Antihypertensive Effectiveness of Intravenous Labetalol in Accelerated Hypertension

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SUMMARY Labetalol, an antihypertensive agent that blocks both beta- and alpha-adrenergic receptors, was administered intravenously to 19 patients with accelerated hypertension who required rapid lowering of blood pressure. Systolic blood pressure was lowered from 209 ± 4 to 143 ± 2 mm Hg; diastolic blood pressure was reduced from 140 ± 2 to 93 ± 2 mm Hg. Side-effects were minimal and included nausea, epigastric burning, rhinorrhea, and premature ventricular contractions. One patient became hypotensive and required treatment. Overall, the study demonstrates labetalol to be a safe and effective agent for the emergency lowering of blood pressure, with demonstrated results comparable to other parenteral agents. (Hypertension 5: 579-583, 1983)

KEY WORDS • labetalol • accelerated hypertension

LABETALOL is a new antihypertensive agent that blocks both beta- and alpha-adrenergic peripheral receptors.1,2 Its beta-adrenergic blocking properties are nonselective and about one-fourth as potent as propranolol with no intrinsic stimulation. Its alpha-blockade reduces total peripheral resistance. It has been used to treat mild, moderate, and severe hypertension in Europe for several years3-5 and has been employed in intravenous form as a primary agent for lowering blood pressure in patients with accelerated hypertension.6,7

The present study reports experience in 19 patients with severe hypertension in whom rapid lowering of blood pressure was indicated and to whom labetalol was administered intravenously.

Methods

Study subjects were patients who sought medical attention at the emergency room of a large state hospital, had a diastolic blood pressure greater than 130 mm Hg and were considered to require emergency lowering of their blood pressure. Patients were excluded who had an obvious situational cause of their blood pressure elevation (e.g., fractured ribs) as were all females of reproductive potential. Patients who had a history of asthma, right-sided congestive heart failure, or heart block were also excluded.

After informed consent was obtained, baseline laboratory, electrocardiographic, and chest roentgenographic data were gathered. The patients were then administered 20 mg of labetalol intravenously over a 2-minute period. Blood pressure and pulse were monitored at 5-minute intervals, and further injections of 40 and 80 mg of labetalol were administered at 10-minute intervals until: 1) supine diastolic blood pressure was less than 95 mm Hg; 2) diastolic blood pressure had fallen greater than 30 mm Hg; or 3) 300 mg of labetalol had been given.

Following the achievement of one of these goals, supine blood pressure and pulse were recorded at 5-minute intervals for 30 minutes and then at 30-minute intervals for 2 hours, followed by hourly determinations. When supine diastolic blood pressure rose by 10 mm Hg, treatment with oral antihypertensive medication, usually labetalol, was begun. The patient was then hospitalized for 2 to 6 days to achieve optimal blood pressure control, and was discharged with arrangements for follow-up care.
**Results**

Table 1 displays some clinical characteristics of the subjects studied. All subjects studied were black; age ranged from 29 to 68 years; 11 were women and eight were men. Hypertension had been known to exist from 1 to 30 years except for one subject who had never had hypertension diagnosed and was taking no medications. The remainder were all receiving antihypertensive drugs (table 1).

Table 2 lists initial blood pressure as well as fundoscopic findings, evidence for left ventricular hypertrophy and serum creatinine. Of the 19 patients, 11 had left ventricular hypertrophy by standard electrographic criteria, 11 had grade three retinopathy by Keith-Wagener classification, seven had significantly elevated serum creatinine levels. Also shown is the total dose of labetalol required to lower blood pressure to an acceptable level. Seven patients required 100 mg or less; eight required a full 300 mg; one subject (Case 13) received 300 mg but did not respond according to established criteria and was subsequently treated successfully with diazoxide; the other three subjects required intermediate dosages for control.

Figure 1 shows the blood pressure response plotted against time for a typical patient (Case 16). As shown, initial blood pressure was 209/130 mm Hg. With repeated injections of labetalol (arrows), blood pressure declined in a gradual fashion and then after 4 hours began to increase, at which time treatment with oral labetalol was administered.

Figures 2 and 3 display the overall responses to treatment of the supine systolic and diastolic blood pressures respectively. Baseline mean systolic blood pressure was 209 ± 4 mm Hg, baseline diastolic pressure 140 ± 2 mm Hg. Individual lines indicate each subject and show that, in each case, both systolic and diastolic blood pressure declined. After treatment, mean systolic blood pressure was 143 ± 2 mm Hg and mean diastolic blood pressure was 93 ± 2 mm Hg. Mean fall in systolic and diastolic blood pressure was 66 ± 4 and 47 ± 3 mm Hg respectively.

