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Labetalol and other agents that block both alpha- and beta-adrenergic receptors

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- **BACKGROUND** Labetalol, a compound that blocks both alpha- and beta-adrenergic receptors, is the only drug of its class currently available in the United States.
- **OBJECTIVE** To review the pharmacology of labetalol and related compounds.
- **SUMMARY** Unlike "pure" beta blockers, labetalol maintains cardiac output, reduces total peripheral resistance, and does not decrease peripheral blood flow. It has been used to treat hypertension of all degrees of severity and may be especially useful in black patients, elderly patients, patients with renal disease, and in pregnancy. It can be used in conditions that produce catecholamine crises, such as pheochromocytoma, clonidine withdrawal, and cocaine overdose. Its hemodynamic profile is attractive for use in myocardial ischemia. The parenteral form is useful in situations where blood pressure must be lowered quickly. The major side effect is orthostatic hypotension, and hepatotoxicity has been reported.
- **CONCLUSIONS** Labetalol has several advantages over pure beta-blocking drugs and offers an alternative in managing hypertension that is difficult to control.

■ INDEX TERMS: LABETALOL; ADRENERGIC ALPHA RECEPTOR BLOCKADERS; ADRENERGIC BETA RECEPTOR BLOCKADERS ■ CLEVE CLIN J MED 1994 61:59–69

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THE IDEAL antihypertensive agent has not yet been found. The 100 preparations currently available can all produce side effects.

The problem is that blood pressure is regulated by a number of systems, and inhibiting one system often produces a compensatory increase in the activity of another as the body attempts to maintain its inappropriately high level of blood pressure.

For example, blockade of the beta-adrenergic system stimulates the alpha-adrenergic system and results in peripheral vasoconstriction. Conversely, blockade of the alpha-adrenergic system produces tachycardia. In theory, a preparation that inhibits both adrenoceptor subtypes would eliminate these problems and enable better blood pressure control than would an agent that blocks only one subtype.

Labetalol is the prototype compound of the class of pharmacologic agents that competitively block both alpha- and beta-adrenergic receptors. Other agents in this class include arotinolol and amosulalol, which, like labetalol, are arylethanolamines (*Figure 1*)

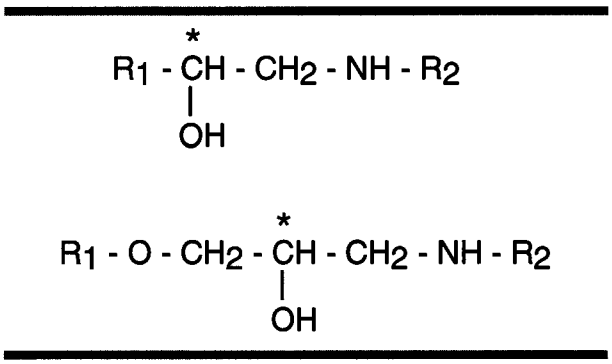

FIGURE 1. The arylethanolamines, (top) include labetalol, arotinolol, and amosulalol. The aryloxyisopropranolamines, (bottom) include celiprolol, nipradilol, bevantolol, and carvedilol. The asterisks show the position of the optic center of the compounds. Only labetalol is available in the United States.

and are available in Asia and Japan. Celiprolol, nipradilol, and bevantolol, available outside the United States, are examples of aryloxyisopropranolamines (*Figure 1*); another, carvedilol, is undergoing clinical trials in the United States. These agents will be discussed later in this article.

LABETALOL

The bulk of the therapeutic information about this family of agents comes from the study of labetalol, which has been marketed in Europe since 1975 and in the United States since 1982. Labetalol is effective in treating mild, moderate, and severe hypertension,[1-11] and the parenteral form is useful when blood pressure needs to be lowered rapidly, as in accelerated or malignant hypertension.[12,13] It is alpha-1-selective but beta-nonselective, and its ratio of beta- to alpha-adrenergic blocking potency is 3:1 with oral administration and 7:1 with parenteral administration[14]; these ratios may change with dose or long-term therapy. Its alpha-blocking properties may be advantageous in attenuating the bradycardia commonly experienced with "pure" beta-adrenergic blockers. Its hemodynamic properties are the result of its combined alpha- and beta-adrenergic blocking activity. Systemic vascular resistance and blood pressure are reduced in a dose-dependent fashion, and there is little effect on cardiac output.[15] Animal studies show evidence of a vasodilating property from a direct[16] or beta-2-agonist action.[17]

