

Risk of Anaphylactic Reaction

While taking beta-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

Drug/Laboratory Test Interactions

The presence of labetalol metabolites in the urine may result in falsely elevated levels of urinary catecholamines, metanephrine, normetanephrine, and vanillylmandelic acid (VMA) when measured by fluorimetric or photometric methods. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, a specific method, such as a high performance liquid chromatographic assay with solid phase extraction (e.g., *J Chromatogr.* 385:241,1987) should be employed in determining levels of catecholamines.

Labetalol HCl has also been reported to produce a false-positive test for amphetamine when screening urine for the presence of drugs using the commercially available assay methods Toxi-Lab A® (thin-layer chromatographic assay) and Emit-d.a.u.® (radioenzymatic assay). When patients being treated with labetalol have a positive urine test for amphetamine using these techniques, confirmation should be made by using more specific methods, such as a gas chromatographic-mass spectrometer technique.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term oral dosing studies with labetalol HCl for 18 months in mice and for 2 years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl using dominant lethal assays in rats and mice and exposing microorganisms according to modified Ames tests showed no evidence of mutagenesis.

Pregnancy

Teratogenic Effects - Pregnancy Category C

Teratogenic studies were performed with labetalol in rats and rabbits at oral doses up to approximately six and four times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. A teratology study performed with labetalol in rabbits at IV doses up to 1.7 times the MRHD revealed no evidence of drug-related harm to the fetus. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Hypotension, bradycardia, hypoglycemia, and respiratory depression have been reported in infants of mothers who were treated with labetalol HCl for hypertension during pregnancy. Oral administration of labetalol to rats during late gestation through weaning at doses of two to four times the MRHD caused a decrease in neonatal survival.

Labor and Delivery

Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers

Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when labetalol hydrochloride injection is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Labetalol hydrochloride injection is usually well tolerated. Most adverse effects have been mild and transient and, in controlled trials involving 92 patients, did not require labetalol HCl withdrawal. Symptomatic postural hypotension (incidence, 58%) is likely to occur if patients are tilted or allowed to assume the upright position within 3 hours of receiving labetalol hydrochloride injection. Moderate hypotension occurred in 1 of 100 patients while supine. Increased sweating was noted in 4 of 100 patients, and flushing occurred in 1 of 100 patients.

The following also were reported with labetalol hydrochloride injection with the incidence per 100 patients as noted:

Cardiovascular System

Ventricular arrhythmia in 1.

Central and Peripheral Nervous Systems

Dizziness in 9, tingling of the scalp/skin in 7, hypoesthesia (numbness) and vertigo in 1 each.

Gastrointestinal System

Nausea in 13, vomiting in 4, dyspepsia and taste distortion in 1 each.

Metabolic Disorders

Transient increases in blood urea nitrogen and serum creatinine levels occurred in 8 of 100

patients; these were associated with drops in blood pressure, generally in patients with prior renal insufficiency.

Psychiatric Disorders

Somnolence/yawning in 3.

Respiratory System

Wheezing in 1.

Skin

Pruritus in 1.

The incidence of adverse reactions depends upon the dose of labetalol HCl. The largest experience is with oral labetalol HCl (see labetalol HCl tablet product information for details). Certain of the side effects increased with increasing oral dose, as shown in the following table that depicts the entire U.S. therapeutic trials data base for adverse reactions that are clearly or possibly dose related.

Labetalol Daily Dose (mg)	200	300	400	600	800	900	1200	1600	2400
Number of patients	522	181	606	608	503	117	411	242	175
Dizziness(%)	2	3	3	3	5	1	9	13	16
Fatigue	2	1	4	4	5	3	7	6	10
Nausea	<1	0	1	2	4	0	7	11	19
Vomiting	0	0	<1	<1	<1	0	1	2	3
Dyspepsia	1	0	2	1	1	0	2	2	4
Paresthesia	2	0	2	2	1	1	2	5	5
Nasal stuffiness	1	1	2	2	2	2	4	5	6
Ejaculation failure	0	2	1	2	3	0	4	3	5
Impotence	1	1	1	1	2	4	3	4	3
Edema	1	0	1	1	1	0	1	2	2

In addition, a number of other less common adverse events have been reported:

Cardiovascular

Hypotension, and rarely, syncope, bradycardia, heart block.