Side effects were minimal, with 11 subjects reporting no side-effects and eight reporting mild side-effects consisting of nausea or epigastric burning (3); wheezing (1); rhinorrhea (1); tingling scalp (1). One subject experienced transient hypotension requiring Trendelenberg positioning and intravenous administration of fluids.

**Discussion**

The present study examines the effects of intravenously administered labetalol on blood pressure in a group of patients with signs and symptoms of accelerated hypertension. The determination to treat with parenteral medication was made on the basis of level of blood pressure, presence of symptoms, and findings of end organ damage. Eleven of the patients had Grade 3 retinopathy, eight had renal insufficiency, 11 had left ventricular hypertrophy with strain, and 12 were...
symptomatic with headache, visual changes, or other symptoms of accelerated hypertension.

We would like to emphasize that these patients were on multiple drug regimens at the time of their entry into the study. Five of the subjects were taking clonidine, but we have no evidence that they had discontinued medication and were experiencing withdrawal hypertension. Only one of the 19 patients had no evidence of end organ involvement, and she was referred from the medical clinic with an initial diastolic blood pressure of 150 mm Hg, making intravenous treatment of her hypertension reasonable, even though she was asymptomatic. Only one of the patients had newly diagnosed hypertension, and this patient was definitely symptomatic on entry into the study having headache, chest pain, and electrocardiographic changes, all of which improved with adequate blood pressure control.

With labetalol therapy, blood pressure was lowered in all patients. In 18 of the 19, the final level achieved met the original preset criteria. In the single nonresponsive patient, the lowering of diastolic blood pressure was still 20 mm Hg; because of his original high diastolic blood pressure and the limit on total amount of labetalol to be given, this patient had to be treated with another agent. He had been administered labetalol in a manner identical to that of other subjects and did

Figure 1. Typical treatment course (Case 16). At onset, blood pressure was 209/130 mm Hg. With incremental boli of labetalol (arrows), blood pressure smoothly declined to the 130-140/80-90 mm Hg range. After 4 hours when blood pressure had reached 142/100 mm Hg, oral labetalol is begun.

Figure 2. Pretreatment and post-labetalol systolic blood pressures for the 19 patients as well as the mean levels. The single patient who did not respond is marked with the asterisk.
Labetalol has been used in Europe for several years as oral therapy for mild, moderate, and severe hypertension. There are also reports of experience with the drug given intravenously as a single injection for the treatment of severe hypertension and as repeated injections for the management of malignant hypertension. It has been shown to be relatively safe, producing satisfactory decrements in blood pressure with minimal side effects. The most common side effects reported have been nausea, vomiting, and scalp tingling; these observations were matched in our present study.

The alpha- and beta-blocking effects of labetalol have previously been evaluated and were not studied here. In one study comparing intravenously administered labetalol and propranolol in the severely hypertensive patient, blood pressure was lowered to a significantly greater degree with labetalol than with propranolol. This occurred without marked changes in pulse rate with labetalol. Since labetalol has only one-fourth to one-fifth of the beta-blocking potential of propranolol, this greater effect on blood pressure lowering but not heart rate suggests a role of peripheral vasodilation as the primary action when the drug is administered intravenously. Hemodynamic studies of labetalol during chronic administration and following intravenous injection document the role of peripheral vasodilation as the predominant depressor mechanism and demonstrate that the beta-blocking characteristics of the drug serve predominantly to prevent reflex tachycardia and increases in cardiac output. Labetalol has been shown to displace downward the log dose pressor response curves to phenylephrine and norepinephrine and to inhibit increases in blood pressure due to cold. The lowering of blood pressure and peripheral resistance with little change in heart rate or cardiac output seen with labetalol and the changes with exercise distinguish it from other beta blockers. These findings support its alpha-adrenoceptor-blocking action as a mechanism of its antihypertensive effect independent of its beta blocking properties.

The question of the antirenin effects of labetalol has been examined in patients with severe hypertension treated with intravenously administered labetalol and consistent lowering of renin and aldosterone occurred. However, the effect of the drug on blood pressure preceded the decrement in renin and aldosterone by a significant time interval and it would seem that the primary antihypertensive effect of the drug is not related to its effects on renin.

The 94% response rate in this study with intravenous labetalol is comparable with the response rate of the other major drugs for treating hypertensive crises. It appears, therefore, that labetalol may be the first of a new class of drugs which is useful in the acute management of the severely hypertensive patient. It is effective, seems to have a minimum of side-effects, and can be used in an emergency room setting; if no other serious problems exist, the patient can be immediately cared for on a general ward setting without elaborate monitoring required.

References


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