

PRODUCT MONOGRAPH

**Pr MYLAN-LABETALOL HYDROCHLORIDE INJECTION, USP
(labetalol hydrochloride)**

5 mg/mL

Antihypertensive Agent

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PRODUCT MONOGRAPH

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(labetalol hydrochloride)

5 mg/mL

THERAPEUTIC CLASSIFICATION

Antihypertensive

ACTION AND CLINICAL PHARMACOLOGY

Mylan-Labetalol Hydrochloride Injection, USP (labetalol hydrochloride) is an adrenergic receptor blocking agent possessing both α_1 (post-synaptic) and beta-receptor blocking activity. Its action on beta-receptors is four times stronger than that on alpha-receptors. It antagonizes β_1 - and β_2 -receptors equally.

The mechanism of the antihypertensive action of labetalol hydrochloride has not been fully established. It is considered that labetalol hydrochloride lowers blood pressure by partially blocking the alpha-adrenoreceptors in the peripheral arterioles, thus causing vasodilation and a resulting reduction of peripheral resistance. At the same time, blockade of the beta-adrenoreceptors in the myocardium prevents reflex tachycardia and subsequent elevation of cardiac output. Peripheral vasodilation is achieved with incomplete blockade of alpha-adrenoreceptors in the arterioles and the barostatic reflexes remain sufficiently active to reduce the incidence of postural hypotension.

At rest, labetalol slightly reduces the heart rate, increases the stroke volume but does not significantly affect cardiac output. It reduces exercise-induced increases in systolic pressure and heart rate, again without significantly influencing cardiac output.

Following oral administration to hypertensive patients, labetalol hydrochloride decreases plasma renin activity and aldosterone levels, both at rest and during exercise, particularly when these were elevated prior to treatment. Labetalol is significantly more efficacious in hypertensive patients with high baseline plasma noradrenaline levels.

Labetalol is metabolized mostly by conjugation with glucuronic acid; the resulting metabolite is inactive. Rapid and extensive distribution within tissue compartments occurs after intravenous administration. The drug is approximately 50% bound to plasma proteins. Labetalol hydrochloride and its metabolites are rapidly excreted in urine, and via bile into the feces. The plasma half-life of labetalol is approximately 5.5 hours after intravenous administration.

Following a bolus intravenous injection, the maximum antihypertensive effect occurs within 5 to 10 minutes in the majority of patients. However, in some patients the peak effect occurs considerably later.

In a clinical pharmacologic study in severe hypertensives, an initial 0.25 mg/kg injection of labetalol hydrochloride administered to patients in the supine position decreased blood pressure by an average of 11/7 mmHg. Additional injections of 0.5 mg/kg at 15 minute intervals up to a total cumulative dose of 1.75 mg/kg of labetalol hydrochloride caused further dose-related decreases in blood pressure. Some patients required cumulative doses of up to 3.25 mg/kg. The maximal effect of each dose level occurred within 5 minutes. Following discontinuation of intravenous treatment with labetalol, the blood pressure rose gradually and progressively, approaching pretreatment baseline values within an average of 16 to 18 hours in the majority of patients.

Similar results were obtained in the treatment of patients with severe hypertension requiring urgent blood pressure reduction with an initial dose of 20 mg (which corresponds to 0.25 mg/kg for an 80 kg patient) followed by additional doses of either 40 mg or 80 mg at 10-minute intervals to achieve the desired effect or up to a cumulative dose of 300 mg.

Labetalol hydrochloride administered as a continuous intravenous infusion with a mean dose of 136 mg (27 to 300 mg) over a period of 2 to 3 hours (mean of 2 hours and 39 minutes) lowered the blood pressure by an average of 60/35 mmHg.

INDICATIONS AND CLINICAL USE

Mylan-Labetalol Hydrochloride Injection, USP (labetalol hydrochloride) is indicated for the emergency treatment of severe hypertension when prompt and urgent reduction of blood pressure is essential.

CONTRAINDICATIONS

Mylan-Labetalol Hydrochloride Injection, USP is contraindicated in patients with the following conditions:

- Uncontrolled congestive heart failure (see WARNINGS, Heart Failure).
- Asthma or a history of obstructive lung disease (see WARNINGS, Bronchospastic Diseases).
- Greater than first degree A-V block.
- Cardiogenic shock and states of hypoperfusion.
- Sinus bradycardia.
- Known sensitivity to labetalol.

