The safety of cumulative doses of labetalol in perioperative hypertension

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■ Intravenous labetalol is commonly used in the management of hypertensive emergencies or urgencies as well as postoperative hypertension. The maximum recommended dose in any clinical setting is 300 mg in 24 hours. The safety of administering high doses of intravenous labetalol (greater than 300 mg in 24 hours) was evaluated in neurosurgical patients (n=9). During 15 distinct periods of 24 hours or less, the mean dose of labetalol given was 623 ± 86 mg. Adverse hemodynamic and biochemical effects were minor and easily reversible. Intravenous labetalol can safely be used in doses exceeding 300 mg per 24 hours in neurosurgical patients.

□ INDEX TERM: LABETALOL □ CLEVE CLIN J MED 1989; 56:371–376

LABETALOL is an antihypertensive agent with unique properties. Its mechanism of action is competitive inhibition of alpha- and beta-adrenergic receptors along with a beta-2 agonist effect.[1,2] The beta blockade is nonselective and predominates over the alpha blockade.[3] The hemodynamic effects of labetalol consist of a reduction in systemic vascular resistance without a change in heart rate, stroke volume, or cardiac output.[4,5] A recent study suggests that these hemodynamic effects may be more pronounced in older individuals (>55 years),[5] which may account for the efficacy of labetalol in the elderly population.

Labetalol, which is available in intravenous and oral preparations, has demonstrated effectiveness in lowering blood pressure in a variety of clinical situations. Efficacy for long-term oral therapy is well established.[6]

Intravenous administration has been used for severe hypertension and hypertensive emergencies,[7–9] as well as for postoperative hypertension.[10] In these studies, labetalol was administered by intermittent intravenous boluses at 10-minute intervals or by continuous infusion. Under these circumstances the full antihypertensive effect of labetalol can be observed within 15 minutes following intravenous injection. All the treatment protocols used in these trials considered the maximum dose of intravenous labetalol to be 150–300 mg during any 24-hour period.

This report describes the use of intravenous labetalol in doses >300 mg per 24 hours in neurosurgical patients identified retrospectively by review of patient charts. Neurosurgery patients were chosen because labetalol is an antihypertensive agent commonly used perioperatively in this group of patients at our institution. Furthermore, blood pressure is strictly monitored and controlled in this patient population; therefore, all data were easily retrieved.

Emphasis is placed on the safety of high, cumulative doses of intravenous labetalol along with any subsequent

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TABLE 1
SUMMARY OF LABETALOL ADMINISTRATION

Patient number	Total dose (mg)*	High-dose labetalol therapy		
		Number of periods	Dose (mg/h)	Mode
1	905	1	435/22	bolus
2	1,074	1	1,074/23	bolus & infusion
3	1,240	2	360/23	bolus & infusion
4	3,654	4	700/11	bolus & infusion
			1,290/24	infusion
			1,248/24	infusion
			416/8	infusion
5	1,085	1	575/10	bolus
6	2,140	2	330/24	bolus
			440/24	bolus
7	1,177	2	527/22	infusion
			325/20	infusion
8	1,060	1	360/24	bolus
9	1,002	1	472/24	bolus & infusion
Total	1,482 ± 297 mg	15	623 ± 86 mg 20.4 ± 1.5 h	

*During normal dose and high-dose periods.

hemodynamic or biochemical complications. The efficacy of intravenous labetalol is well established[6–9] and cannot be adequately addressed in this paper because all patients received other antihypertensive medications in addition to labetalol.

MATERIALS AND METHODS

Patients

Nine patients were retrospectively identified by review of neurosurgical patient charts. There were five women and four men, all of whom were white. The mean age was 39 ± 14 years (range, 17–71 years) and mean weight was 70 ± 19 kg (range 45–117 kg). Only one patient had a history of hypertension, which was adequately controlled with hydrochlorothiazide (50 mg daily). Eight of the nine patients underwent a neurosurgical procedure: resection of an arteriovenous (AV) malformation (five patients); clipping of an intracranial aneurysm (three patients). One had a ruptured cerebral aneurysm, but the patient's condition was never stable enough to undergo surgery.

Labetalol

Charts were reviewed for cumulative doses of intravenous labetalol administered by either intermittent boluses or continuous infusion. The total dose administered overall as well as the total dose per each 24-hour interval was noted. Individual labetalol doses and their respective dosing intervals were also recorded.