Liver and Biliary System

Hepatic necrosis, hepatitis, cholestatic jaundice, elevated liver function tests.

Hypersensitivity

Rare reports of hypersensitivity (e.g., rash, urticaria, pruritus, angioedema, dyspnea) and anaphylactoid reactions.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl during investigational use and extensive foreign marketing experience.

Clinical Laboratory Tests

Among patients dosed with labetalol hydrochloride tablets, there have been reversible increases of serum transaminases in 4% of patients tested and, more rarely, reversible increases in blood urea.

OVERDOSAGE

Overdosage with labetalol HCl causes excessive hypotension that is posture sensitive and, sometimes, excessive bradycardia. Patients should be placed supine and their legs raised if necessary to improve the blood supply to the brain. If overdosage with labetalol HCl follows oral ingestion, gastric lavage or pharmacologically induced emesis (using syrup of ipecac) may be useful for removal of the drug shortly after ingestion. The following additional measures should be employed if necessary: **Excessive bradycardia**-administer atropine or epinephrine. **Cardiac failure**-administer a digitalis glycoside and a diuretic. Dopamine or dobutamine may also be useful. **Hypotension**-administer vasopressors, e.g., norepinephrine. There is pharmacologic evidence that norepinephrine may be the drug of choice. **Bronchospasm**-administer epinephrine and/or an aerosolized beta₂-agonist. **Seizures**-administer diazepam.

In severe beta-blocker overdose resulting in hypotension and/or bradycardia, glucagon has been shown to be effective when administered in large doses (5 to 10 mg rapidly over 30 seconds, followed by continuous infusion of 5 mg/hr that can be reduced as the patient improves).

Neither hemodialysis nor peritoneal dialysis removes a significant amount of labetalol from the general circulation (<1%).

The oral LD₅₀ value of labetalol HCl in the mouse is approximately 600 mg/kg and in the rat is greater than 2 g/kg. The IV LD₅₀ in these species is 50 to 60 mg/kg.

DOSAGE AND ADMINISTRATION

Labetalol hydrochloride injection is intended for IV use in hospitalized patients. DOSAGE MUST BE INDIVIDUALIZED depending upon the severity of hypertension and the response of the patient during dosing.

Patients should always be kept in a supine position during the period of IV drug administration. A substantial fall in blood pressure on standing should be expected in these patients. The patient's ability to tolerate an upright position should be established before permitting any ambulation, such as using toilet facilities.

Either of two methods of administration of labetalol hydrochloride injection may be used: a) repeated IV injection, or b) slow continuous infusion.

Repeated Intravenous Injection

Initially, labetalol hydrochloride injection should be given in a 20 mg dose (which corresponds to 0.25 mg/kg for an 80 kg patient) by slow IV injection over a 2-minute period.

Immediately before the injection and at 5 and 10 minutes after injection, supine blood pressure should be measured to evaluate response. Additional injections of 40 or 80 mg can be given at 10-minute intervals until a desired supine blood pressure is achieved or a total of 300 mg of labetalol HCl has been injected. The maximum effect usually occurs within 5 minutes of each injection.

Slow Continuous Infusion

Labetalol hydrochloride injection is prepared for continuous IV infusion by diluting the vial contents with commonly used IV fluids (see below). Examples of two methods of preparing the infusion solution are:

Add 40 mL of labetalol hydrochloride injection to 160 mL of a commonly used IV fluid such that the resultant 200 mL of solution contains 200 mg of labetalol HCl, 1 mg/mL. The diluted solution should be administered at a rate of 2 mL/min to deliver 2 mg/min.

