LABETALOL IN NORMOTENSIVE PATIENTS WITH ANGINA PECTORIS

Kim Fox, Arshed A. Quyyumi
National Heart Hospital, London, England

SUMMARY. Labetalol, an alpha-beta-blocker, has been shown to have vasodilating as well as beta-blocking properties. From the theoretical point of view such a drug is likely to be beneficial in the treatment of angina pectoris. There are very few studies investigating the effects of labetalol in normotensive patients with angina pectoris. The three major controlled trials that have been published show that labetalol reduces angina frequency and prolongs exercise duration. In one study the effects of labetalol in anginal subjects using ambulatory monitoring was performed and showed a reduction in silent ischemia as well as a reduction in angina pectoris. Thus labetalol would appear to be an effective antianginal agent. Further studies are necessary to determine if the antianginal effect is entirely due to the beta-receptor-blocking activity of the drug or whether labetalol's vasodilating property has important additional benefit.

KEY WORDS. labetalol, beta-blocker, alpha-blocker, angina pectoris, ischemia, vasodilation

It has become clear in recent years that the mechanisms causing angina include not only an increase in myocardial oxygen demand but alterations in coronary blood flow. While coronary spasm in patients with normal coronary arteries is relatively uncommon, angina pectoris is not infrequently modulated both by coronary artery tone and by alterations in myocardial oxygen demand. This proposal has important implications in the selection of drug therapy.

Pharmacodynamic Effects of Beta-Blocking and Alpha-Beta-Blocking Agents

Beta-receptor antagonists have been widely used in the treatment of angina [1]. Blockade of the beta-1-receptor cause a fall in heart rate and blood pressure together with a negative inotropic effect. The net result is reduction of the myocardial oxygen consumption. However, these agents also increase peripheral vascular resistance which theoretically can increase myocardial oxygen demand [2]. Blockade of beta-receptors is likely directly to cause coronary vasocostriction, while combined blockade of beta-1- and beta-2-receptors, particularly during increased catecholamine release, leads to unopposed alpha-adrenergic activity [3, 4]. These events would tend to increase coronary tone and to reduce coronary blood flow and may be detrimental particularly when increased coronary tone plays an important role in the mechanism of angina pectoris.

Alpha-adrenoreceptor-blocking agents increase coronary blood flow and reduce coronary and peripheral vascular resistance [5, 6]. However, pure alpha-adrenergic blockade may be a disadvantage to patients with angina pectoris. The alpha-receptor antagonist phentolamine can cause a reduction in peripheral vascular resistance and a fall in blood pressure, yet any potential benefit in terms of reduction of myocardial oxygen demand obtained by the fall in blood pressure will be counterbalanced by the reflex tachycardia that occurs [7]. Thus in some patients the use of pure alpha-blocking agents may actually exacerbate angina. Selective alpha-1-receptor blockade with prazosin tends to cause less tachycardia but even with this drug exacerbation of angina has been described [8].

Labetalol is a unique compound since it possesses both beta-blocking and alpha-1-receptor blocking activities [9, 10]. Labetalol's beta-blocking activities are nonselective in isolated tissue preparation and the drug is about three times more potent in beta-blocking than in alpha-blocking activity. Theoretically, therefore, labetalol should have advantages not available using conventional beta-blockade, particularly where coronary tone is important. Labetalol decreases peripheral vascular resistance by its alpha-blocking activity and may be useful in those patients with angina pectoris who have either mild congestive heart failure or peripheral vascular disease.

Address correspondence and reprint requests to: Dr. Kim Fox, National Heart Hospital, London WIT 8BA, England
Effects of Labetalol in Hypertensive Angina

In patients with hypertension and angina pectoris an improvement of exercise capacity has been found using labetalol in dosages ranging from 300 to 1,600 mg/day [11, 12]. In these studies labetal reduced the frequency of anginal attacks, increased exercise time, and increased exercise workload. There was a reduction in the resting supine and standing blood pressure and heart rate; the increments in systolic blood pressure with exercise were blunted. A reduction in resting heart rate × blood pressure product and inhibition of the heart rate × blood pressure increments with exercise was also found.

However, these studies were performed in hypertensive subjects and there are very few control data in normotensive anginal subjects.

Effects of Labetalol in Normotensive Angina

Upward and colleagues investigated 12 normotensive patients with stable angina pectoris in a single-blind dose-ranging study [13]. After a 2-week placebo period, labetalol was given in increasing doses up to a maximum of 600 mg daily. There was a reduction in both the frequency of angina attacks and glyceryl trinitrin consumption. Maximal symptom-limited exercise tests were performed 3 and 12 hours after dosage, there was an improvement in exercise tolerance accompanied by a blunting of the heart rate/blood pressure response to exercise. Trough exercise tolerance did not differ from that performed 3 hours after the dosage.

We investigated the effects of labetalol in the treatment of normotensive patients with angina [14]. The purpose of our study was to determine the dose required to treat angina patients using labetalol using an open single-blind dose titration. Each patient subsequently entered a double-blind crossover study comparing labetalol with placebo. Recordings were taken of the frequency of angina and exercise tolerance was measured using a treadmill. In addition we determined the effects of labetalol on the frequency of both painful and silent ischemia.

Ten patients were investigated; all received 200 and 400 mg/day of labetalol and six who remained asymptomatic on 400 mg/day were given 600 mg/day. Labetalol caused a dose-related reduction in resting heart rate throughout the 24 hours and a reduction of both the systolic and diastolic arterial pressure. All patients continued to have angina with labetalol 200 mg daily but three patients became pain-free with 400 mg/day and three of the six patients treated with 600 mg/day had no chest pain while the other three patients had a greatly decreased frequency of pain at 600 mg/day.

Labetalol significantly reduced episodes of angina pain (Figure 1). The optimum dose was 200 mg/day in one patient, 400 mg/day in four patients, and 600 mg/day in five patients (mean 480 mg/day). There was an increase in the duration of exercise before the development of ST segment depression when compared to placebo (Figure 2) and also there was an increase in the total duration of exercise (p < 0.01) (Figures 2 and 3). The mean heart rate and systolic blood pressure at the onset of 1-mm ST segment depression and at the termination of exercise was lower using labetalol treatment. The blood pressure effect was found to occur at 400 mg/day; the effect on exercise duration continued to 600 mg/day (Figure 4).

In addition to reducing the frequency of angina, labetalol reduced the frequency of ST segment depression recorded by 48-hour ambulatory monitoring at the end of each of the treatment phases. There was a reduc-

Fig. 1. Effects of labetalol on angina frequency. There was a significant reduction in the weekly number of episodes of angina during treatment with labetalol. Reproduced from [15] by courtesy of British Heart Journal.

![Graph showing effects of labetalol on angina frequency.](image-url)