Blood pressure and heart rate were recorded at 15-minute intervals as long as the patient was in the neurosurgical intensive care unit. The response to labetalol was assessed by noting the blood pressure and heart rate at several times, including before administering any labetalol (Time 0), 15 minutes before beginning high-dose labetalol (Time 1), 15 minutes after beginning high-dose labetalol (Time 2), and the maximum response observed during the high-dose period (Time 3). All subjects received other antihypertensive medications during the high-dose labetalol periods. The target systolic blood pressure in this patient population ranged from 90 to 120 mmHg.

Complications

Adverse hemodynamic responses during the high-dose labetalol period were defined as a decrease in heart rate or blood pressure requiring a reduction in the dose of labetalol and/or administration of intravenous fluids. Biochemical and hematologic complications were identified by noting routine blood values one to three days before initiating the high-dose labetalol and again at one to three days after completing the high-dose period.

RESULTS

Eight of the nine patients recovered and left the hospital. One patient who suffered a subarachnoid hemorrhage from a ruptured cerebral aneurysm exhibited progressive neurologic deterioration that pre-

TABLE 2
EFFECTS ON BLOOD PRESSURE AND HEART RATE (n = 9)

Time	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Heart rate (beats/min)
Before any labetalol (time 0)	121.7 ± 6.6	58.7 ± 4.4	90.3 ± 3.7
Before high-dose labetalol (time 1)	118.0 ± 5.1	58.3 ± 3.2	90.6 ± 4.6
Initial response (time 2)	102 ± 4.9	50.7 ± 1.9	88.8 ± 4.6
Maximum response (time 3)	91.4 ± 5.1	44.2 ± 2.0	87.2 ± 6.1

cluded any surgical intervention, and she died 14 days later. At the time of hospital discharge, two patients required antihypertensive medications. One of these patients was the individual who had been treated for hypertension prior to entering the hospital.

All nine patients received high doses of intravenous labetalol (>300 mg per 24 hours). There was a total of 15 distinct periods of 24 hours or less in which labetalol was administered in doses exceeding 300 mg. Five of the patients were given labetalol in the first one to two days following surgery. The remaining four patients received labetalol following an acute neurologic event but prior to any surgery.

The mean total dose of labetalol administered per patient during the entire observation period was 1,482 ± 297 mg (*Table 1*). This includes labetalol given in normal recommended doses (<300 mg/24 h) and high doses (>300 mg/24 h). *Table 1* summarizes the 15 periods of high-dose labetalol therapy. The mean cumulative dose during these periods was 623 ± 86 mg (range, 325–1,290 mg) given over 20.4 ± 1.5 hours (range, 8–24 hours). Four patients had two or more high-dose periods each. The highest total dose given to any single patient was 3,654 mg given over 3.5 consecutive days encompassing four high-dose periods. Administration was by intermittent boluses, continuous infusion, or a combination.

The effects on blood pressure and heart rate during the high-dose labetalol periods are summarized in *Table 2*. Immediately before starting the high-dose labetalol period (Time 1), mean systolic and diastolic blood pressures were 118.0 ± 5.1 mmHg and 58.3 ± 3.2 mmHg, respectively. The mean heart rate at Time 1 was 90.6 ± 4.6 beats per minute. Fifteen minutes following the first dose of labetalol given during the high-dose phase (or the first 15 minutes of a continuous infusion) (Time 2), the blood pressure and heart rate decreased to 102 ± 4.9 mmHg systolic, 50.7 ± 1.9 mmHg diastolic, and 88.8 ± 4.6 beats per minute, respectively ($P<.05$ for systolic and diastolic blood pressures compared to Time 1). At the time of maximum dose response (Time 3), the blood pressure was 91.4 ± 5.1 mmHg systolic and 44.4 ± 2.0 mmHg diastolic. The heart rate remained unchanged at 87.2 ± 6.1 beats per minute ($P<.05$ for systolic and diastolic blood pressures compared to Time 1).

TABLE 3
BIOCHEMICAL AND HEMATOLOGIC VALUES

	Preoperative	Postoperative
Total bilirubin (mg/dL)	0.49 ± 0.09	0.94 ± 0.23*
LDH (IU/L)	162 ± 20	266 ± 37*
SGOT (IU/L)	24 ± 7	50 ± 24*
Alkaline phosphatase (mU/mL)	57 ± 5	59 ± 14*
BUN (mg/dL)	16 ± 3	20 ± 4*
Creatinine (mg/dL)	0.8 ± 0.05	0.8 ± 0.07*
WBC (x10^9/L)	10.55 ± 1.2	13.4 ± 1.6*
Platelets (x10^9/L)	260,000 ± 12,500	167,000 ± 23,600†

*P = not significant for preoperative *v* postoperative value.
†P = .005 for preoperative *v* postoperative value.

