WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 13, Issue 4, 981-993. Review Article ISSN 2277–7105

A BRIEF REVIEW ON LABETALOL

K. Chandrika[1]*, Dr. D. Rama Brahma Reddy[2] and Dr. T. J. Mohan Rao[3]

[1]Doctor of Pharmacy (PharmD) V. Year, Department of Pharmacy Practice, Nalanda Institute of Pharmaceutical Sciences. Kantepudi (V), Sattenapalli (M), Dist. Guntur-522438 Andhra Pradesh, India.

[2]Principal, Department of Pharmacognosy and Phytochemistry, Nalanda Institute of Pharmaceutical Sciences. Kantepudi (V), Sattenapalli (M), Dist. Guntur-522438 Andhra Pradesh, India.

[3]Associate Professor, Department of Pharmacology, Nalanda Institute of Pharmaceutical Sciences. Kantepudi (V), Sattenapalli (M), Dist. Guntur-522438 Andhra Pradesh, India.

Article Received on
31 December 2023,

Revised on 21 Jan. 2024,
Accepted on 11 Feb. 2024

DOI: 10.20959/wjpr20244-31413

***Corresponding Author**
K. Chandrika
Doctor of Pharmacy (PharmD) V. Year, Department of Pharmacy Practice, Nalanda Institute of Pharmaceutical Sciences. Kantepudi (V), Sattenapalli (M), Dist. Guntur-522438 Andhra Pradesh, India.

ABSTRACT

Labetalol is an orally active adrenoceptor blocking is competitive antagonist at both alpha and beta adrenoceptor sites. Its beta blocking effects resemble those of propranolol, but its overall hemodynamic effects are akin to those of combination of propranolol and an alpha adrenoceptor blocking drugs such as phenoxybenzamine. Unlike with conventional beta adrenoceptor blocking drugs, acute administration of labetalol reduces peripheral vascular resistance and blood pressure and has little effect on cardiac output. Labetalol may be particularly useful in some patients whose blood pressure is not adequately controlled by beta adrenoceptor blocking drugs alone or combined with diuretics but possibly at the expense of postural hypotensive effect. Labetalol is more potent at beta that alpha1 adrenoceptors in man, the ratio of beta-alpha antagonism is 3:1 after oral and 6:9:1 after intravenous administration. Labetalol is readily absorbed in man after oral administration, but the drug, which is lipid soluble, undergoes considerable hepatic first pass metabolism and has an absolute bioavailability of approximately 25%. Other reported side effects of the drug include gastrointestinal disturbances, tiredness, headache,

scalp tingling, skin rashes, urinary retention. In this review, the pharmacokinetics, pharmacodynamics, pharmacological effects, mechanism of action, indications of labetalol were revisited. A comparison between labetalol and other drugs, contraindications in the usage of labetalol were also discussed.

KEYWORDS: Labetalol, Alpha- adrenoceptor antagonist, Beta adrenoceptor antagonist, Hypertension, Pharmacology.

INTRODUCTION

Labetalol is one of the most commonly used antihypertensive medications for the treatment of hypertension during pregnancy, and increasingly common and leading cause of maternal mortality and morbidity worldwide. Labetalol is a reasonable choice for treatment of severe or nonsevere hypertension in pregnancy. Labetalol is a combined alpha and beta adrenoceptor blocking agents used to treat hypertension it acts as a nonselective competitive antagonist at beta aderenoceptor as well as a competitive antagonist of post synaptic alpha adrenoceptors. It is available in intravenous and oral formulations. The mechanism of action of labetalol is through blocking the action of certain endogenous chemicals such as adrenalin and heart and blood vessels this blocking action resulted in lowering of heart rate, blood pressure and also reducing the work strain of heart due to its both alpha and beta blocking activity, labetalol is used in the treatment of hypertension due to pheochromocytoma and in hypertensive emergencies. Beta adrenergic blockers are one of the most suitable first line alternative in the treatment of hypertension based on positive effects on the reduction of morbidity and mortality in various clinical trials. Similarly, beta blockers such as labetalol are suitable as the initial treatment for the management of angina pectoris in a long term.

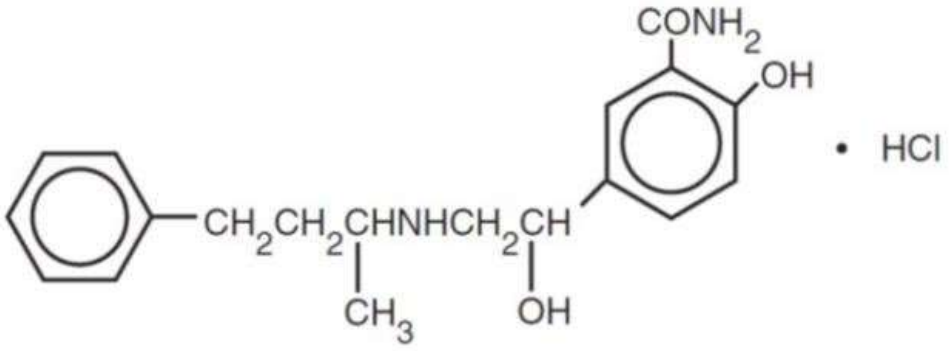
PHARMACOLOGICAL CLASS

As a compound with antagonistic effects, labetalol is a unique third generation antihypertensive agent that can initiate both non-selective beta -adrenergic antagonist actions and selective alpha1-adrenergic antagonist, with vasodilators and antihypertensive properties that acts within a single substances. Labetalol is a reversible adrenoceptor antagonist with a mixture of 4 isomers with 2 pairs of chiral isomers.