Pharmacokinetics and metabolism

The pharmacokinetics of labetalol have been determined in extensive studies performed in animals and man.[18-20] Following oral administration, approximately 90% to 100% of labetalol is absorbed from the gastrointestinal tract, but only 25% of an oral dose reaches the systemic circulation unchanged due to extensive first-pass metabolism in the liver or the intestinal mucosa. Bioavailability varies greatly among subjects, with a range reported from 11% to 86% (mean 33%).[19] Food delays absorption but increases bioavailability, possibly as a result of decreased first-pass metabolism or hepatic blood flow. Increased bioavailability may also be seen in the elderly[21] or hepatically impaired. Consequently, the dosage may need to be modified in these groups. Renal failure does not appear to alter pharmacokinetics.[22] Concomitant treatment with cimetidine increases bioavailability by as much as 30% to 54%.[23]

Labetalol has a high volume of distribution: 567 to 805 L in healthy volunteers and 392 L in hypertensive patients.[19] During long-term administration, most of the drug is found in the peripheral tissue compartment. Low plasma binding (50%)[18] as well as high plasma clearance (1500 mL/minute)[19] further support this finding. Little placental transfer occurs, mainly due to labetalol's negligible lipid solubility. The partition coefficient of labetalol between chloroform and a buffer of pH 7.4 is 1.2, compared with 9.0 for propranolol. Propranolol causes fetal beta-adrenoceptor blockade in sheep when administered to the mother, but labetalol does not.[24] Labetalol, but not its metabolites, has been shown to bind reversibly to the melanin pigment of the eyes but has not been found to have long-term ocular toxicity.[25]

Peak plasma concentrations following oral doses are achieved within 1 to 2 hours.[18,20] Excretion occurs over 8 to 12 hours, the majority of excreted drug (about 75%) being in the form of an inactive glucuronide. The plasma elimination half-life following oral administration is between 3 and 7.5 hours.[19,20] The antihypertensive effect, which is apparent within 20 minutes to 2 hours, reaches its peak at 1 to 4 hours, and persists in a dose-dependent manner for about 8 to 12 hours after a single 200-mg dose or 12 to 24 hours after a single 300-mg dose.[20] The maximal steady-state blood pressure response with twice-a-day dosage occurs at 1 to 3 days, and the close correlation observed between daily doses and mean steady-state plasma concentrations

indicates that the kinetics vary in a linear fashion with dose. Other investigators have found large variations in plasma concentrations during sustained therapy, probably due to individual differences in clearance and bioavailability.

Following intravenous (IV) administration of 1.5 mg/kg, a rapid biexponential clearance of labetalol is seen: its mean distribution half-life is 5.9 minutes and its elimination phase half-life is 4.9 hours. Labetalol's hypotensive effect begins within 2 to 5 minutes after an IV dose, reaches its peak at 5 to 15 minutes, and persists for about 2 to 4 hours or longer.[18]

The plasma concentration of free labetalol required to produce a hypotensive effect in hypertensive rats, dogs, and humans has been calculated to be about 5×10^{-8} to 10^{-7} M. A linear correlation between maximum inhibition of exercise-induced tachycardia and the logarithm of the plasma concentration was found 2 hours after an oral dose of 100, 200, or 400 mg. Although IV administration produces an almost immediate effect on blood pressures, a study of 12 hypertensive patients found no correlation between individual values for the area under the curve for plasma concentration vs time and the area under the curve for blood pressure fall vs time.[19] Mean plasma concentrations and mean hypotensive effects declined with time in hypertensive patients after oral doses, but wide interpatient variation occurred.[20] Other investigators reported no correlation between plasma concentration and blood pressure response, again likely due to the wide variation in individual sensitivity to labetalol's antihypertensive action.[26]

Effects on catecholamines and the renin-angiotensin-aldosterone system

In one study, labetalol decreased plasma angiotensin II and aldosterone concentrations 2 and 3 hours after IV administration. These effects happened much later than the effect on blood pressure, and were most pronounced in patients who had elevated levels of angiotensin II and aldosterone initially.[27] Other studies, however, have not demonstrated changes in the renin-angiotensin system.[28] Some investigators[28,29] report a decrease in plasma renin activity and plasma aldosterone levels during long-term therapy, an effect that is attenuated by diuretics, suggesting that this effect is mediated by plasma volume expansion.[30] Labetalol does not substantially increase the plasma or urinary catecholamine concentrations.[31] It is important to note that an unidentified metabolite or metabolites of labetalol may interfere with the fluorimetric method for catecholamine determination and the spectrometric assay for metanephrines, resulting in falsely high values for those substances. Using these methods to screen labetalol-treated patients for pheochromocytoma may lead to a false-positive diagnosis. These errors are prevented by measuring urinary excretion of 4-hydroxy-3-methoxy-mandelic acid; if this level is high, urinary or plasma catecholamine concentrations should be measured by high-performance liquid chromatography (HPLC).[32]