Of note is one patient given three separate 100-mg boluses of labetalol over a period of 30 minutes. Blood pressure and heart rate decreased from initial values of 110/40 mmHg and 90 beats per minute, respectively, to 88/40 mmHg and 85 beats per minute 15 minutes following completion of the third 100-mg bolus. A second patient received 485 mg of labetalol over 45 minutes. Blood pressure and heart rate were 130/75 mmHg and 85 beats per minute prior to drug administration. Fifteen minutes following completion of the infusion the blood pressure had decreased to 112/65 mmHg and the heart rate remained unchanged at 85 beats per minute.

It must be kept in mind that all nine patients were receiving other antihypertensive medications concomitantly with the high doses of labetalol. Seven patients were treated with nitroprusside infusions. Other medications included hydralazine in six patients, furosemide in four patients, clonidine and nifedipine in two patients each, and captopril, methyldopa and propranolol in one patient each.

Hemodynamic complications during the high-dose periods were very few. One patient had transient sinus bradycardia (heart rate, 48 beats per minute) while receiving a continuous infusion of labetalol at a rate of 2

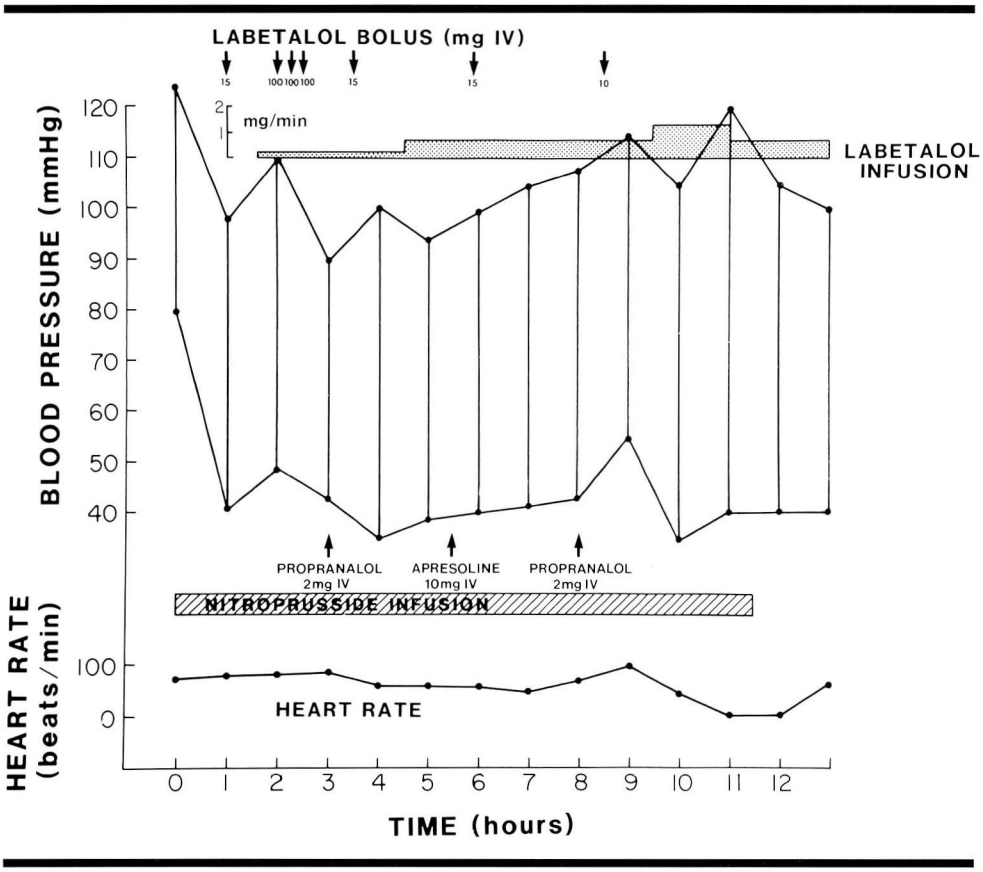

FIGURE 1. Blood pressure and heart rate response to 700 mg of labetalol given over 10.5 hours (Case 1).

mg/minute. He was also receiving intravenous propranolol, 2 mg every six hours. The heart rate increased to 80 beats per minute over a period of 75 minutes following a reduction in the infusion to 0.7 mg/minute and discontinuation of the propranolol. A second patient had transient hypotension (71/40 mmHg) while receiving a continuous labetalol infusion of 1 mg/minute. The hypotension occurred at the end of a 22-hour period when a total dose of 527 mg of labetalol had been administered. He was also receiving a nitroprusside infusion. The blood pressure rose to 96/52 mmHg 15 minutes following the discontinuation of both infusions. No other hemodynamic complications were noted and no permanent sequelae occurred.