WARNINGS

Heart Failure

Cardiac failure should be controlled with digitalis and diuretics before labetalol hydrochloride treatment is initiated. Mylan-Labetalol Hydrochloride Injection, USP should not be given to patients with digitalis-resistant heart failure. Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. A few patients developed heart failure while on labetalol hydrochloride. Therefore, administration of labetalol hydrochloride to patients with controlled failure or those likely to develop such failure, must be carried out under careful supervision. The drug does not abolish the inotropic action of digitalis on heart muscle.

Patients with angina should be warned against abrupt discontinuation of beta-adrenergic blocking agents. There have been reports of severe exacerbation of angina, and of myocardial infarction or ventricular arrhythmias occurring in patients with angina pectoris, following abrupt discontinuation of therapy. The last two complications may occur with or without preceding exacerbation of angina pectoris. Therefore, when discontinuation of labetalol hydrochloride is planned in patients with angina pectoris, the dosage should be gradually reduced over a period of about two weeks and the patient should be carefully observed. The same frequency of administration should be maintained. In situations of greater urgency, labetalol therapy should be discontinued stepwise and under conditions of closer observation. If angina markedly worsens or acute coronary insufficiency develops, it is recommended that treatment with labetalol be re-instituted promptly, at least temporarily.

Skin

Various skin rashes and conjunctival xerosis have been reported with beta-blockers. A severe syndrome (oculomucocutaneous syndrome) whose signs include conjunctivitis sicca and psoriasiform rashes, otitis, and sclerosing serositis has occurred with the chronic use of one beta-adrenergic blocking agent (practolol). This syndrome has not been observed in association with labetalol hydrochloride or any other such agent. However, physicians should be alert to the possibility of such reactions and should discontinue treatment in the event that they occur.

Ophthalmologic

Animal studies have shown that labetalol binds to the melanin of the uveal tract. The significance of this in humans is not known but periodic ophthalmic examinations are advisable while the patient is taking labetalol hydrochloride.

Hepatic/Biliary/Pancreatic

There have been rare reports of severe hepatocellular injury with labetalol hydrochloride therapy. Injury has occurred after both short term and long term treatment and may be slowly progressive despite minimal symptomatology. The hepatic injury is usually reversible but rare cases of hepatic necrosis and death have been reported. Appropriate laboratory testing should be performed at regular intervals during labetalol hydrochloride therapy. Tests should also be done at the first sign or symptom of liver dysfunction (eg.,

pruritus, dark urine, persistent anorexia, jaundice, right upper quadrant tenderness or unexplained flu-like symptoms). If there is laboratory evidence of liver injury or the patient is jaundiced, labetalol hydrochloride should be stopped and not restarted.

Sinus Bradycardia

Severe sinus bradycardia may occur with the use of labetalol from unopposed vagal activity remaining after blockade of beta₁-adrenergic receptors; in such cases, dosage should be reduced.

Endocrine and Metabolism

In patients with thyrotoxicosis, possible deleterious effects from long-term use of labetalol hydrochloride have not been adequately appraised. Beta-blockade may mask the clinical signs of continuing hyperthyroidism or complications, and give a false impression of improvement.

Therefore, abrupt withdrawal of labetalol hydrochloride may be followed by an exacerbation of the symptoms of hyperthyroidism, including thyroid storm.

Pheochromocytoma

While labetalol hydrochloride has been shown to be effective in lowering the blood pressure and relieving symptoms in patients with pheochromocytoma, paradoxical hypertensive responses have been reported in a few patients with this tumour. Use caution when administering Mylan-Labetalol Hydrochloride Injection, USP to patients with pheochromocytoma.

Cerebral Hypoperfusion

During treatment with Mylan-Labetalol Hydrochloride Injection, USP, signs of cerebral hypoperfusion may occur if blood pressure is reduced too rapidly. Signs include: confusion, somnolence, lightheadedness, dizziness, nausea, vomiting, pallor, sweating, blurred vision, headache, hallucinations and loss of consciousness. Symptoms and signs of myocardial hypoperfusion include chest pain and ischemic changes in the electrocardiogram. Although they have not been seen with the use of intravenous labetalol hydrochloride, a number of other adverse reactions including cerebral infarction and optic nerve infarction have been reported with other agents when severely elevated blood pressure was reduced over time-courses of several hours to as long as 1 or 2 days. The desired blood pressure lowering should therefore be achieved over as long a period of time as is compatible with the patient's status.

