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LABETALOL: A BRIEF CURRENT REVIEW

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ABSTRACT

Labetalol is a combined α- and β-adrenoceptor antagonist, which is still currently used to treat hypertension. It acts as a nonselective competitive antagonist at β-adrenoceptors and a competitive antagonist of postsynaptic α-adrenoceptors. In this review, the pharmacokinetics, pharmacodynamics, pharmacological effects, mechanism of action, and indications of labetalol were revisited. Recent updates on the side effects and toxicities of labetalol on various bodily systems are also elaborated. A comparison between labetalol and other drugs, which are used for similar indications were also performed. Controversies regarding the usage of labetalol, either acutely or chronically, were also elaborated. Contraindications and precautions in the usage of labetalol were also discussed.

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Introduction

Labetalol is a combined α- and β-adrenoceptor blocking agent used to treat hypertension. It acts as a nonselective competitive antagonist at β-adrenoceptors as well as a competitive antagonist of postsynaptic α-adrenoceptors. It is available in intravenous and oral formulations [1]. The mechanism of action of labetalol is through blocking the actions of certain endogenous chemicals such as adrenaline on the heart and blood vessels. This blocking action resulted in the lowering of the heart rate, blood pressure, and also reducing the work-strain of the heart. Due to its both β and α blocking activity, labetalol is used in the treatment of hypertension due to pheochromocytoma, and in hypertensive emergencies [2]. According to the 7th Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), β-adrenergic blockers are one of the most suitable first-line alternatives in the treatment of hypertension, based on positive effects on the reduction of morbidity and mortality in various clinical trials [3]. Similarly, β-blockers such as labetalol are suitable as the initial treatment for the management of angina pectoris in a long-term. They are equally effective for the relief of angina pectoris (with or without hypertension) due to vasoconstriction as a response to a variety of internal and external influences. Labetalol also attenuates increased coronary vascular resistance and improves coronary hemodynamics, especially in stressed patients, in a manner that is favorable in myocardial ischemia condition [4]. Besides, the 2001 American Heart Association and American College of Cardiology (AHA/ACC) guidelines recommend starting and continuing therapy by β-blockers in all post-myocardial infarction (MI) patients for secondary prevention of MI [5].

Pharmacological class

As a compound with antagonistic effects, labetalol is a unique third-generation antihypertensive agent that can initiate both non-selective β-adrenergic antagonist actions and selective α1-adrenergic antagonist, with vasodilatory and antihypertensive properties that acts within a single substance. Labetalol is a reversible adrenoceptor antagonist with a mixture of 4 isomers with 2 pairs of chiral isomers (two centers of asymmetry). Two of the isomers are relatively inactive, while the third and fourth

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are a potent α-blocker and a potent β-blocker, respectively. Labetalol has a 3:1 ratio of β:α antagonism after oral dosing [6]. The α-blockade leads to the reduction of systemic vascular resistance, thereby lowering blood pressure without significantly altering the cardiac output and heart rate. In terms of dosage, labetalol uptake is individualized. The recommended oral daily doses range from 200 to 2400 mg/day according to the requirements of patients [6]. For example, patients with severe hypertension may need 1200 to 2400mg labetalol daily (with or without thiazide diuretics). For hypertensive emergency, a 20-mg dose via intravenous injection should be administered over 2 minutes initially followed by 40-80mg IV over 10min for a maximum of 300mg in total. Alternatively, the drug can also be administered 1-2 mg/min by continuous IV infusion until the total dose of 300mg.

Chemical structure

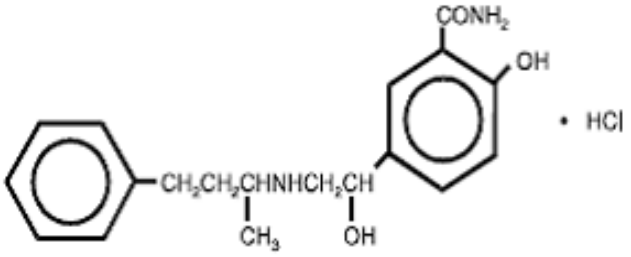

Figure 1: Chemical structure of labetalol

Table 1: Summary of labetalol information

Drug Ingredient	Labetalol hydrochloride
Proprietary Name	Trandate
Drug class	β-adrenergic receptor antagonists