Mechanism of action

Receptor-binding studies have demonstrated that labetalol interacts with alpha- and beta-adrenoceptors. Drug displacement studies indicate that the affinity of labetalol is about 10 times higher for the beta- than for the alpha-adrenoceptor. Its affinity for the alpha-adrenoceptor is about 10 times less than phentolamine's, and its affinity for the beta-adrenoceptor is about 10 times less than propranolol's.[33]

In vitro experiments using atrial strips, mesenteric veins, and intact tracheal tubes from guinea pigs demonstrated that labetalol is seven times less potent than phentolamine mesylate in blocking alpha-adrenoceptors and 11 to 18 times less potent than propranolol in blocking beta-adrenoceptors. Both beta-1- and beta-2-adrenoceptors are blocked to a similar degree.[34] Labetalol inhibits the contractile responses to alpha-receptor agonists such as phenylephrine in isolated aortic strips. It is four to eight times less potent in blocking alpha-receptors than beta-receptors in isolated tissues. An intrinsic sympathomimetic activity of labetalol at beta-2-adrenoceptors has been suggested in studies of the isolated rat uterus and in human volunteers.[17]

In vivo experiments in animals and humans have confirmed these alpha- and beta-blocking properties.[14] The finding of nonselective beta blockade is supported by the effects of IV labetalol on phenylephrine-induced tachycardia and on heart rate changes with the Valsalva maneuver. These experiments suggest that labetalol is about one fourth as potent as propranolol as a beta blocker, and the ratio of alpha to beta blockade is about 1:7.

Labetalol's alpha-blocking properties have been demonstrated in human studies in which labetalol inhibited the increase in blood pressure induced by phenylephrine and norepinephrine while leaving

TABLE 1
COMPARISON OF HEMODYNAMIC EFFECTS OF PROPRANOLOL, PRAZOSIN, AND LABETALOL*

	Beta-adrenoceptor blockade (propranolol)	Alpha-adrenoceptor blockade (prazosin)	Alpha-beta-adrenoceptor blockade (labetalol)
Heart rate	↓	↔↑	↔↓
Cardiac output	↓	↔↑	↔
Stroke volume	↔↑	↔↑	↔↑
Systemic vascular resistance	↔↑	↓	↓

* ↑ increase, ↓ decrease, ↔ no change; data from reference 40

reflex reductions in heart rate and cardiac output unaffected.[35] Labetalol, unlike phentolamine, also blocks the cold pressor response in man, suggesting that prejunctional alpha blockade does not occur with labetalol.[36] Further support for alpha-1-selectivity is found in the observation that labetalol is ineffective in preventing clonidine-induced sedation in rats, an effect mediated by alpha-2-adrenoceptors in the central nervous system.[37]

Long-term studies suggest that labetalol's beta-blocking activity is constant, but there are differing reports about its sustained alpha-blocking activity. In one study, the disappearance of postural hypotension after 1 month's treatment with labetalol suggested a decline in alpha-blocking activity.

There is some evidence that labetalol exerts a direct vasodilative effect that contributes to its hypotensive activity. Following elimination of sympathetic tone with hexamethonium, IV labetalol (0.01 to 0.1 mg/kg) significantly lowers blood pressure; hydralazine also lowers blood pressure, but propranolol has no effect. These observations are likely due to direct vasodilation by labetalol and hydralazine.[16]

Like other beta blockers, labetalol has membrane-stabilizing properties that produce local anesthesia and antiarrhythmic effects. In experiments with human platelets, labetalol inhibits aggregation in vitro, completely preventing collagen-induced activation and the secondary activation wave caused by catecholamines and other aggregating stimuli. The release of beta-thromboglobulin and platelet factor 4 and the generation of thromboxane B_2 from collagen-stimulated platelets are inhibited by labetalol. Membrane-stabilizing properties may be responsible for some of these observations. Additionally, some aspects of the modulation of platelet function appear to be related to effects on calcium availability.[38]