Bronchospastic Diseases

Mylan-Labetalol Hydrochloride Injection, USP should not be used in patients with asthma or a history of obstructive airway disease unless no alternative treatment is available. In such cases, the risk of inducing bronchospasm should be appreciated, therefore, careful monitoring of patients is mandatory and bronchodilators should be used concomitantly. In patients already on therapy, the dose of bronchodilators may have to be increased. In spite of these precautions the patient's respiratory status may worsen, and in such cases Mylan-Labetalol Hydrochloride Injection, USP should be discontinued. If bronchospasm should occur after the use of labetalol hydrochloride, it can be treated

with a beta₂-adrenergic receptor stimulant by inhalation, e.g. salbutamol (the dose of which may need to be greater than the usual dose in asthma), and, if necessary, intravenous atropine 1 mg.

PRECAUTIONS

Postural Hypotension

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 Mylan-Labetalol Hydrochloride Injection, USP. Establish blood pressure equilibrium before permitting any ambulation.

Hypoglycemia

Beta-receptor blocking drugs may enhance hypoglycemia in patients prone to this condition. Also, diabetics on insulin or oral hypoglycemic medication may have an increased tendency towards hypoglycemia when treated with these drugs.

Allergic Reactions

There may be increased difficulty in treating an allergic-type reaction in patients on beta-blockers. In these patients, the reaction may be more severe due to pharmacological effects of beta-blockers and problems with fluid changes. Epinephrine should be administered with caution since it may not have its usual effects in the treatment of anaphylaxis. On the one hand, larger doses of epinephrine may be needed to overcome the bronchospasm, while on the other, these doses can be associated with excessive alpha adrenergic stimulation with consequent hypertension, reflex bradycardia and heart block and possible potentiation of bronchospasm. Alternatives to the use of large doses of epinephrine include vigorous supportive care such as fluids and the use of beta agonists, including parenteral salbutamol or isoproterenol to overcome bronchospasm and norepinephrine to overcome hypotension.

Use in Geriatrics

The bioavailability and half-life of labetalol hydrochloride are increased in the elderly. In addition, the hypotensive response is greater in this age group following oral or intravenous administration. Therefore, lower doses of Mylan-Labetalol Hydrochloride Injection, USP are likely to be required in elderly patients.

Use in Pregnancy

Although no teratogenic effects were seen in animal testing, the safety of the use of labetalol hydrochloride during pregnancy has not been established. Labetalol crosses the placental barrier in women and has been found to bind to the eyes of foetal animals. Mylan-Labetalol Hydrochloride Injection, USP should be used in pregnant women only if the expected benefit to the mother justifies the potential risk to the foetus.

Use in Lactating Women

Labetalol has been found in the breast milk of lactating women. If the use of Mylan-Labetalol Hydrochloride Injection, USP is considered essential, then mothers should stop nursing.

Use in Pediatrics

Safety and effectiveness in children have not been established.

Drug Interactions

When used with diuretics and/or other antihypertensive agents the dose of labetalol hydrochloride must be appropriately adjusted (see **DOSAGE AND ADMINISTRATION**).

Labetalol hydrochloride and halothane have additive hypotensive effects. High doses of halothane (3%) with labetalol hydrochloride predispose the patient to the myocardial depressant effects of halothane and an undesirable reduction in myocardial performance. The anesthesiologist should be informed when a patient is receiving labetalol hydrochloride.

Care should be taken if Mylan-Labetalol Hydrochloride Injection, USP is used concomitantly with either Class I antiarrhythmic agents or calcium antagonists of the verapamil class since these drugs may potentiate the cardiac depressant activities of labetalol hydrochloride.

Labetalol hydrochloride blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. When labetalol hydrochloride is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

In one survey, 2.3% of patients taking labetalol hydrochloride in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol hydrochloride alone. The contribution of each of the treatments to this adverse reaction is unknown, but the possibility of a drug interaction cannot be excluded.

Drug-Laboratory Test Interactions

The presence of a metabolite of labetalol hydrochloride in the urine may result in falsely elevated levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol hydrochloride, specific radioenzymatic or high performance liquid chromatographic assay techniques should be used to determine levels of catecholamines or their metabolites.