Labetalol, chemically designated as 2-hydroxy-5-[1-hydroxy-2-[(1methyl-3-phenyl propyl)amino]ethyl]benzamidemonohydrochloride, has a molecular formula of C19H24N2O3•HCl and a molecular weight of 364.9 g/mol. The two chiral carbons consequently exist as 4 stereoisomers. The first 4 isomers (S,S)- and (R,S)- are inactive while the 3rd and 4th, (S,R)- and (R,R)- are potent α_1 and β blockers, respectively [6]. The fourth isomer, known as dilevalol, is made up of a mixed selective α_1 blocker and non-selective β blocker. This configuration of labetalol leads to strong agonist activity. However, as the size of substituent attached to amine become greater, the molecule is typically found to be an antagonist, as they have receptor affinity with no intrinsic activity. Labetalol is white or off-white crystalline powder in nature and is very polar in its structure. Hence, labetalol tablets should be kept at temperatures of 2-30°C in a well-closed container and protected from excessive moisture. Labetalol is most stable in solutions having a pH of 2-4 [7].

Pharmacokinetics

Labetalol can be administered either through injection or orally. In oral administration, even though administering labetalol with food delays the gastrointestinal absorption, it, however, increases the absolute bioavailability of the drug. In intravenous administration, patients are kept in a supine position to avoid hypotension. As long as the ability to tolerate an upright position is established, patients should not be involved in any ambulatory activities. Following direct IV injection, there is no dilution necessary, and labetalol must be slowly injected over 2 min at intervals of 10min. The patient's blood pressure is monitored before and 5 and 10 min after each injection [8].

Through oral administration, labetalol is completely absorbed through the gastrointestinal tract before undergoing the first-pass metabolism. The peak plasma level occurs after 1-2 h and is associated with reducing blood pressure. Following oral administration, labetalol is subjected to the first-pass metabolism in the liver and/or gastrointestinal (GI) mucosa. Due to the extensive first-pass metabolism, the absolute bioavailability of labetalol is 25% of the IV infusion. However, absolute bioavailability increases when labetalol is administered with food [9]. The hypotensive impact of the drug will appear differently depending on the administration route. Following oral administration, the effect generally takes place between 20 min to 2 hours. Meanwhile, following direct IV injection, the time taken is significantly faster, which is within 2-5min to a maximum of 5-15 min.

Labetalol is widely and rapidly diffused into the extravascular space following IV administration. Approximately 50% of labetalol is bound to plasma protein (albumin) at plasma concentrations of 0.1-50 µg/ml, and about 0.05% is bound to melanin. The apparent volume of the drug's distribution is 3.2-15.7 l/kg. Extensive metabolism of labetalol occurs mainly in the liver and some possibly in GI mucosa. Using the principal of conjugation with glucuronic acid at the secondary alcohol group, a major metabolite of O-alkyl glucuronide, with smaller amounts of O-phenyl glucuronide and N-glucuronide (inactive

glucuronide metabolites) are formed. Labetalol is widely metabolized in the liver and GI mucosa, mostly by conjugation with glucuronic acid. [10] The major metabolite is O-alkyl glucuronide, with smaller amounts of O-phenyl glucuronide and N-glucuronide (inactive glucuronide metabolites) being formed by conjugation at the secondary alcohol group [10].
Labetalol and its inactive metabolites are excreted by both liver and kidneys, thus, the drug is improbable to accumulate in the body [11]**.** These metabolites are present in plasma and are excreted in the urine and, via bile, into the feces. During the first 24 h of dosing, about 55-60% of which appears in the urine as an unchanged or conjugated drug, and about 30% is excreted in feces within four days. Less than 5% of a dose is excreted unchanged in the urine. Labetalol is not considerably eliminated (<1% of a dose) by hemodialysis or peritoneal dialysis. The plasma elimination half-life of labetalol is 6-8 hours following IV or oral administration, respectively. The elimination half-life of the drug appears to be unchanged in individuals with hepatic or renal impairment, but may be increased in patients with severe renal impairment (e.g. creatinine clearance of <10 ml/min) undergoing dialysis. Impairment of liver function requires a dosage reduction, due to a decrease in the first-pass metabolism of the medicine. The bioavailability of labetalol is substantially increased in geriatric patients (but within the reported range) and geriatric individuals [11].