Systemic hemodynamic effects

In a study comparing the effects of labetalol and propranolol in dogs that had undergone bilateral vagotomies, labetalol reduced heart rate, cardiac contractility, and cardiac output, effects attributed to beta blockade.[34] Labetalol had no effect on total peripheral resistance at low doses and reduced it at higher doses, but propranolol increased total peripheral resistance over the range of doses tested. Consequently, labetalol caused larger decreases in blood pressure than propranolol at equipotent cardiac beta-adrenoceptor-blocking doses. The increased reduction in blood pressure observed in the labetalol-treated animals was apparently a result of peripheral vasodilation due to vascular alpha-1-adrenoceptor blockade.

Intravenous administration of labetalol in healthy subjects and in hypertensive patients produces a rapid, substantial fall in systemic blood pressure, primarily via reduction of total peripheral resistance. Heart rate is maintained or slightly reduced due to blockade of reflex tachycardia. Unlike pure beta blockers (which decrease cardiac output), labetalol maintains cardiac output, reduces total peripheral resistance, and does not decrease peripheral blood flow. In one study,[39] in which labetalol was administered IV, blood pressure reduction was found to be due to small reductions in both cardiac output and systemic vascular resistance. After exercise, blood pressure fell to a greater degree and cardiac output decreased substantially, principally due to a reduction in heart rate, but there was an increase in stroke volume. Orthostatic hypotension occurred in this group of subjects. In patients treated with oral labetalol for 12 months,[40] blood pressure fell, but increased stroke volume compensated for mild decrements in heart rate, and cardiac output was unchanged. The blood pressure decline was entirely due to changes in peripheral resistance, and no orthostatic changes were noted (*Table 1*).

In patients with mild-to-moderate hypertension treated with labetalol for up to 6 years, a reduction in blood pressure of approximately 22% at rest and during exercise was demonstrated.[15] The total peripheral resistance index was reduced considerably, while the cardiac index was found to have returned to pretreatment levels with an increase in stroke index. These observations suggest a possible regression of structural changes in the left ventricle and in the resistance vessels.

The effects of labetalol on renal function have

been examined in three studies. No substantial alteration in glomerular filtration rate, renal plasma flow, filtration fraction, or free water clearance was demonstrated after long-term labetalol therapy in doses up to 2400 mg daily.[4] One group of investigators reported that glomerular filtration rate actually increased during labetalol therapy, in contrast to the effect of pure beta blockers, which lower renal plasma flow and glomerular filtration rate. The concomitant alpha blockade appears to be an important factor in preventing alterations in renal hemodynamics.

CLINICAL APPLICATIONS OF LABETALOL

Long-term treatment of hypertension

Labetalol has been used successfully in Europe and the United States to manage mild, moderate, and severe hypertension and has proven to be an effective and safe agent with few side effects.[1] Extensive clinical trials confirm the hypotensive activity of labetalol compared with placebo or other antihypertensives. Tolerance did not develop in long-term trials, while a sustained lowering of blood pressure and systemic vascular resistance was maintained.[15]

In patients with severe and previously uncontrolled hypertension (supine diastolic blood pressure >125 mm Hg), labetalol has been found to be effective when used alone compared with methyldopa and furosemide used in combination. Daily doses of up to 2400 mg of labetalol were used, with 500 to 1000 mg being the average daily dose. Other investigators have found labetalol to be effective when beta blockers or other antihypertensives have inadequately controlled blood pressure.[2] However, there have been reports of decreasing efficacy over long periods of treatment when labetalol was used alone to treat severe hypertension.

Trials in patients with mild or moderate hypertension have shown labetalol and methyldopa to have equal efficacy.[3] When nifedipine was compared with labetalol and then used in combination with it, both supine and standing blood pressures were decreased more by labetalol than by nifedipine, and the combination was more effective than either agent alone.[4] Labetalol (up to 600 mg daily) was found to be more effective than hydrochlorothiazide in reducing standing blood pressure in mildly hypertensive patients, but the combination produced greater decreases in blood pressure than either agent alone.[5] A number of studies have compared labetalol with pure beta blockers; most found that in mild or moderate hypertension, there was no difference in mean resting supine blood pressures, but that sitting and standing blood pressures were decreased to a greater degree in labetalol-treated patients than in patients treated with other agents. Heart rate, both at rest and during exercise, was decreased more in patients treated with pure beta blockers than in labetalol-treated patients.[6]