ADVERSE REACTIONS

The most serious reported adverse effects of labetalol hydrochloride are severe postural hypotension, jaundice and bronchospasm.

In well controlled clinical trials, the most common transient adverse reactions reported at routinely administered therapeutic doses, were postural hypotension and/or dizziness (16.9%), fatigue/malaise (13.1%), and headache (8.0%). Other transient effects include acute retention of urine and difficulty in micturition. The following summarizes the adverse effects reported.

Cardiovascular: Postural hypotension/dizziness (16.9%), angina pectoris (3.2%), Raynaud's phenomenon (3.2%), pedal edema (1.9%), palpitations (1.3%), bradycardia (< 1%).

Gastrointestinal: Nausea/vomiting (6.1%), dyspepsia (1.9%), constipation (1.6%), dry mouth/sore throat (1.6%).

Respiratory: Dyspnea (3.8%), nasal congestion (1.3%).

Dermatological: Drug rash (3.2%), paresthesia (especially "scalp tingling") (3.8%), pruritus (0.6%) and angioedema.

Urogenital: Impotence (2.2%), failure of ejaculation (0.6%), dysuria (0.6%).

Musculoskeletal: Aches/pains (3.5%), muscle cramps (1.3%).

Central Nervous System: Fatigue/malaise (13.1%), headache (8.0%), depression (2.6%), loss of libido (1.3%), dreaming (1.3%).

Miscellaneous: Visual blurring (4.2%), epistaxis (1.6%).

In addition, in the more extensive trials, bronchospasm and severe bradycardia were reported with an incidence of less than 1%. There are rare reports of raised liver function tests, jaundice (both hepatic and cholestatic), and hepatic necrosis (see Warnings).

Other published or unpublished reports describe other rare, isolated adverse events in patients who were taking labetalol hydrochloride (oral or injectable), as follows: bronchospasm and reduction in PEF, difficulty in micturition including acute urinary retention, ejaculatory failure, Peyronie's disease, toxic myopathy, tremor, taste distortion, hypersensitivity, hypoesthesia, rashes of various types such as generalized maculopapular, lichenoid, urticarial, bullous lichen planus, psoriasiform, facial erythema, reversible alopecia and very rarely drug fever. A skin lesion resembling disseminated lupus erythematosus occurs rarely in one patient receiving high dose of labetalol hydrochloride. There are rare reports of patients who developed lupus-like syndromes while on labetalol hydrochloride which cleared upon discontinuation of treatment. Positive antinuclear factor and antimitochondrial antibodies have been reported in patients receiving the drug, but the significance of these findings is not clear.

Clinical Laboratory Tests

Elevations of BUN and serum creatinine following bolus injections were reported in 6.8% of patients.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (<http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - mail to: Canada Vigilance Program
Health Canada, Postal Locator 0701E
Ottawa, ON
K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (<http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

OVERDOSAGE

Symptoms

Excessive hypotension which is posture-sensitive, and sometimes, excessive bradycardia.

Treatment

Patients should be laid supine and their legs raised, if necessary. Hemodialysis removes less than 1% of circulating labetalol, and is therefore not recommended. The following additional measures should be employed if necessary:

Excessive Bradycardia: Administer atropine to induce vagal blockage. If bradycardia persists, isoproterenol may be administered cautiously. In refractory cases, the use of a cardiac pacemaker may be considered.

Congestive Heart Failure: Conventional therapy with cardiac glycosides and diuretics.

Hypotension: Administer vasopressors, e.g. norepinephrine.

Bronchospasm: Administer a beta₂-stimulating agent and/or a theophylline preparation.

Oliguric renal failure has been reported after massive overdosage of labetalol hydrochloride orally. In one case, the use of dopamine to increase blood pressure may have aggravated the renal failure.

For management of a suspected drug overdose, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

DOSAGE AND ADMINISTRATION

The administration of intravenous Mylan-Labetalol Hydrochloride Injection, USP should be restricted to hospitalized patients. **DOSAGE MUST BE INDIVIDUALIZED** according to the severity of the hypertension, to the nature and duration of previous therapy and to the response of the patient during dosing.

Patients should be kept supine during the period of intravenous drug administration because a substantial fall in blood pressure on standing may be anticipated in these patients. The patient's ability to tolerate the upright position (e.g. use of toilet facilities) should be established, especially during the 3 hours post-injection.

