Beneficial effect of labetalol in hypertensive patients with angina pectoris

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Summary

Labetalol (Trandate; Allen & Hanbury) was administered to 17 hypertensive patients with angina pectoris, which had persisted despite blood pressure control on treatment including ß-blocking agents. In comparison with placebo, labetalol significantly reduced the frequency and severity of attacks of angina pectoris, without further improvement in control of blood pressure at rest, during isotonic exercise or on performance of the cold pressor test. Labetalol significantly reduced blood pressure levels during isometric exercise but did not reduce the systolic pressure- heart rate product. Labetalol improved the angina without evidence of causing a reduction of cardiac work (and presumably oxygen consumption by the myocardium) in comparison with the other antihypertensive agents used in this study. A possible mechanism whereby labetalol increases myocardial blood supply in hypertensive patients with angina pectoris is by an increase in coronary perfusion due to its vasodilator action.

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The treatment of angina pectoris in patients with arterial hypertension may present special problems. Interaction of antihypertensive agents with the major factors responsible for angina pectoris, coronary artery obstruction and an increase in myocardial oxygen demand, may generate complex situations. The angina pectoris may not be relieved, as expected, when the blood pressure is reduced if a disproportionate reduction in coronary flow accompanies the lower arterial pressure. We have observed a number of hypertensive patients with coexistent angina pectoris in whom reasonable control of blood pressure by antihypertensive therapy, including ß-adrenergic blocking agents, did not relieve the angina.

Initial uncontrolled observations suggested that labetalol (Trandate; Allen & Hanbury), an antihypertensive agent with both α- and ß-adrenergic antagonistic activity, produced greater relief of angina in these patients when the blood pressure was lowered. Our provisional report on 8 patients confirmed these observations;[1] more recent studies, a placebo-controlled study in 6 patients[2] and an open study in 9 patients,[3] provided similar results and supported our earlier findings. The present report documents controlled observations in an extended series of hypertensive patients with angina pectoris and provides further evidence of the benefit of labetalol in such patients.

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Patients and methods

Twenty hypertensive patients who had a longstanding history of chest pain on effort which responded to sublingual nitroglycerine and was not relieved by standard antihypertensive treatment were entered into the study. Informed consent was obtained from all patients. The inclusion of placebo was explained but patients were not told when placebo would be added. The clinical details of the 17 patients who completed the protocol and who are included in the analysis are shown in Table I. Three patients were excluded: one male patient developed myocardial infarction during the initial placebo period while on his usual antihypertensive medication; one female patient had no further angina after her initial visit; another female patient missed two clinic visits and was excluded because of uncertainty about compliance.

All patients had moderate-to-severe hypertension, had received long-term antihypertensive therapy and sublingual nitroglycerine or oral nitrate therapy for angina pectoris. Four patients were on perhexilene for persistent angina. Clonidine was used in 2 patients who could not tolerate ß-blockers. One of these patients had severe cardiac failure (cardiothoracic ratio of 0,59 on chest radiograph); the other complained of severe fatigue and reduction of effort tolerance when a ß-blocker was taken.

Study protocol

Patients were seen every 2 weeks. Administration of a thiazide diuretic was continued throughout for all patients.

Initial placebo period: Patients were observed during 5 visits over a period of 2 months while on their existing medication (see Table I). At the initial visit placebo tablets resembling labetalol tablets were added to the existing regimen, the number being increased at each visit. Patients were told that either labetalol or placebo would be used at this stage. Existing antihypertensive and anti-angina medications were left unaltered.

Labetalol titration period: Labetalol 50 mg 3 times a day was added to the existing medication and increased to 100, 150, 200, 300 and 400 mg 3 times a day during the subsequent 2-weekly intervals. The existing antihypertensive medication and perhexilene, but not the thiazide diuretic or sublingual nitroglycerine, were withdrawn in stepwise fashion. Titration was stopped if the blood pressure was reduced to below 140/90 mmHg. At the end of this period, therefore, patients were on labetalol 450 - 1 200 mg/d and a thiazide diuretic (see Table I).

Labetalol maintenance period: The final dose of labetalol reached during the titration period, the thiazide diuretic and sublingual nitroglycerine (as required) were continued for a period of 2 months.

Second placebo period: The labetalol tablets were abruptly replaced by the equivalent number of placebo tablets, and the previous antihypertensive medication (but not perhexilene) were added as in the initial placebo period, and patients were seen for a further 2 months at 2-weekly intervals. Patients were told that control of blood pressure was inadequate and that it was hoped to obtain improved control by addition of their original medication.