Several studies have documented the efficacy of labetalol in treating black hypertensive patients, who historically have responded relatively poorly to pure beta-adrenoceptor blocking agents.[7,8] Black patients had a better response to labetalol than white patients did, and they required less diuretic added to their regimen to control their blood pressure in a study comparing labetalol and propranolol.[9]

Labetalol has also been used successfully in elderly patients, in whom isolated systolic hypertension accounts for a substantial portion of high blood pressure. In a prospective, randomized, multicenter, double-blind study of 133 elderly patients with isolated systolic hypertension, labetalol decreased systolic blood pressure to an average of 144 mm Hg, a mean reduction of 26 mm Hg compared with a 9-mm Hg reduction with placebo, with which it shared a similar safety profile.[10] In a study using 24-hour ambulatory blood pressure monitoring in elderly patients, labetalol and enalapril were equally effective in lowering supine diastolic blood pressure and were equally well tolerated. Labetalol, however, was more effective in lowering ambulatory blood pressure and heart rate throughout the day.[11]

Orthostatic hypotension induced by antihypertensives can be a serious problem in the elderly, who have reduced baroreceptor sensitivity due to stiffening of the carotid arteries. Lower dosages (200 mg or less twice a day) have been found to produce little or no orthostatic effect but still effectively lower blood pressure in this age group, possibly due to increased bioavailability in the elderly.[10]

Hypertensive emergencies and urgencies

Labetalol has been shown, in studies in Europe and in the United States, to be effective and safe in the management of hypertensive emergencies. It can be infused in dosages up to 2 mg/hour or given by repeated IV bolus injections up to a total dose of 300 mg.[1] However, large bolus injections of 1 to 2 mg/kg have been reported to produce precipitous falls in blood pressure. All patients receiving parenteral

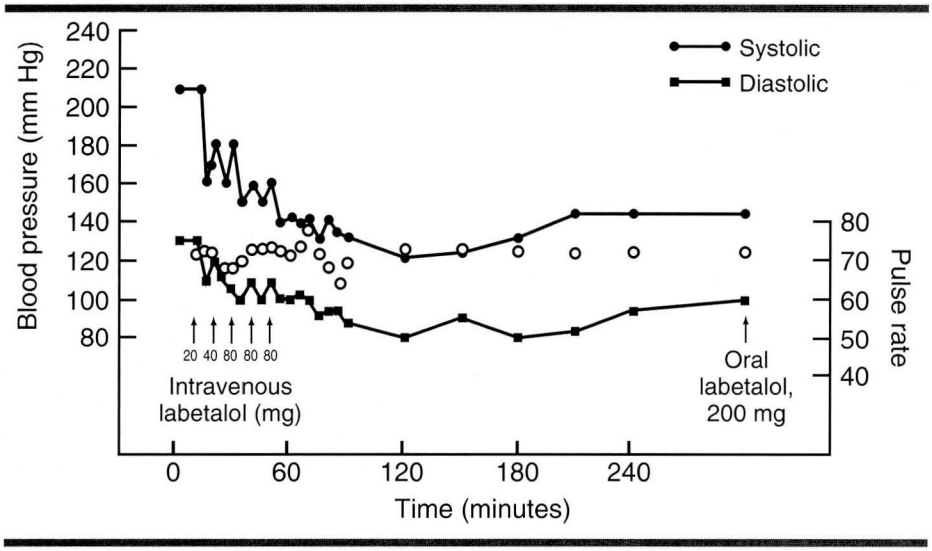

FIGURE 2. Responses of pulse and recumbent blood pressure to sequential bolus infusions of labetalol (arrows). Smooth decline in blood pressure is seen with little alteration in pulse rate. From reference 1.

therapy should be closely and continuously monitored, but intra-arterial blood pressure monitoring is not necessary. In one multicenter study conducted in the United States,[12] 59 patients (36 with symptomatic accelerated hypertension) with supine blood pressures averaging 211/134 mm Hg were given repeated injections of labetalol beginning with a bolus of 20 mg in order to minimize hypotension and avoid the possibility of sensitivity to the drug. Ten percent of the patients achieved the goal blood pressure with a single 20-mg bolus. The initial bolus was followed by repeated incremental doses of 20 to 80 mg given at 10-minute intervals until the therapeutic goal was achieved (*Figure 2*). No significant adverse experiences were reported, and 90% of the patients achieved the goal blood pressure.