Pharmacodynamics
Labetalol has a long-term action and a wide therapeutic window. Labetalol lowers blood pressure by antagonizing various adrenergic receptors and inhibiting catecholamine access to both β- and postsynaptic α-adrenergic receptor sites. Labetalol may induce vasodilation. Those who are susceptible to bronchospasms should not use labetalol unless they are intolerant of or unresponsive to other antihypertensives [6].

Mechanism of action
Labetalol selectively antagonizes α-1-adrenergic receptors and non-selectively antagonizes β-adrenergic receptors. Via oral administration, the drug has three times the β-blocking ability than α-blocking ability or in a ratio of 3:1. After intravenous administration, the ratio increases to nearly seven times or 6.9:1 to be exact. The antagonism of different receptors gives different results in patients. Antagonism of α-1-adrenergic receptors leads to vasodilation and decreased vascular resistance, followed by a reduction in blood pressure. Antagonism of β1-adrenergic receptors leads to a slight decrease in the heart rate while antagonism of β2-adrenergic receptors leads to some of the side effects of labetalol such as bronchospasms. Labetalol leads to sustained vasodilation over the long term without a significant decrease in stroke volume or cardiac output, and a minimal decrease in the heart rate [6].
Labetalol competitively blocks adrenergic stimulation of β-receptors in the vascular smooth muscle (α1-receptors), myocardium (β1-receptors), and bronchial (β2-receptors). The blockade leads to reducing the systemic arterial blood pressure, specifically through blocking β-adrenoceptor notably in the heart, and from reflex-mediated drive caused by the peripheral vasodilation and systemic vascular resistance by blocking α-adrenoceptors in peripheral arterioles. Therefore, both the α- and β-blocking actions of intravenous (IV) or orally administered labetalol reduce blood pressure in hypertensive patients. Labetalol does not reduce cardiac output after moderate exercise or at rest. Normally elevated systolic pressure during exercise is lessened by labetalol; however, diastolic pressure changes are not affected. The β2-receptor blockade inhibited the reduction of isoproterenol-induced diastolic blood pressure [12].

Pharmacological effects
Labetalol induces dose-related inhibitory effects on the tachycardia induced by Valsalva's manoeuvre and dose-related inhibitory effects on increases in heart rate and systolic blood pressure induced by exercise. Labetalol has only a few inhibitory effects on the tilting-induced tachycardia because blood pressure decreases in a dose-related manner [13]. Labetalol is a competitive and specific antagonist of the α-adrenoceptor agonist effects of locally infused noradrenaline and systemically administered phenylephrine. Besides, labetalol reduced diastolic and systolic blood pressure in the supine, standing and sitting positions [13]. The onset and duration of the α- and β-adrenoceptor antagonist effects of oral labetalol is not dissociated in time, and there is a close relationship between the pharmacological effects and alteration in the plasma concentration [13]. In comparative investigations with propranolol, similar β-antagonist effects have been proved, but propranolol is 4-6 times more potent [13]. However, a detailed comparison is complicated by the combined α- and β-adrenoceptor antagonist effects of labetalol, particularly as the predominant impact of labetalol in normotensive subjects is reducing blood pressure; whereas the predominant effect of propranolol is to reduce heart rate [13]. Also, in normal subjects, propranolol inhibits ventilatory function, while labetalol in an equal amount of β-adrenoreceptor-blocking doses does not have such an effect [13].