The blood pressure should be monitored during and after completion of the infusion or intravenous injections. Rapid or excessive falls in either systolic or diastolic blood pressure during intravenous 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.

Geriatrics: Lower doses of Mylan-Labetalol Hydrochloride Injection, USP are likely to be required in elderly patients (see PRECAUTIONS).

Pediatrics: Safe and effective use of labetalol hydrochloride in children have not presently been elucidated.

Patients with liver function impairment will likely require lower doses since metabolism of the drug will be diminished.

Either of two methods of administration of Mylan-Labetalol Hydrochloride Injection, USP may be used:

- repeated intravenous injection, or
- slow continuous infusion.

Repeated Intravenous Injection

Initially, Mylan-Labetalol Hydrochloride Injection, USP should be given in a dose of 20 mg labetalol hydrochloride (which corresponds to 0.25 mg/kg for an 80 kg patient) by slow intravenous injection over a two-minute period.

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

Slow Continuous Infusion

Mylan-Labetalol Hydrochloride Injection, USP is prepared for intravenous continuous infusion by diluting the vial contents with commonly used intravenous fluids (see below Compatibility With Commonly Used Intravenous Fluids). Examples of two methods of preparing the infusion solution are:

The contents of two vials (2 x 20 mL) or 1 vial (40 mL) are added to 160 mL of a commonly used intravenous fluid such that the resultant 200 mL of solution contains 200 mg of labetalol hydrochloride (1 mg/mL). The diluted solution should be administered at a rate of 2 mL/min to deliver 2 mg/min.

Alternatively, the contents of two vials (2 x 20 mL) or 1 vial (40 mL) of Mylan-Labetalol Hydrochloride Injection, USP can be added to 250 mL of a commonly used intravenous fluid. The resultant solution will contain 200 mg of labetalol hydrochloride, 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 downward 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 hydrochloride 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 medication started when it has been established that the supine diastolic blood pressure has begun to rise. The effective intravenous dose is usually in the range of 50 to 200 mg. A total dose up to 300 mg may be required in some patients.

Compatibility With Commonly Used Intravenous Fluids

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

Mylan-Labetalol Hydrochloride Injection, USP was tested for compatibility with commonly used intravenous fluids at final concentrations of 1.25 mg and 3.75 mg

labetalol hydrochloride per mL of the mixture. Mylan-Labetalol Hydrochloride Injection, USP was found to be compatible with and stable (24 hrs, refrigerated or at room temperature) in Sodium Chloride Injection USP 0.9% and Dextrose Injection USP 5%.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each mL of Mylan-Labetalol Hydrochloride Injection, USP contains: labetalol hydrochloride 5 mg, dextrose anhydrous 45 mg, disodium edetate 0.1 mg, methylparaben 0.8 mg (0.08%), propylparaben 0.1 mg (0.01%), anhydrous citric acid 0.017 mg, anhydrous citric acid and/or sodium hydroxide to adjust pH, and water for injection.

Mylan-Labetalol Hydrochloride Injection, USP, 5 mg/mL is available in multidose amber vials as 20 mL fill in 20 mL vials & 40 mL fill in 50 mL vials, boxes of 1.

STORAGE AND STABILITY

Store in the original package at room temperature 15°C - 30°C, protected from light.

Compatibility with Commonly Used Intravenous Fluids: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Multidose vial: Discard 28 days after initial puncture.

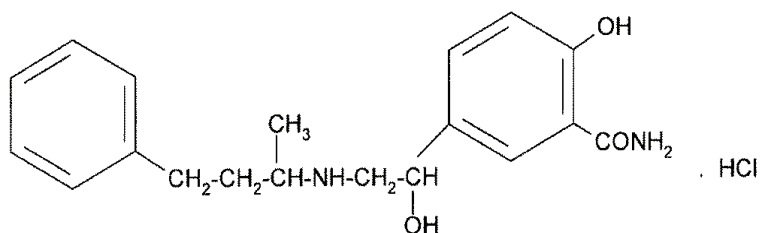
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: labetalol hydrochloride

Chemical Name: 2-hydroxy-5-[1-hydroxy-2-[(1-methyl-3-phenylpropyl)amino]ethyl]benzamide hydrochloride

Structural Formula:



Molecular Formula: $C_{19}H_{24}N_2O_3 \cdot HCl$

Molecular Weight: 364.9 g/mol

Physical Characteristics: Labetalol hydrochloride is a white to off-white powder with a melting point around 180°C with decomposition. Labetalol hydrochloride is soluble in water and in alcohol; it is insoluble in ether and chloroform. The pH of a 1% w/v solution of labetalol hydrochloride is between 4.0 – 5.0.