The response to IV labetalol is comparable to that observed with diazoxide, but unlike diazoxide,[13] labetalol does not activate the renin-angiotensin system, induce increases in heart rate or cardiac output, or cause salt retention. Adverse reactions during IV administration are mostly mild and transient (nausea, vomiting, sweating, flushing, headaches, faintness, excessive hypotension) and usually abate with stopping the infusion, placing the patient in the Trendelenburg position, and administering IV fluids. Due to possible orthostatic hypotension, IV administration should be performed with the patient in the supine position.

Patients presenting to the emergency department or outpatient settings with asymptomatic severe hypertension (diastolic blood pressure >120 mm Hg) are commonly treated with oral loading of antihypertensive medications. Protocols using oral clonidine and nifedipine have been shown to be effective, but side effects and some serious complications have been reported.[42] In a recent study,[43] oral labetalol was compared with oral clonidine in treating severe but nonemergent hypertension (mean baseline blood pressures 199/132 mm Hg) without acute end-organ damage. Labetalol was administered as an initial dose of 200 mg followed by hourly 200-mg doses up to 1200 mg. Clonidine was administered as an initial oral dose of 0.2 mg, followed by hourly 0.1-mg doses up to 0.7 mg. Within 6 hours, 94% of the patients treated with labetalol had their diastolic blood pressures reduced (mean reduction 54/37 mm Hg), compared with 83% of the clonidine-treated patients (mean reduction 52/32 mm Hg). Side effects were more common in the clonidine-treated group, with 66% of the patients reporting mild to severe sedation, dizziness, and dry mouth. Forty-four percent of the labetalol-treated patients reported side effects, which were generally mild and included dizziness, drowsiness, and headache. The authors concluded that labetalol was as effective as clonidine and had few side effects when used in the outpatient setting. Single oral doses of 300 to 400 mg have been used, but this route of administration does not allow for adequate control of titration.

Renal impairment

A number of studies[7,41] have demonstrated that patients with impaired renal function can achieve effective blood pressure control with labetalol alone or in combination with diuretics or other antihypertensive agents. It has been concluded that labetalol has no deleterious effects on renal function at rest or during exercise.

Ischemic heart disease and left ventricular dysfunction

The hemodynamic profile of labetalol is attractive for use in patients with myocardial ischemia with or without hypertension. Labetalol's efficacy as an antianginal agent is attributed to its alpha-adrenoceptor blocking component, which minimizes the potential coronary spasm that may occur from beta blockade alone, while its beta-blocking component may offset potential arrhythmias from vasodilation secondary to alpha blockade.[44]

Normotensive patients with angina who were treated with IV (0.5 mg/kg) or oral (200 mg fixed dose) labetalol were able to exercise longer before angina or ischemic changes on electrocardiogram were recorded.[45] Exercise-induced tachycardia and increases in aortic pressures were blunted, and cardiac output was unchanged or slightly lowered, but not significantly so. Coronary sinus flow was decreased as heart rate and aortic pressure were lowered.

Hypertensive patients with angina also benefited from labetalol therapy: their blood pressure was lowered and their exercise capacity improved with dosages in the range of 300 to 1600 mg/day.[46]

Labetalol, like atenolol, was found to improve diastolic filling indices and therefore may have an impact on reversal of diastolic dysfunction in mild hypertension, which is suggested to precede left ventricular hypertrophy.[47] The additional property of alpha blockade enhances ventricular relaxation by maintaining cardiac output at lower filling pressures. Myocardial alpha-adrenoceptors have been described; conceivably, blocking these receptors may improve ventricular compliance and filling.

In a study of acute myocardial infarction with systemic hypertension,[48] IV labetalol was administered in incremental doses between 30 and 440 mg. The blood pressure was safely and effectively lowered from 184/122 mm Hg to 118/84 mm Hg while heart rate, left ventricular filling pressure, cardiac index, and total peripheral resistance likewise decreased; stroke volume remained essentially unchanged. Other reports had similar findings, but in one study,[49] infusions of 0.5 mg/kg/hour reduced blood pressure and cardiac output without changing the heart rate or left ventricular filling pressure in a group of patients in the early stages of uncomplicated myocardial infarction. The authors suggested that the combination of alpha and beta blockade may be hemodynamically advantageous in this situation because it reduces myocardial oxygen consumption.