Clinical uses/ Indications
Labetalol is widely used to treat severe hypertension, hypertensive episodes following acute myocardial infarction, general hypertension management (alone or combined with other antihypertensive drugs), as well as for hypertensive anesthesia [14]. In treating hypertensive emergency (severe hypertension), labetalol is parenterally used for an immediate decrease in blood pressure, e.g. for the control of blood pressure in patients with pheochromocytoma and in pregnant women with pre-eclampsia. Labetalol is the only β-blocker for the treatment of postoperative and intraoperative hypertension and for parenteral management of hypertensive emergencies [14]. In hypertensive episodes following acute myocardial infarction, the presence

of high blood pressure may increase the risk of a heart attack. These problems may be less likely to occur if blood pressure is controlled. Labetalol, a β-blocker, acts through affecting the response to nerve impulses in specific parts of the body such as the heart. Therefore, the heart rate slows and blood pressure decreases. When the blood pressure drops, the oxygen and blood amount increases to the heart.

Labetalol is also used in hypotensive anesthesia. Controlled hypotension during anesthesia is crucial to reduce bleeding resulting from surgical procedures. Oral labetalol pre-medication considerably decreases preoperative mean arterial pressure and heart rate in patients and allows blunting of the pressure reflexes associated with induction of tracheal intubation and anesthesia [15]. Premedication with oral labetalol before hypotensive anesthesia effectively decreases blood loss, heart rate, and the amount of blood transfused with a better surgical field quality. Labetalol infusion allows appropriate hemodynamic control during the operation manifested since it significantly reduces MAP with a subsequent significant decrease of operative field bleeding [15]. The low-dose infusion and oral pre-medication of labetalol as a modality for hypotensive anesthesia improve anesthetic and surgical outcomes [15].

Adverse effects

Labetalol is normally well tolerated. Adverse effects are minor but can include fatigue, dizziness, and postural hypotension less commonly fever, impotence, and depression [16]. Most side effects are transient and mild and occur early in the treatment course. The more prevalent side effects are dizziness (1-20%), lightheadedness (1-20%), nausea (≤19%), tingling sensation of the scalp (4-12%), and fatigue (1-11%). [17] However, several other less common adverse effects in different body systems have been reported. In the cardiovascular system, symptomatic postural hypotension may occur if the patient is tilted or allowed to assume the upright position within 3h of receiving labetalol [18]. Occasional bradycardia, ventricular arrhythmia, and heart block have also been reported. In peripheral and central nervous systems, paresthesia is likely to occur that is usually described as scalp tingling. In most cases, it is transient and mild and usually occurs at the beginning of treatment. In patients suffering from collagen disorders e.g. systemic lupus erythematosus, drug fever occasionally occurs, and they are positive for anti-nuclear antibodies. There are some reports of side effects on eyes including blurred vision, eye irritation, and dry eyes. In the immunological system, antimitochondrial antibodies are formed in some cases. In hepatic system, hepatic necrosis and the first sign or symptom of liver dysfunction such as unexplained “flu-like” symptom, right upper quadrant pain, jaundice, persistent anorexia, dark urine, and pruritus have been reported. Hepatitis and cholestatic jaundice are manifested through elevated liver function tests. In the musculoskeletal system, muscle cramps, toxic myopathy, and tremors have been reported in pregnant women prescribed with labetalol for hypertension [18].

Labetalol might induce bronchospasm (wheezing) in the respiratory system. In skin and appendages, labetalol might induce rashes of various types such as generalized maculopapular, lichenoid reaction, urticaria, bullous lichen planus, psoriasiform, and facial erythema. Peyronie's disease and reversible alopecia could also be seen after labetalol intake. Difficulty in micturition, including acute urinary bladder retention, has also been reported in the urinary system. There are rare reports of hypersensitivity (rash, urticaria, pruritus, angioedema, dyspnoea) and anaphylactoid reactions. The use of labetalol tablets is unlikely to impair the patients’ ability to operate machinery or drive [19]. However, it should be considered that sometimes fatigue or dizziness may occur [19]. This adverse effect is not relevant in IV labetalol injection, as the onset of action is fast compared to oral intake. If the benefit of labetalol outweighs the potential risk, it should be administered only during the first three months of pregnancy [19]. The possibility of the consequences of α- and β-adrenoceptor blockade in the neonate and fetus should not be disregarded because labetalol crosses the placental barrier [19]. Neonatal and perinatal distress (hypothermia, hypoglycemia, respiratory depression, hypotension, bradycardia) have been rarely reported [19]. These symptoms might develop 1-2 days after birth. Response to supportive measures (glucose and IV fluids) is usually rapid but with the risk of severe pre-eclampsia, especially after prolonged supportive treatment [19]. Recovery from labetalol adverse effects in neonates could take longer. This may be associated with diminished liver metabolism in premature infants. Neonatal and intra-uterine deaths due to labetalol have been reported, but other medicines (respiratory depressants, vasodilators) and the effect of prematurity, intrauterine growth retardation, and pre-eclampsia, could also be implicated [19].

