. Boakes & Prichard (1973) demonstrated an increase in effort-tolerance in patients with angina pectoris after acute intravenous administration of labetalol.

By its pharmacological action, labetalol would oppose the increase in coronary vascular resistance that occurs during β-adrenoreceptor antagonism (Parratt & Grayson, 1966) and, as shown in this study, may prove effective in producing antihypertensive control as well as improvement in angina pectoris. The rationale for this action, however, remains speculative and requires proof by definitive experimentation.

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References