Labetalol has been compared as an antianginal agent with the calcium antagonists nicardipine and diltiazem, which are potent vasodilators, and with the pure beta blockers metoprolol and propranolol.[45] The calcium antagonists were found to improve left ventricular pump function as reflected by the left ventricular end-diastolic pressure-cardiac output relationship, while the beta blockers depressed function, and labetalol's effect was intermediate. The calcium antagonists with peripheral vasodilating properties and labetalol can therefore be safely used in patients without history of heart failure who have ischemic heart disease.

Hypertension during pregnancy

Several clinical trials have demonstrated labetalol's efficacy and safety in pregnant patients with hypertension. In one trial of 176 pregnant women with mild-to-moderate hypertension (diastolic blood pressure >89 mm Hg) who received either methyldopa 500 mg twice daily or labetalol 400 mg twice daily by random assignment, there were no differences in the percentage of babies who were premature or small for their gestational age.[50] Heart rate, blood pressure, blood glucose level, respiratory rate, and Silverman score of the babies did not differ between the two treatment groups. Additional antihypertensive therapy was given to reach a target blood pressure of <86 mm Hg in 13% of the patients receiving labetalol and 26% of those receiving methyldopa. There were four stillbirths in the methyldopa group, three attributed to refractory hypertension and proteinuria. One patient in the labetalol group who required additional hydralazine gave birth at the 29th week to a baby that died at 24 hours of a bilateral pneumothorax.

Other studies comparing methyldopa with labetalol have found no significant differences in birth weight, gestational age at birth, or Apgar scores. One group reported better blood pressure control and a lower frequency of proteinuria in women treated with labetalol.[51] Because the most significant perinatal prognostic factor in pregnancy-induced hypertension is the presence or absence of proteinuria, the effect of labetalol on proteinuria was studied in a recent trial.[52] One hundred and fourteen women with single pregnancies and hypertension (diastolic blood pressure ≥90 mm Hg) without proteinuria were randomly assigned to receive labetalol or no antihypertensive therapy. Although labetalol

TABLE 2
ADVERSE EFFECTS OF LABETALOL*

Symptom	Prevalence (%)
Tiredness	5.5
Dizziness	5.2
Headache	4.2
Gastrointestinal symptoms	3.0
"Tingly" sensations in scalp	1.9
Postural hypotension	1.4
Dyspnea	1.2
Depression	0.8
Sexual dysfunction	0.6

*Data from the British Committee on Safety of Medicines. Special report to the British Committee on Safety of Medicines, incidence of side effects associated with labetalol, June 1978, British-monitored release trials of 6,638 patients

brought the blood pressure under control in 88% of the women receiving it, there was no difference in the frequency, quantity, or timing of subsequent proteinuria between the treatment and control groups.

As there is still debate over the usefulness of treating mild-to-moderate hypertension in pregnancy, close attention should be paid to perinatal safety. Although trials comparing beta blockers with methyldopa report no differences in mortality between the two treatment groups, the beta blockers are placentally transferred[24] and may affect fetal heart rate, blood pressure, and possibly, glucose control.

When rapid reductions in blood pressure are required such as in severe preeclampsia, labetalol has proven effective when administered IV.[53]

Pheochromocytoma, withdrawal from alpha-2 agonists, and cocaine crisis

Three clinical situations, in which catecholamine excess is manifest with resultant uncontrolled hypertension and predisposition to cardiac arrhythmias, may be amenable to treatment with labetalol.

First is the preoperative management of pheochromocytoma.[54] Titrated dosages of up to 6400 mg daily have been used, and an IV dose of 50 mg prior to surgical removal of these tumors gives adequate coverage during the procedure.

Second, abrupt withdrawal of clonidine can produce severe hypertension, which can be prevented or treated with labetalol.[55] Labetalol may be administered prophylactically, but close monitoring of blood pressure is necessary so that adequate dosages are given.