Toxicity

Hepatoxicity: Labetalol therapy is associated with mild-to-moderate elevations of serum aminotransferase levels in up to 8% of patients, a rate far higher than with other β-blockers [20]. However, these elevations are often transient, associated with no symptom, and can be resolved even with continued therapy [20]. Idiosyncratic, clinically apparent hepatic injury due to labetalol is rare, but numerous cases have been reported in case series and also in isolated case reports [20]. The liver injury usually arises after 4-16 weeks of therapy and an increase in the serum enzymes is typically hepatocellular with an acute hepatitis-like onset and course [20]. Although in most cases, the liver problems are resolved once labetalol is stopped, several cases of acute liver failure need for emergency liver transplantation, or death associated with the administration of labetalol, especially in delays in discontinuing the drug [20]. Labetalol is a β-blocker with the highest apparent risk of clinically causing hepatic injury [20].

Hypotension: Excessive hypotension which is posture sensitive and, sometimes, excessive bradycardia. Patients must be placed supine, and their feet elevated if necessary to increase blood flow to the brain. If the overdose of labetalol HCl follows

gastric lavage, oral ingestion, or drug-induced emesis (using ipecac syrup) may be useful to remove the drug shortly after administration [21].

Renal Failure: Oliguric renal failure has been reported after a massive orally overdose of labetalol.

Cardiac failure: Congestive heart failure, intraventricular conduction delays, and atrioventricular blocks, can occur with more severe poisoning. Coma and cardiopulmonary arrest can develop secondary to severe hypotension or bradycardia. In some of the patients with latent cardiac failure, continued myocardial depression with β-blocking agents over some time can cause cardiac failure. β-blockade has a potential risk of more depressing myocardial contractility and more severe failure. Labetalol HCl does not eliminate the inotropic function of digitalis on the heart muscle [22].

Bronchospasm: Bronchospasm may develop, particularly in patients with asthma or COPD, and respiratory depression may develop in patients with severe hypotension. Labetalol with β-2 adrenergic blocker may cause parasympathetic action, which results in bronchial muscle contraction.

Hypoglycemia: Hypoglycemia may develop in diabetics or those with decreased glycogen stores. Blockade of β2-adrenergic receptors would be expected to decrease glycogenolysis in the skeletal muscle and liver and potentially lead to a decrease in the plasma glucose level. Hypoglycemia may be more likely when there is hepatic glycogen depletion as a result of fasting. Labetalol is a non-selective β-blocker it has an α-blocking effect, too. When given intravenously, the ratio of α-blockade to β-blockade is about 1:7. Blockade of β2 and α-adrenergic receptors can decrease glycogenolysis in the liver, while blockade of β2-adrenergic receptors would also decrease glycogenolysis in skeletal muscle. But there are a few reports regarding labetalol-induced hypoglycemia, other than the increased risk of neonatal hypoglycemia secondary to maternal labetalol therapy, which should be considered in the treatment process.

Comparison with other drugs with similar indications

The affinity of labetalol to α-receptors is less than that of phentolamine, but labetalol is α_1-selective. Its β-blocking ability is slightly less than that of propranolol. Hypotension induced by labetalol is accompanied by less tachycardia in comparison to phentolamine and similar α blockers [13].