TABLE I. CLINICAL CHARACTERISTICS OF PATIENTS COMPLETING THE PROTOCOL

Patient	Sex	Age (yrs)	Admission* BP (mmHg)	Optic fundi (K-W scale)	Initial angina score	LVH on ECG	Blood urea (mmol/l)	CT ratio At entry	CT ratio At completion	Max. dose of labetalol (mg/d)	Existing medication
1	M	65	170/105	11	4	+	7,7	0,61	0,61	600	M 1,5 g, C1 450 μg, T1, At 100 mg
2	M	40	150/120	11	4	+	6,5	0,50	0,50	600	MP 6 mg, T1, Ac 200 mg†
3	F	53	180/120	1	5	+	8,6	0,52	0,53	450	R 3 caps, C1 900 μg, MP 3 mg†
4	M	49	150/110	11	4	+	8,9	0,58	0,54	600	MP 12 mg, T1, P 240 mg
5	F	46	180/130	11	4	+	6,6	0,64	0,62	600	M 1,5 g, T2, P 360 mg
6	F	50	180/110	11	4	+	5,9	0,59	0,58	600	MP 4 mg, C1 450 mg, T2
7	M	61	170/90	1	5	-	9,2	0,53	0,53	450	T2, P 360 mg, N
8	F	43	220/150	11	0	+	5,8	0,58	0,58	600	MP 4 mg, T1, Ac 200 mg†
9	F	47	160/100	11	0	+	6,5	0,51	0,50	900	MP 6 mg, T1, At 200 mg
10	M	57	180/120	11	1	+	6,4	0,52	0,52	600	MP 4 mg, T1, Ox 360 mg
11	F	57	240/130	11	4	+	5,7	0,67	0,69	600	MP 6 mg, T2, At 200 mg
12	F	52	120/90	1	3	-	6,0	0,56	0,56	600	T1, At 100 mg†
13	M	57	150/90	1	4	+	9,2	0,55	0,56	600	C1 600 μg, T1, Ox 360 mg
14	M	54	140/90	11	2	+	5,0	0,57	0,56	600	MP 4 mg, At 100 mg, T1
15	F	53	130/90	1	4	-	7,1	0,60	0,54	600	R 2 caps, P 240 mg
16	F	50	220/120	11	0	-	3,8	0,48	0,41	1 200	MP 18 mg, At 100 μg, T2
17	F	53	180/120	11	2	+	5,4	0,52	0,51	900	M 2,0 g, At 100 mg, T2†
Mean		52,2 ± 1,5	172 ± 7					0,56 ± 0,12	0,55 ± 0,13	653 ± 44	
(±SD)			111 ± 4								

*Admission blood pressure refers to blood pressure on admission to the clinic, not the study
†Higher doses of β-blockers limited by side-effects
BP = blood pressure; K-W = Keith-Wagener; LVH = left ventricular hypertrophy; CT ratio = cardiothoracic ratio; M = methyldopa; C1 = clonidine; T = thiazide diuretic; At = atenolol; P = propranolol; Ac = acebutolol; Ox = oxprenolol; MP = prazosin; R = rauwiloid plus thiazide.

Measurements

All patients had been attenders at the Hypertension Clinic at Groote Schuur Hospital for at least 1 year and were familiar with clinic routine and staff. At each visit patients sat quietly for 10 minutes during which questioning was completed and the blood pressure and pulse rate were recorded (standard sphygmomanometer, the diastolic pressure being taken at the point of disappearance of Korotkoff sounds). Patients then stood erect for 2 minutes and the blood pressure measurement was repeated. Next the blood pressure and pulse rate were recorded in the erect position immediately after walking 60 metres (isotonic exercise). At the initial visit the maximal force exerted on a handgrip dynamometer was obtained for each patient. At each subsequent visit the patient was required to maintain half the maximal force for 60 seconds, at which time the blood pressure was recorded (isometric exercise). Thereafter the patient's left arm was abruptly immersed up to the elbow in water and ice and the blood pressure recorded after 60 seconds (cold pressor test).

All patients had a standard 12-lead ECG and a chest radiograph, as well as serum electrolyte, urea and creatinine measurements performed at the end of the first placebo and the labetalol maintenance periods.

Scoring of angina pectoris

The angina status was scored after direct questioning of patients, who were asked to keep a diary indicating the number and severity of attacks and their consumption of nitroglycerine tablets. The score was allocated as follows: 5 — severe attacks on effort or at rest with marked limitation of effort by angina (nitrite consumption was more than 4 tablets per day); 4 — angina only on effort, 1 - 4 attacks per day with some limitation of effort (nitrite consumption 1 - 4 tablets per day); 3 — angina at times on effort and minimal limitation of effort (nitrite consumption 0 - 1 tablet per day); 2 — occasional attacks but definable as angina (nitrites sporadically required); 1 — chest pain only on unusual effort and nitrites not used; 0 — unlimited ordinary daily activity without the occurrence of chest pain.

