SUMMARY. Beta-adrenergic blockade is established therapy in the management of both hypertension and angina pectoris. This review evaluates the use of combined alpha-adrenergic and beta-adrenergic blockade for these conditions, with reference to labetalol. There are three major differences between labetalol and propranolol or similar conventional beta-blockers. First, in the mechanism of the antihypertensive effect, peripheral vasodilation plays a prominent role during the use of labetalol. In particular, acute therapy with labetalol rapidly reduces the blood pressure because of this reduction in the systemic vascular resistance. During prolonged therapy with labetalol over many years, blood pressure remains reduced with a sustained fall in the systemic vascular resistance. Second, in patients with combined hypertension and angina pectoris, fixed doses of labetalol (200 mg twice daily) gave the same blood pressure values, effort tolerance, and nitrate usage as did atenolol 100 mg once daily in a double-blind, double-dummy, crossover study. Labetalol gave higher heart rates at rest and during exercise (both p < 0.01). The higher heart rate with labetalol could be an advantage in some patients with effort angina and a disadvantage in others. Third, in hypertensive asthmatics, labetalol appears to have a relative bronchospasming effect, when compared with propranolol. The possession by labetalol of beta-2-stimulating qualities (intrinsic sympathomimetic activity) may explain part of the dilating effect and the bronchospasming quality. Thus labetalol 1) lowers blood pressure by a mechanism involving vasodilation, 2) has an equiantianginal effect to atenolol yet at a higher heart rate, and 3) may be bronchospasming. Differences among various beta-blockers may be important in matching the properties of the beta-blocker chosen to the requirements of the individual patient.

KEY WORDS. labetalol, hypertension, angina, alpha- plus beta-blockade, vasodilation, bronchospasm.

Labetalol is a combined adrenergic blocking drug already established in the therapy of systemic hypertension. It is a nonselective beta-adrenoceptor antagonist agent with added alpha1-antagonist vasodilator properties relatively recently introduced in the United States [1], although long used in Europe. Labetalol is distinguished from propranolol and some other beta-blockers by the addition of vasodilatory properties, mediated by its alpha1-adrenergic blocking property, and possibly also by the additional property of intrinsic sympathomimetic activity (ISA) which confers mild beta 2-adrenergic stimulating qualities on the compound. The present article reviews the possible role of these additional vasodilatory properties in the mechanism of the antihypertensive and antianginal effects of labetalol.

Evidence for the Vasodilatory Effects of Labetalol in Hypertension

Alpha1-Adrenergic Blocking Qualities of Labetalol

The peripheral vasodilatory effects of labetalol are well established [2, 3]. Evidence for alpha1-adrenergic blocking activity is as follows. First, in human volunteers, labetalol gives a dose-dependent decrease of the pressor response induced by phenylephrine [4]. Furthermore, in hypertensive patients, 1) 50% of the rise of the systemic vascular resistance induced by phenylephrine is antagonized by labetalol [5]; and 2) the dose of phenylephrine required to increase diastolic blood pressure is more than doubled during labetalol therapy [6]. Substantial evidence obtained from animal experiments also shows that labetalol can antagonize alpha1-adrenergic stimulation [7]. Furthermore, labetalol also binds to alpha2-adrenergic receptors [8]. However, it should be noted that 1) labetalol has a much more powerful beta than alpha1-adrenergic blocking effect [7], and 2) the binding of labetalol to
alpha-adrenergic receptors is relatively weak when compared with phentolamine [8]. Thus the question is raised whether labetalol might induce vasodilation by mechanisms other than alpha₂-adrenergic blockade.