Table 3 describes the major biochemical and hematologic parameters evaluated one to three days before and one to three days after the high-dose labetalol period. There were no statistically significant changes in any of the laboratory values except for the platelet count, which ranged from 220,000 to 330,000/μL before labetalol and from 73,000 to 291,000 /μL afterward. No bleeding complications occurred. Five patients exhibited an elevation in LDH. In four of the five patients, the increase was less than two times the normal value; in the fifth patient, the increase was greater than two times normal, and there was an associated increase in SGOT and alkaline phosphatase. One patient had increased total bilirubin up to 2.2 mg/dL in addition to a mild increase in LDH. All of these biochemical abnormalities resolved spontaneously without requiring a change in labetalol dosage.

CASE REPORTS

Case 1

A 39-year-old white woman was admitted to the hospital because of severe headache of sudden onset. There was no history of hypertension. Cerebral angiography demonstrated a basilar tip cerebral aneurysm. The baseline blood pressure was 124/80 mmHg. Prior to surgical correction, the patient received a labetalol infusion and intermittent boluses of labetalol to maintain the systolic arterial pressure at 100–110 mmHg. She also received a nitroprusside infusion and other antihypertensive medications depicted in *Figure 1*. The patient received a total of 700 mg of labetalol during a 10.5-hour period. The only complication was a transient sinus bradycardia (48 beats per minute), but the patient was also receiving intravenous propranolol. The patient continued to receive intravenous labetalol for a cumulative dose of 3,654 mg during a period of 3.5 days, up until the time she went to surgery.

Case 2

A 34-year-old white woman was admitted to the hospital because of headaches and diplopia. There was no history of hypertension, and she was taking no medi-

cations. She was found to have a cerebellar AV malformation, and she underwent surgical resection. Following surgery, the blood pressure was 120/80 mmHg, and she was receiving a nitroprusside infusion. Intermittent boluses of labetalol were given, and a labetalol infusion was started as well (*Figure 2*). During the first 24 hours postoperatively, she received a total of 1,074 mg of intravenous labetalol to maintain the systolic pressure <120 mmHg. *Figure 2* shows the changes in heart rate and blood pressure during this period. Eventually, the patient recovered and at discharge was taking no medications.

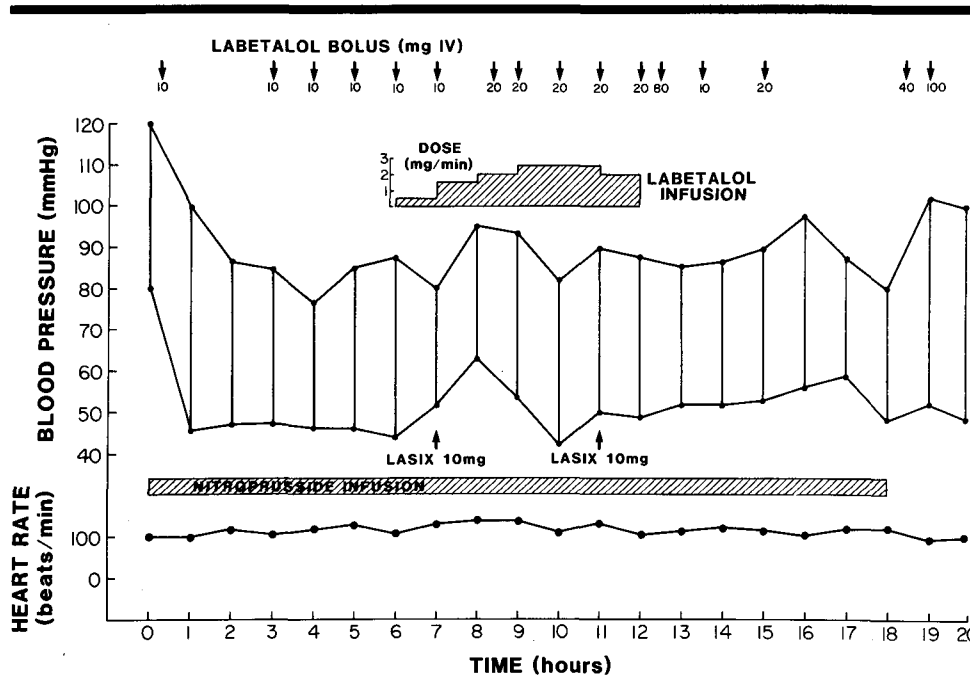

FIGURE 2. Blood pressure and heart rate response to 1,074 mg of labetalol given over 24 hours (Case 2).