Statistical methods

The mean values and standard errors of the mean were calculated and are used throughout. Student's t tests, paired or unpaired as appropriate, were used with the two-tailed test to compensate for possible unequal variances during the different periods. A significance level of $P<0,05$ was required for a significant difference between mean values.

Results

The responses as regards heart rate, blood pressure and angina scores of the 17 patients who completed the study are shown in Table II. The readings obtained for each patient during the various visits in each treatment period were averaged and entered for the calculation of the group mean values.

Effect of labetalol on cardiovascular responses

No significant effect was attributable to the change from the existing medication to labetalol with reference to heart rate or blood pressure responses at rest, during isotonic exercise and on performing the cold pressor test. Labetalol did not exaggerate the postural fall in blood pressure at rest or following isotonic exercise. The performance of isometric exercise and the cold pressor test was accompanied by substantial increments in both systolic and diastolic pressure. During the initial placebo period the mean systolic blood pressure increased from 165 ± 6,3

TABLE II. RESTING HEART RATE, BLOOD PRESSURE RESPONSES (MEAN VALUES ± 1 SEM) SYSTOLIC PRESSURE-HEART RATE PRODUCTS AND ANGINA SCORES OF 17 PATIENTS DURING THE VARIOUS STUDY PERIODS (EACH PHASE LASTED 8 WEEKS)

	Placebo added	Labetalol titration	Labetalol maintenance	Final placebo + initial therapy
Heart rate (/min)	68 ± 3,2	72 ± 2,2	71 ± 2,4	65 ± 1,8
Blood pressure (mmHg)				
Resting	165 ± 6,3	166 ± 6,9	159 ± 6,2	166 ± 8,4
	106 ± 4,4	108 ± 3,1	103 ± 3,6	101 ± 4,4
Erect	162 ± 5,9	165 ± 6,7	156 ± 5,8	160 ± 4,4
	109 ± 4,2	110 ± 3,3	104 ± 3,3	102 ± 3,6
Isotonic exercise	160 ± 6,5	161 ± 7,0	156 ± 6,4	157 ± 9,7
	102 ± 3,8	104 ± 3,2	99 ± 3,5	98 ± 4,7
Isometric exercise	185 ± 6,7	184 ± 6,7	175 ± 7,1*	179 ± 7,1
	126 ± 4,5	124 ± 2,9	119 ± 2,8*	119 ± 3,5
Cold pressor response	180 ± 6,6	177 ± 6,0	176 ± 6,5	177 ± 8,5
	120 ± 3,9	121 ± 3,5	117 ± 3,4	117 ± 4,5
Systolic pressure- heart rate product (x 10^{-2})				
Resting	111 ± 8	121 ± 10	119 ± 8	118 ± 9
Isotonic exercise	123 ± 10	135 ± 10	135 ± 11	125 ± 12
Isometric exercise	134 ± 7	153 ± 9	146 ± 9	133 ± 7
Angina score	2,94 ± 0,42	1,94 ± 0,32*	1,41 ± 0,27†	2,25 ± 0,34

*$P < 0,05$.
†$P < 0,001$.

mmHg at rest to 185 ± 6,7 mmHg with performance of handgrip exercise and to 180 ± 6,6 mmHg during the cold pressor test ($P <$ 0,001 in both instances), while the mean diastolic pressure increased from 106 ± 4,4 mmHg at rest to 126 ± 4,5 mmHg with the handgrip exercise and to 120 ± 3,9 mmHg during the cold pressor test ($P < 0,001$). Substitution of labetalol for the other antihypertensive agents reduced the systolic and diastolic pressures significantly during isometric exercise ($P < 0,05$), but there was no effect on the incremental responses during the cold pressor test.

Since small (but statistically insignificant) increases in heart rate occurred during the labetalol maintenance period, the systolic pressure x heart rate product was calculated for each patient. There was no significant effect of labetalol on the product at rest, or during isotonic or isometric exercise. As judged by this crude index of myocardial oxygen consumption, labetalol, in comparison with the other antihypertensive agents used, did not further reduce myocardial oxygen consumption during these cardiovascular stresses.