Vasodilation by Beta-Adrenergic Receptor Stimulation

Several lines of evidence favor a role for direct vasodilation [9] and more specifically beta-adrenergic receptor stimulation in the mechanism of the vasodilation of labetalol. Intra-arterial labetalol increased femoral arterial blood flow in the dog hindlimb by a mechanism which did not appear to involve alpha₁-receptor blockade, as shown by major differences between the effects of prazosin in innervated and denervated limbs, whereas there were smaller and insignificant differences in the case of labetalol. The vasodilation caused by labetalol was largely abolished by intravenous propranolol, in keeping with a role for a beta-mediated mechanism [10]. Tadepalli and Novak [4] evaluated the cardiac stimulating qualities versus the peripheral vasodilation in their assessment of the beta-stimulating properties of labetalol. In reserpine-treated adrenalectomized cats, labetalol induced a modest tachycardia which was reversed by propranolol. They do not support the idea of a “direct vasodilatory action” of labetalol, independent of beta-stimulation, as has been suggested [9, 11]. Their data lead them to suggest that the intrinsic sympathomimetic action of labetalol, in their preparation, was more marked on the cardiac than on the vascular beta-adrenergic receptors. Thus the animal experiments suggest that labetalol has an additional vasodilatory effect, beyond that mediated by alpha₂-receptor blockade, probably caused by beta-receptor stimulation. However, there appear to be no convincing data to substantiate the claim [10] that the vasodilatory effect of labetalol is specifically beta₂ and not beta₁ in its receptor effects.

Labetalol: Acute Vasodilatory Effects on Blood Pressure in Humans

Especially noteworthy is that the early studies by Richards et al. [12] showed that the infusion of labetalol to normotensive human subjects was accompanied by a rapid drop in arterial pressure within 2 minutes. In contrast, an intravenous infusion of atenolol caused no fall in arterial pressure at 15 minutes and significant falls only after 1 to 3 hours in the case of the diastolic pressure [13]. Similar differences have been found between oral labetalol and atenolol by Holtzman et al. [14], who showed that the major mechanism of labetalol’s hypotensive effect was by acute vasodilation. In severely hypertensive subjects, labetalol (100 to 125 mg intravenous bolus) was compared with propranolol (10 mg intravenous bolus); within 5 minutes labetalol had had a hypotensive effect which was sustained for 3 hours, whereas propranolol did not decrease the pressure at all [15]. (The hemodynamics of the acute intravenous effects of labetalol given to hypertensives are reviewed by Frishman [11].)

Labetalol: Subacute and Chronic Vasodilatory Effects in Hypertension

During short-term (5 weeks) oral therapy with labetalol, systemic vascular resistance decreased whereas with propranolol it increased [16]. With atenolol, metoprolol, and acebutolol there were few changes, suggesting a difference between selective and nonselective beta-blockers at this stage of therapy (Figure 1).

In an important long-term study, Lund-Johansen [3] examined both the acute and chronic blood pressure lowering effect of labetalol and followed up 15 patients after 1 and 6 years of labetalol therapy (mean dose 400 mg daily, 3 of 15 patients with 800 mg labetalol daily also given 25 mg hydrochlorothiazide). During the acute intravenous study, the blood pressure was mostly reduced by a fall in the systemic vascular resistance (−14%) but also partially by reduction in the cardiac output (−10%). During the chronic follow-up study, the systemic vascular resistance was reduced 15% to 20% after 6 years, and the cardiac index was essentially unchanged. In contrast, in 8 untreated hypertensive subjects studied over a 17-year period, the cardiac index progressively fell whereas the total systemic vascular resistance increased. Therefore the long-term fall in vascular resistance achieved by labetalol becomes all the more significant (Figure 2; also see Figure 1). As a caveat, it is however important to note that the untreated patients appeared to have borderline hypertension with lower initial values than did the labetalol group.

Unfortunately there are no entirely strict data, done on patients in comparable parallel study groups, to compare the long-term effects of labetalol with those of any of the conventional beta-blockers. However, in a somewhat similar group of patients also studied by Lund-Johansen [17], 10 patients were given atenolol (mean dose 100 mg daily) over a 5-year period. Mean arterial pressure fell but there was no change in the systemic vascular resistance (see Figure 1). The decrease in blood pressure was ascribed to a fall in cardiac output, which in turn was caused by a reduced heart rate, especially during exercise.