Labetalol vs. α-methyldopa: Labetalol has been endorsed for its superiority over other β-blockers as a first-line drug for hypertension in pregnancy (pre-eclampsia). This has been proven from a particular study in which labetalol and α-methyldopa were introduced in pregnant women with recorded diastolic blood pressures above 100 mmHg. (Labetalol vs. methyldopa in the treatment of hypertension induced by pregnancy [23]. From the study, it was concluded that labetalol is effective and safe in the control of hypertension complicating pregnancy. This is because labetalol can boast of some characteristic merits over α-methyldopa. It is free from postural hypotension due to α-receptor blockade, altered sleep pattern, postpartum depression, galactorrhea, and constipation side effects. It leads to proper and sustained control of blood pressure and also prevents tachycardia. Labetalol does not affect the uteroplacental blood flow. In antepartum fetal surveillance, α-methyldopa causes falsely non-reassuring fetal heart patterns on electronic fetal monitoring. In renal failure, α-methyldopa accumulates and sometimes complicates pre-eclampsia. Finally, labetalol appears to better prevent the developmental retardation of the fetus [24].

Labetalol vs. atenolol: Labetalol lowers the risk of precipitating the asthmatic attacks. This is proved from a placebo-controlled double-blind study, in which the effects of single doses of labetalol (300mg) and atenolol (100mg) were evaluated in 11 patients with asthma and hypertension. When compared with atenolol, labetalol significantly decreased the effect of inhaled salbutamol on forced expiratory volume in 1 second (FEV1). β-adrenoceptor blocking medicines cannot be recommended in patients with airways obstruction, which is in marked contrast to the effects of non-selective β-adrenoceptor blockers, where baseline values after isoprenaline were not achieved. If such differences were confirmed in direct comparison, they would support the hypothesis that α-adrenergic receptors are involved in the control of bronchial muscle tone in asthmatics [25]. Labetalol is relatively safer than pure non-selective β-adrenoceptor blocking drugs.

Labetalol vs. metoprolol: In the treatment of patients with mild to moderate hypertension, labetalol and metoprolol have the same effectiveness and safety. The antihypertensive effect of oral metoprolol and labetalol was assessed in 91 patients with mild to moderate hypertension (diastolic blood pressure of 90-115 mmHg) in a double-blind parallel-group multicentre clinical trial [26]. Both drugs decreased heart rate; but, metoprolol affected significantly better. Nausea, dyspepsia, and dizziness were more prevalent with labetalol, and bradycardia was more familiar with metoprolol. At the end of this period, both treatment groups had baseline levels of blood pressure, but the heart rate exceeded the baseline in patients who were treated with metoprolol. Furthermore, 2 of the patients had a symptomatic rebound in their hypertension that required treatment; none of the labetalol-treated patients experienced this rebound. This indicates the potential safety advantage of labetalol. In patients with angina pectoris and hypertension, it was reported that there are no adverse withdrawal effects after the discontinuation of labetalol. The combined α- and β-adrenergic blocking property of labetalol was hailed as a pharmacological advancement that provided a breakthrough conceptual approach for managing patients with hypertension at the time [26].

Labetalol vs. propranolol: Ventricular arrhythmias are common in patients with mitral valve prolapse. 10 patients with documented ventricular arrhythmia and echocardiographically confirmed mitral valve prolapse were included in a particular study with the aim of evaluating the combined α- and β-blockade (labetalol) value in comparison to β-blockade alone (propranolol) in the treatment of ventricular arrhythmia [27]. Labetalol and propranolol both decreased the blood pressure and heart rate response. However, labetalol was more effective in the control of ventricular arrhythmias, especially in patients with

mitral valve prolapse who had a symptomatic premature ventricular contraction and no inducible ventricular tachycardia. However, life-threatening arrhythmias have been reported and may cause sudden death. These results showed that in mitral valve prolapse syndrome, α-adrenergic receptors are important in the pathogenesis of ventricular arrhythmias and that labetalol may be a suitable alternative to isolated β-blockade that is worth considering in the management of this condition.

Controversies associated with labetalol

Hepatocellular damage is an unusual complication of antihypertensive therapy. It has been most often described as associated with methyldopa. A recently reported fatal case of hepatocellular necrosis was received by the Food and Drug Administration (FDA) in which labetalol was strongly implicated as the offending agent. Although at the time of initial marketing, labetalol was known to cause reversible liver enzyme elevations, jaundice, and cholestasis, the serious hepatocellular disease associated with the drug had not been reported previously [28]. The FDA has so far received 11 case reports (3 fatal) in the US in which liver damage was associated with labetalol. Follow-up with each of the reporting physicians failed to provide laboratory or historic evidence for other drug-induced, toxic, or viral causes of liver damage, and the case series showed no historical and demographic risk factors that would be expected if non-A, non-B hepatitis were the cause. It is possible, however, that the superimposed alcohol use in a case may have potentiated an underlying primary toxic effect of labetalol. Labetalol is the β-blocker with the highest risk for developing clinically apparent liver damage [20].