Effect on angina pectoris

A significant reduction in the angina score occurred after the introduction of labetalol. During the initial placebo phase (with existing medication) 2 patients had angina scores of 5, 8 had scores of 4, 1 had a score of 3, 2 had scores of 2 and 1 had a score of 1. These values represent the average rounded value for the four visits during the initial placebo period. In 3 patients the scores averaged less than 0,5; they were assigned scores of 0 for the purpose of the analysis. These patients were, however, retained in the trial and included in the analysis in order to ascertain whether such placebo-responders might demonstrate an exacerbation of angina during the subsequent treatment periods. During the labetalol maintenance period the highest angina score registered was 3 (4 patients) while 3 patients scored 2, 6 patients scored 1 and 4 patients scored 0. In no patient with a score of greater than 1 was the angina completely eliminated during the labetalol maintenance period. When labetalol was replaced by the original antihypertensive medications the angina scores of 7 patients remained unaltered; the scores of 5 patients increased by 1 point, the scores of 3 increased by 2 points, and in 1 patient (who

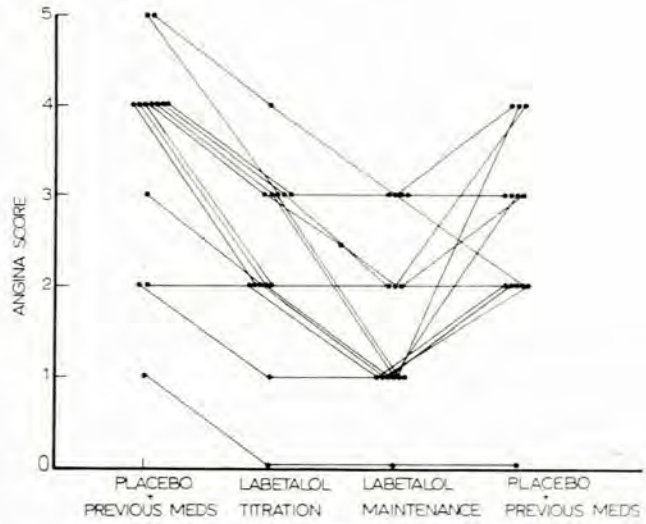

Fig. 1. Angina scores of patients with mean angina scores of 1 or higher during the placebo period. Patients whose angina disappeared during the placebo period showed no deterioration during the subsequent periods and are not included. The deterioration of angina after switching from labetalol to the placebo and reinstituting the original medication (placebo + previous medication) is evident.

had a score of 5 initially), the score increased from 1 to 4. In 1 patient the angina score progressively improved and continued to improve during the final treatment period. This patient had a score of 5 initially, 4 during the titration period, 3 during the labetalol maintenance period and 2 during the final placebo (plus original antihypertensive medication) period. In no patient was the score higher during the labetalol maintenance period than during the initial placebo period (Fig. 1).

Side-effects

No serious side-effects were encountered. Scalp tingling on exercise was reported by 2 patients. There was no significant change in the cardiothoracic ratio on chest radiography or in the serum urea, creatinine or electrolyte levels in any of the patients.

In 2 patients who had a history of intermittent calf claudication a striking improvement was noticed during the labetalol titration period and this was maintained during the labetalol maintenance period. In the 2 patients who had reported severe fatigue during treatment with ß-blockers, this symptom did not occur with labetalol treatment.

Discussion

Labetalol is unique, since it possesses clinically important $ß_1$-, $ß_2$- and α_1-adrenoceptor antagonist properties as well as a direct vasodilating action.[4] With long-term administration it causes a sustained reduction of blood pressure in hypertensive patients by lowering the heart rate and peripheral vascular resistance at rest and during exercise; its action resembles that of a combination of prazosin and a ß-adrenergic antagonist.[5] The finding that a sustained reduction in the product of heart rate and systolic pressure is achieved with labetalol led to the prediction that it would be likely to exert a beneficial effect in hypertensive patients with angina pectoris.[6]

The findings of the present study, in which labetalol produced relief of angina, confirm our earlier observations.[1] Labetalol treatment reduced the incidence and severity of angina pectoris during the titration period and maintained this effect for a further 8 weeks of maintenance therapy. After the switch from labetalol back to placebo and the reintroduction of the original medication, the angina status of half the patients deteriorated, without any increase in blood pressure and heart rate. A similar observation was made by Halprin *et al.*[2] in whose 6 patients angina also recurred as soon as labetalol therapy was withdrawn; this observation would have been of greater validity had the investigators switched from labetalol to placebo rather than discontinuing it. Added to a thiazide regimen, labetalol was as effective in reducing blood pressure as the combination of agents used during the initial phase.