Alternatively, add 40 mL of labetalol hydrochloride injection to 250 mL of a commonly used IV fluid. The resultant solution will contain 200 mg of labetalol HCl, approximately 2 mg/3 mL. The diluted solution should be administered at a rate of 3 mL/min to deliver approximately 2 mg/min.

The rate of infusion of the diluted solution may be adjusted according to the blood pressure response, at the discretion of the physician. To facilitate a desired rate of infusion, the diluted solution can be infused using a controlled administration mechanism, e.g., graduated burette or mechanically driven infusion pump.

Since the half-life of labetalol is 5 to 8 hours, steady-state blood levels (in the face of a constant rate of infusion) would not be reached during the usual infusion time period. The infusion should be continued until a satisfactory response is obtained and should then be stopped and oral labetalol HCl started (see below). The effective IV dose is usually in the range of 50 to 200 mg. A total dose of up to 300 mg may be required in some patients.

Blood Pressure Monitoring

The blood pressure should be monitored during and after completion of the infusion or IV injection. Rapid or excessive falls in either systolic or diastolic blood pressure during IV treatment should be avoided. In patients with excessive systolic hypertension, the decrease in systolic pressure should be used as an indicator of effectiveness in addition to the response of the diastolic pressure.

Initiation of Dosing with Labetalol Tablets

Subsequent oral dosing with labetalol tablets should begin when it has been established that the supine diastolic blood pressure has begun to rise. The recommended initial dose is 200 mg, followed in 6 to 12 hours by an additional dose of 200 or 400 mg, depending on the blood pressure response. Thereafter, **inpatient titration with labetalol tablets** may proceed as follows:

Inpatient Titration Instructions

Regimen	Daily Dose*
200 mg b.i.d.	400 mg
400 mg b.i.d.	800 mg
800 mg b.i.d.	1600 mg
1200 mg b.i.d.	2400 mg

* If needed, the total daily dose may be given in three divided doses.

The dosage of labetalol tablets used in the hospital may be increased at 1-day intervals to achieve the desired blood pressure reduction.

For subsequent outpatient titration or maintenance dosing, see **DOSAGE AND ADMINISTRATION** in the labetalol tablets Product Information for additional recommendations.

Compatibility with commonly used intravenous fluids

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever solution and container permit.

Labetalol hydrochloride injection was tested for compatibility with commonly used IV fluids at final concentrations of 1.25 to 3.75 mg of labetalol HCl per milliliter of the mixture. Labetalol hydrochloride injection was found to be compatible with and stable (for 24 hours refrigerated or at room temperature) in mixtures with the following solutions:

Ringer's Injection, USP
Lactated Ringer's Injection, USP
5% Dextrose and Ringer's Injection
5% Lactated Ringer's and 5% Dextrose Injection
5% Dextrose Injection, USP
0.9% Sodium Chloride Injection, USP
5% Dextrose and 0.2% Sodium Chloride Injection, USP
2.5% Dextrose and 0.45% Sodium Chloride Injection, USP
5% Dextrose and 0.9% Sodium Chloride Injection, USP
5% Dextrose and 0.33% Sodium Chloride Injection, USP.

Labetalol hydrochloride injection was NOT compatible with 5% sodium bicarbonate injection, USP. Care should be taken when administering alkaline drugs, including furosemide, in combination with labetalol. Compatibility should be assured prior to administering these drugs together.

HOW SUPPLIED

Labetalol Hydrochloride Injection, USP is supplied as follows:

	Labetalol Hydrochloride Injection, USP (5 mg per mL)	Package Factor
NDC		
25021-300-20	100 mg per 20 mL Multi-Dose Vial	1 vial per carton
25021-300-40	200 mg per 40 mL Multi-Dose Vial	1 vial per carton

Storage Conditions

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Do not freeze.

Protect from light. Retain in carton until time of use.

LATEX-FREE

Sterile, Nonpyrogenic.



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