To illustrate the depth of labetalol-induced liver injury, a 63-year-old woman developed nausea and dark urine approximately three months after starting labetalol (200 mg daily) for hypertension. This patient developed an acute hepatitis-like clinical picture three months after starting labetalol. Despite not being properly diagnosed, labetalol was continued, though the patient on her own stopped taking it and did not return to further management of her hypertension. When seen six months later, labetalol was restarted, and a similar clinical syndrome arose 2-3 months later, but with a progressive and ultimately fatal course. Labetalol has been implicated in at least 12 cases with acute hepatic damage, mainly with a hepatocellular pattern of enzymes elevation, a latency period of 2-16 weeks, and emergency liver transplantation or fatal outcome in several cases. In contrast, most cases with clinically apparent hepatic injury due to other β-blockers have had a milder course and outcome and a shorter latency period (2-12 weeks). Moreover, acute liver injury has been described with dilevalol that is one of the 4 stereoisomers of labetalol with predominantly β-adrenergic blocking activity [29].

Contraindication/ Precautions pertaining to labetalol

Hyperthyroidism, thyroid disease, thyrotoxicosis: In patients with thyrotoxicosis or hyperthyroidism, labetalol should be administered with caution because β-blockers can mask tachycardia that is a useful parameter in monitoring thyroid diseases. In a patient with hyperthyroidism, abrupt withdrawal of β-blockers can cause a thyroid storm. However, β-blockers are useful in the treatment of conditions related to hyperthyroid. [8]

Phaeochromocytoma: Labetalol has been used to reduce blood pressure in patients with pheochromocytoma because of its impacts on blocking both α and β receptors. However, contradictory hypertensive episodes have occurred in a small number of these patients while receiving labetalol. Generally, an α-blocking agent is recommended before starting β-blocker therapy. [8]

Cerebrovascular disease: Due to the potential effects of β-blockade on blood pulse and pressure, in patients with cerebrovascular insufficiency or stroke β-blockers should be administered with caution. Alternative treatment should be considered if symptoms or signs of decreased cerebral blood flow develop after initiation of labetalol. [8]

Acute bronchospasm, emphysema, chronic obstructive pulmonary disease (COPD), bronchitis, and asthma: Labetalol is contraindicated in patients with asthma and should be avoided in acute bronchospasm since β-blockade inhibits bronchodilation. Labetalol should be administered at the lowest effective dose or even avoided where possible in patients with nonallergic bronchospastic disease [e.g., bronchitis, emphysema, COPD]. In patients with pulmonary diseases, β1-selective β-blockers are preferred to nonselective agents e.g. labetalol; however, all β-blockers should be administered with caution in these patients, especially in treatment with high-dose. [8]

Diabetes mellitus: β-blockers have been shown to increase the risk of developing diabetes mellitus in hypertensive patients. Labetalol should be administered with caution in diabetic patients with poor control, especially brittle diabetes. β-blockers can enhance or prolong hypoglycemia by interfering with glycogenolysis, which may be less pronounced with β1-selective β-blockers than nonselective agents. [8]

Conclusion

Labetalol mechanism of action is the result of combined α1-adrenergic and β-adrenergic receptors blockade, with a greater effect on β-receptors as compared to α-receptors. Labetalol can be administered orally, as a bolus or continuous infusion. Labetalol administration has been reported to produce negative inotropic and chronotropic impacts, thus making labetalol one of the suitable agents in the management of hypertensive crises. Labetalol has been endorsed for its superiority over other β-blockers as a first-line drug for hypertension in pregnancy (pre-eclampsia). Serious side effects that have been reported include hepatotoxicity, hypotension, bradycardia, cardiac failure, renal failure bronchospasm, and hypoglycemia.

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