PHARMACOLOGY

Effects on Cardiovascular System

Dogs:

Intravenous labetalol hydrochloride, in doses of 0.1 to 10 mg/kg, caused a dose-dependent decrease in blood pressure and heart rate. Doses up to 1 mg/kg resulted in progressive shifts to the right of the dose-pressor response curve for noradrenaline. There was no further increase in β -blockade with the higher doses. Beta-adrenergic blockade was seen with doses of 0.1, 0.5 and 1.0 mg/kg as shown by antagonism of isoproterenol-induced vasodilation and tachycardia.

Intravenous labetalol hydrochloride, in doses of 0.1 to 3.0 mg/kg, caused a dose-dependent reduction in arterial blood pressure (11 – 16%), heart rate (16 – 27%), aortic blood flow (10 – 38%), and cardiac contractility (9 – 52%). Changes in anaesthetized dogs lasted for more than one hour. Consistent reductions in stroke volume (21%) occurred at the highest dose and in total peripheral resistance at 1 and 3 mg/kg.

Oral doses of 0.25 to 5 mg/kg lowered systolic blood pressure by 10 to 35 mmHg for about 5 hours with no consistent changes in heart rate.

Labetalol hydrochloride has not been shown to possess intrinsic sympathomimetic activity.

Intravenous labetalol hydrochloride, in doses of 0.03 to 1 mg/kg, caused direct vasodilation of resistant blood vessels in dogs rendered devoid of adrenergic tone.

Using the guinea pig intradermal wheal test, it was demonstrated that labetalol possesses local anaesthetic activity approximately equipotent to that of propranolol.

Humans:

Intravenous labetalol hydrochloride, in doses of 10, 40 and 160 mg caused dose-related inhibition of phenylephrine-induced increase in mean blood pressure and of isoproterenol-induced tachycardia. After 40 mg of labetalol hydrochloride, a 2-fold increase in the dose of phenylephrine (β -blockade) and an 8-fold increase in the dose of isoproterenol (β -blockade) were required to elicit responses equivalent to pretreatment levels. The tachycardia induced by Valsalva manoeuvre was also abolished by the 40 mg IV dose.

Doses of 0.5 mg/kg of labetalol hydrochloride administered IV to 12 hypertensive patients resulted in the following statistically significant mean percentage changes: blood pressure was lowered by 18.5% ($p < 0.001$) and total peripheral vascular resistance by $13.5 \pm 22\%$ ($p < 0.02$). No significant changes in resting heart rate or cardiac output were observed.

Labetalol hydrochloride significantly reduced the pressor response to immersion of the hand in ice-cold water for 60 seconds (**cold pressor test**), signifying the postsynaptic β -blocking action of the drug.

After oral treatment with labetalol hydrochloride (average dose 1200 mg), plasma renin and angiotensin II levels were reduced, especially if elevated prior to treatment. Intravenous labetalol hydrochloride, in doses of 1 – 2 mg/kg, reduced plasma levels of angiotensin II and aldosterone in hypertensive patients.

Effects on Pulmonary Function

A single 400 mg oral dose of labetalol hydrochloride administered to healthy male subjects caused a reduction in Peak Expiratory Flow Rate (PEFR) at rest and during exercise.

In 11 hypertensive asthmatic subjects, a 300 mg oral dose of labetalol hydrochloride caused a slight reduction in resting FEV₁, and significantly reduced the effect of inhaled salbutamol in FEV₁.

Other Effects

Labetalol hydrochloride administered to 17 hypertensive men in daily oral doses of 600 to 1200 mg caused a small increase in fasting blood glucose levels but no alteration in insulin activity or response to an oral glucose tolerance test.

TOXICOLOGY

Acute Toxicity

Animal	Sex	Route of Administration	LD ₅₀ (in mg/kg)
Mouse	M	PO	655
Mouse	F	PO	577
Mouse	M	IV	53
Mouse	F	IV	49
Rat	M	PO	2379
Rat	F	PO	2055
Rat	M	IV	51
Rat	F	IV	50
Dog	M	IV	34
Dog	F	IV	38

Signs of Toxicity

Mice: hypoactivity, dyspnea, prostration, piloerection, ataxia, clonic convulsions.