DISCUSSION

Intravenous labetalol has been used effectively to treat severe hypertension and hypertensive emergencies as well as postoperative hypertension.[7–10] Due to its combined alpha and beta blockade, labetalol can effectively lower arterial pressure without causing a reflex tachycardia. Thus it has been demonstrated to be safe when administered to subjects with severe hypertension and atherosclerotic heart disease, acute myocardial infarction, or congestive heart failure.[9–11] Labetalol has also been safely given to hypertensive patients with acute neurologic syndromes such as acute cerebrovascular accidents, transient ischemic attacks, and hypertensive encephalopathy.[9]

Regardless of the clinical situation, the maximum recommended cumulative dose for intravenous labetalol has been 300 mg in any 24-hour period. In this paper, we evaluate the safety of labetalol in nine neurosurgical patients who received cumulative doses exceeding 300 mg in 24 hours.

Pharmacologically induced hypotension (BP ≤100 mmHg systolic) has become one of the medical maneuvers thought to prevent rebleeding in the early period following aneurysmal subarachnoid hemorrhage.[12,13] Maintaining systolic arterial pressure below 100 mmHg may also be helpful in preventing cerebral edema.[14] For these reasons, systemic arterial pressure is closely monitored and controlled in these clinical settings. Since labetalol has been shown not to cause a significant reduction in cerebral blood flow,[15] it can be a useful antihypertensive agent in patients with acute neurologic syndromes in whom cerebral autoregulation may be abnormal. Therefore labetalol is a frequently utilized antihypertensive in the neurosurgery intensive care unit at the Cleveland Clinic.

The 15 high-dose labetalol periods are summarized in *Table 1*. The mean cumulative dose (623 ± 86 mg) was more than twice the maximum recommended cumulative dose in 24 hours. Despite the high doses of labetalol given, only two patients experienced hemodynamic complications, both of which had other contributing factors in addition to labetalol. One patient (Patient 4) had a transient sinus bradycardia (48 beats per minute) but was also receiving intravenous propranolol. A second patient (Patient 7) exhibited hypotension (71/40 mmHg) during labetalol and nitroprusside infusions. Both patients recovered without sequelae.

Biochemical and/or hematologic abnormalities were noted in a total of five patients (*Table 3*). Five patients exhibited a transient rise in serum LDH levels. In four of the five patients, the increase was less than two times

normal. The fifth exhibited elevated LDH greater than two times normal in association with an increase in SGOT and alkaline phosphatase. No other patients exhibited an increase in other hepatic transaminases. One patient with a mild rise in LDH also had a mild increase in total bilirubin (2.2 mg/dL). All biochemical abnormalities resolved spontaneously without sequelae. Other factors could potentially account for these biochemical changes, including other medications and the fact that three of the five patients were in the postoperative period.

In a multicenter trial of intravenous labetalol for severe hypertension (maximum dose 300 mg), no biochemical abnormalities were noted.[9] A previous report of long-term oral labetalol therapy described increases in SGOT and/or SGPT in 27 of 331 patients (8%).[6] In nearly half of these patients (13), the abnormalities resolved despite continued drug administration. The remaining 14 patients had persistent hepatic enzyme abnormalities presumably related to labetalol. No mention was made of isolated LDH elevations.

Three patients had decreased platelet counts to less than 150,000/μL following high-dose labetalol (*Table 3*). Only one of these patients had a platelet count less than 100,000/μL. No bleeding complications occurred in any patient and platelet counts recovered spontaneously in all patients. Other studies reporting on intravenous[9] and oral[6] labetalol did not note any changes in platelet counts in relation to the drug.

It is not possible to evaluate the direct effect of labetalol alone on heart rate and blood pressure in this series of patients since other antihypertensive medications were administered concomitantly.

CONCLUSION

Labetalol can be administered intravenously to neurosurgical patients in cumulative doses exceeding 300 mg in 24 hours. It can be used with a variety of other antihypertensives to assist in maintaining the systolic arterial pressure <90–120 mmHg following an acute neurologic event such as an aneurysmal subarachnoid hemorrhage or following surgical correction of an AV malformation or intracranial aneurysm. The main adverse effect of such high doses seems to be a transient rise in serum LDH levels. Hemodynamic complications are not a frequent problem provided the patient is monitored closely.

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