Third, the most recent use of labetalol in situations of catecholamine excess is in managing cocaine crises. "Crack" cocaine is responsible for ever-increasing numbers of admissions to emergency departments. Cocaine overdose results in systemic toxicity manifested by overwhelming sympathetic stimulation of the central nervous system, respiratory system, and cardiovascular system, which progresses rapidly to death. After an adequate airway has been secured, labetalol may be given in a 20-mg IV bolus with titrated doses and continuous infusion of up to 300 mg/24 hours until the patient's condition stabilizes and the blood pressure returns to normal.[56]

Miscellaneous clinical uses

Labetalol has been used to manage the hypertension associated with severe tetanus.[57] In one series, 15 patients were treated with a continuous infusion (1 to 10 mg/hour), incremental injections (95 to 75 mg), or oral doses of 200 to 800 mg, and 12 of the 15 patients responded adequately. Labetalol is reported to be useful in conjunction with halothane anesthesia in producing controlled hypotension for various surgical procedures including repair of coarctation of the aorta and ear surgery. An additional application has been in reducing intraocular tension in patients with glaucoma.[58]

ADVERSE EFFECTS

The major adverse side effects are summarized in *Table 2*. Most symptoms are transient and do not require stopping treatment with the drug. Orthostatic hypotension does occur with IV treatment as previously discussed, but appears to abate with oral treatment after several weeks.

Hepatotoxicity has been occasionally reported. In one study,[59] 8% of 337 patients developed transient reversible transaminase elevations. Two thirds of these patients experienced resolution, but five patients were discontinued from the study and again developed transaminase elevations after restarting labetalol. In addition, 11 case reports have been received by the Food and Drug Administration, including one patient who died. It is recommended that labetalol be used with caution in patients with a history of liver disease.

Ejaculatory failure has been reported in a small number of male patients.

Most studies indicate that labetalol is neutral in

its effect on plasma lipid levels.

Labetalol should be used with caution or avoided in clinical situations where beta blockade could be harmful, although at therapeutic doses labetalol's negative effect on cardiac contractility is less than that of pure beta blockers. Heart failure precipitated by labetalol has been reported; heart failure should be controlled with conventional agents before initiating labetalol.[44] Labetalol may cause heart block and is contraindicated in patients with severe bradyarrhythmias or greater than first-degree heart block.

Bronchospasm in sensitive patients receiving labetalol has been reported; caution should be exercised in treating patients with asthma.

However, in a clinical study, labetalol was found to be well tolerated in patients with mild or moderate hypertension and chronic obstructive pulmonary disease with a mild reversible component.[60] Dosages as high as 1200 mg daily had no deleterious effect on expiratory airflow over a 4-week period of administration. Both the forced expiratory flow, mid-expiratory phase and the forced expiratory volume in 1 second were monitored as indices of airway obstruction before and after exercise. No significant changes were noted at 2 hours after a maximal dose. Spirometric changes observed after exercise were variable with no individual patient's forced expiratory volume in 1 second or forced expiratory flow, mid-expiratory phase decreasing more than 15%. Overall spirometric values were unchanged from baseline and were not significantly different from those of the control group, who received hydrochlorothiazide for blood pressure control.

Only a few cases have been reported in which labetalol worsened symptoms of peripheral vascular disease, and it should be noted that a few patients who had circulatory disturbances while taking other beta blockers experienced improvement or became symptom-free when they changed to labetalol.

There are no contraindications for the use of labetalol in patients with diabetes mellitus, and masking of hypoglycemia occurs either rarely, or not at all.

OTHER DRUGS WITH COMBINED ALPHA- AND BETA-BLOCKING PROPERTIES

Figure 1 lists drugs of this category that are available for clinical use in various parts of the world. In general, their antihypertensive efficacy is similar to that of labetalol. Celiprolol was demonstrated to be well tolerated in a postmarketing surveillance study; only 2.15% of 2311 patients discontinued celiprolol because of adverse events. Carvedilol has been shown to have a hemodynamic profile similar to labetalol's[61,62] and has been demonstrated to be an effective antihypertensive agent. Other drugs of this category such as prizidilol, medroxalol, and dilevalol have been withdrawn from clinical testing.

SUMMARY

Pure beta-blocking drugs reduce heart rate and cardiac output, but produce reflex stimulation of alpha-adrenoceptors, causing vasoconstriction; pure alpha blockers dilate peripheral arterioles but reflexively stimulate beta-adrenoceptors, causing tachycardia. Thus, blockade of either receptor type evokes stimulation of the other, limiting the antihypertensive effect.

Labetalol, a weak blocker of both receptor types, acts synergistically to lower blood pressure with minimal physiological disturbance. The parenteral preparation is effective in hypertensive emergencies, and the oral form is useful in long-term management of hypertension of all degrees of severity, particularly in the elderly, blacks, pregnant patients, and those with renal failure. It may be useful in ischemic heart disease with ventricular dysfunction, and in catecholamine excess states. The major adverse effect, orthostatic hypotension, is usually transient and does not require stopping the drug. Hepatotoxicity has been reported.

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