Rats: hypoactivity, dyspnea, salivation, clonic convulsions.

Four beagle dogs were treated with single oral doses of labetalol hydrochloride 500, 750 and 1000 mg/kg. No deaths resulted. The following signs were observed in dogs treated with 750 mg/kg or higher: emesis, redness of the mucous membranes, dry nose, mild sedation, slight tachycardia, bradypnea and hypothermia.

In beagle dogs, death occurred within 15 minutes of an IV dose of 40 mg/kg and was preceded by prostration. Survivors (5/12) from doses up to 100 mg/kg, experienced temporary lethargy, hypotension and bradycardia.

Subacute Toxicity

In rats, labetalol hydrochloride was administered by gavage in doses of 0, 50, 110 and 250 mg/kg/day (24 rats/dose) for 3 months. Polydipsia, dilute polyuria, proteinuria, elevated serum liver enzymes, polycythemia and nephrocalcinosis were noted. Cellular casts were found in the urine of animals in the high dose group.

Labetalol hydrochloride was administered IV to beagle dogs (10/sex) in doses of up to 20 mg/kg/day for 15 days. No drug-induced toxicity was noted.

Chronic Toxicity

Labetalol hydrochloride was administered by gavage to Wistar rats for 1 year in doses of 1, 100, 140, and 200 mg/kg/day (32 rats/dose). A slight, but statistically significant lengthening of the clotting time was found in all treated groups. Increased plasma levels of alkaline phosphatase, SGOT and SGPT were noted towards the end of the study period. Increases in heart weights were observed in all treated groups.

Labetalol hydrochloride was administered orally to beagle dogs in doses of 0, 25, 50 and 100 mg/kg once daily, 7 days per week for 52 weeks (6 dogs/dose).

Muscle tremors, abnormal gait, vomiting and loose stools of abnormal colour were observed at 50 and 100 mg/kg doses. Occult blood was occasionally seen in the faeces of animals in the high dose group.

One male and one female in the high dose group died during testing. Both showed gastrointestinal mucosal congestion and the female had increased blood urea and SGPT levels. Cause of death was not established.

Body weight gain was significantly lower in high dose males.

Four dogs developed minor corneal ulcers. Reflex tear secretion was normal in all animals.

Heart rate was reduced at all doses (ECG recordings).

No drug-related changes in gross weight of organs or histopathological findings were noted.

Reproduction and Teratologic Studies

Labetalol hydrochloride was administered by gavage to AHA rats in doses of 0, 50, 100 and 200 mg/kg/day (32 rats/dose) for 10 weeks prior to mating and throughout the mating period. A dose-related reduction in fertility was observed in the treated animals (F₀ generation). No reproductive impairment was noted in the subsequent F₁ and F₂ generations.

Primiparous Wistar rats were administered labetalol hydrochloride by gavage throughout pregnancy (19 days) in doses of 0, 125, 150, 175, 200, 250 and 300 mg/kg/day (8 rats/dose). No congenital malformations were observed. There was a retardation of foetal growth in the 250 and 300 mg/kg dose groups.

Mated female New Zealand white rabbits were administered labetalol hydrochloride by gavage from day 7 through day 19 of gestation, in doses of 0, 50, 100 and 200 mg/kg/day (14 rabbits/dose). There were no apparent drug-related effects on the course of pregnancy or foetal development.

Mutagenicity Studies

Studies with labetalol hydrochloride, using dominant lethal assays in mice and rats, and exposing microorganisms according to modified Ames tests, did not show any evidence of drug-related mutagenicity.

Carcinogenicity Studies

Labetalol hydrochloride was admixed in the diet of CR/H Glaxo mice in doses of 0, 100, 140 and 200 mg/kg/day for 18 months (100 mice/dose). No drug-related carcinogenicity was apparent.

Sprague-Dawley CD rats were fed labetalol hydrochloride in doses of 0, 100, 140 and 225 mg/kg/day for 24 months (110 rats/dose). Increased incidences of ovarian cysts, corneal lesions, reactive lymphoid hyperplasia of the cervical lymph nodes, and enlargement of seminal vesicles were noted in the active treatment groups. No drug-related carcinogenicity was apparent.

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