The major aim of this study, however, was not to assess labetalol as an antihypertensive agent, but to determine in a group of patients with the combined problems of severe hypertension and angina pectoris whether labetalol improved angina pectoris. Although the design of the study incorporated a placebo control, the severity of the hypertension and the implications of the symptom of angina pectoris in such patients precluded not only a double-blind study but also the acquisition of baseline data without any antihypertensive agents. The difficulty of assessing the responses of both hypertension and angina pectoris to therapeutic intervention is well known. We attempted to overcome such problems, firstly by using the placebo control for labetalol therapy and secondly by prolonged periods of observation in all phases of the study. The values obtained for all measurements during these 8-week periods were entered into the statistical analysis in an attempt to further reduce observer bias and to limit the influence of spontaneous fluctuations of blood pressure and angina pectoris. By conducting the study over a long period and by frequent visits to the clinic it was hoped to reduce stress and anxiety in the patients as well, since both these factors might aggravate hypertension and angina pectoris.

The beneficial effect of labetalol on the angina in these patients occurred despite the absence of further improvement in hypertensive control. There was no reduction in the systolic pressure-heart rate product during any of the cardiovascular stresses. Although the blood pressures during isometric exercise were lower in the labetalol therapy period than in the period of observation while patients were on other antihypertensive agents (including the combination of prazosin and a ß-blocker in several patients), the systolic pressure-heart rate product was not reduced. It can be concluded that the reduction in angina and improvement in effort tolerance was probably not related to a greater reduction in oxygen consumption by the myocardium. Although the systolic pressure-heart rate product is derived from simple measurements, it serves as a crude but reliable index of myocardial oxygen reserve in patients with angina pectoris.[7] An alternative mechanism whereby labetalol may reduce angina pectoris is by effecting an improvement in coronary blood flow, as has been demonstrated in dogs.[8] Since ß-adrenergic antagonists invariably reduce coronary flow,[9] the increase of coronary flow during labetalol therapy is most likely related to its alphalytic action. The response of angina to labetalol in this study is surprising, since 10 of our 17 patients had been on prazosin, which is also a potent α_1-adrenergic antagonist, and they should have responded if this were the mechanism. There is little doubt that α-adrenergic receptor-mediated action increases coronary vascular resistance;[10] antagonism of this action improves coronary perfusion. A possibility exists that in this group of hypertensive patients with angina pectoris, which did not respond to reduction of blood pressure and a ß-blocker in 15 patients and clonidine in the remaining 2 patients, arterial hyperreactivity rather than coronary obstruction might have been an important factor. Clonidine has been found to be of use in reducing angina pectoris.[11]

The manifestations of peripheral arterial insufficiency and vasospastic phenomena may be aggravated by ß-blocker therapy. It has been observed that symptoms related to Raynaud's phenomenon or peripheral arterial insufficiency are improved by labetalol.[12] The intermittent calf claudication in 2 of our patients was relieved by labetalol. The question can therefore be posed whether labetalol, by its alphalytic or direct vasodilating action, might have improved the angina pectoris by opposing coronary artery spasm related to arterial hyperreactivity. Coronary arterial spasm has become accepted as a well-defined entity in the causation of angina pectoris in some patients.[13] Labetalol, by virtue of its alphalytic action, should reduce such spasm, which has been shown to be the case with other α-adrenoceptor antagonists.[14]

These observations, together with those of others, suggest that a number of hypertensive patients with angina pectoris unrelieved by ß-blocking agents, may obtain symptomatic relief from labetalol. Further controlled clinical trials are required to assess the incidence of those who respond to labetalol. Although the mechanisms of its anti-anginal effect remain unclear, it may well be possible to elucidate these by using, for example, thallium perfusion scanning, to demonstrate whether labetalol improves coronary flow in such patients. The recent demonstration that labetalol reduces ischaemic damage and infarct size after coronary artery occlusion in rats[15] serves as a further stimulus to the evaluation of this agent in clinical situations, such as hypertension with a threat of myocardial ischaemia.

Addendum

Subsequent to the completion of this manuscript two further publications on the subject of labetalol and angina have appeared. The initial observations of Halprin[2] have been extended to

involve 10 patients studied with placebo control. Labetalol reduced the frequency of angina and increased exercise time and intensity, while reducing blood pressure at rest and during exercise.[16]

Gagnon *et al.*[17] have studied 11 patients with obstructive coronary artery disease. Within minutes of intravenous administration of labetalol arterial pressure fell, accompanied by a reduction in total peripheral and coronary vascular resistance. A significant increase in coronary sinus blood flow occurred as systemic blood pressure fell.

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