The recommended oral daily doses range from 200 to 2400mg / day according to the requirements of patients. For example, patient with severe hypertension may need 1200 to 2400mg labetalol daily (with or without thiazide diuretics). For hypertensive emergency, a

20mg dose via intravenous injection should be administered over 2minutes initially followed by 40 to 80mg IV over 10min for a maximum of 300mg in total. Alternatively the cam also be administered 1to 2mg / min by continuous IV infusion until the total dose of 300mg.

Chemical structure



Chemical structure of labetalol

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] benzamide monohydrochloride, has a molecular formula of $C_{19}H_{24}N_20_3$.HCL and a molecular weight of 364.9g/mol. The two chiral carbons consequently exists 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 and β blockers, respectively. The fourth isomer, known as dilevalol, is made up of a mixed selective α blockers and non selective β blocker. This configuration of labetalol leads to strong agonist activity. However as the size of substituents attached to amine become greater, the molecule is typically found to be 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 temperature of 2-30^{o}C in a well-closed container and protected from excessive moisture. Labetalol is most stable in solutions having a pH of 2-4.

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, increase 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 2mins at intervals of 10mins. The patient's blood pressure is monitored before and 5 and 10 min after each injection.

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 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. The hypotensive impact of the drug will appear differently depending on the administration route. Following oral administration, the effect generally takes place between 20 mins to 2 hours. Meanwhile following direct IV injection, the time taken is significantly faster, which is within 2-5 mins to a maximum of 5-15mins. 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 concentration of 0.1-50ug/ml, and about 0.05% is bound to melanin. The apparent volume of the drugs distribution is 3.2-15.7L/kg. Extensive metabolism of labetalol occurs mainly in the liver and some possibly in GI mucosa. Using the principle 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. The major metabolite is O- alkyl glucuronide, with smaller amounts of O-phenyl glucuronide and N-glucuronide being formed by conjugation at the secondary alcohol group. Labetalol and its inactive metabolites are excreted by both liver and kidneys; thus, the drug is improbable to accumulate in the body. These metabolites are present in plasma and are excreted in the urine and via bile, into the -feces. During the first 24 hours of dosing, about 55-60% of which appears in the urine as an unchanged or conjugated drug, and about 30% is ex 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 6-8hrs 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 (e.g. creatinine clearance of ≤ 10ml/min) undergoing dialysis. Impairment of liver function require 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.

Pharmacodynamics

Labetalol has a long-term action and a wide therapeutic window. Labetalol lower 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 antihypertensive.

Mechanism of action

Labetalol selectively antagonizes α-1- adrenergic receptors and non-selectively antagonize β-adrenergic receptors. Vis oral administered the drug has three times the β-blocking ability or in a ratio of 3:1. After intravenous administered the ratio increases to nearly seven or 6.9:1 to be ads to slight decrease in the heart rate while antagonism of β_2-adrenergic receptors leads to some of the side effects of labetalol such as bronchospasms. Labetalol leads exact. The antagonism of different reception 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 decreases in heart rate while antagonism of β2- adrenergic receptors leads to some of the side effects of labetalol such as bronchospasms. Labetalol leads to the sustained vasodilation over the long term without significant decreases in stroke volume or cardiac output, and minimal decreases in the heart rate.

Labetalol competitively blocks adrenergic stimulation of β-receptors in the vascular smooth muscle (α1-receptors), myocardium (β1-receptors), 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 reduced 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.

Pharmacological effects

Labetalol induces dose related inhibitory effects on the tachycardia induces by Valsalva's man oeuvre and dose related inhibitory effects on increases in the 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. Labetalol is a competitive and specific antagonists 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. The onset and duration of the α- and β- adrenoceptor antagonist's effects of oral labetalol is not dissociated in the time, and there is a close relationship between the pharmacological effects and alteration in the plasma concentration. In the comparative investigation with propranolol, similar β-antagonist effects have been proved, but propranolol is 4-6 times more potent. However a detailed comparison is complicated by the combined α-andβ adrenoceptor antagonist effects of labetalol, particularly as the predominant impact of labetalol in normotensive subjects is reducing blood pressure; where as the predominant effect of propranolol is to reduce heart rate. Also, in normal subjects, propranolol inhibits ventilator function, while labetalol in an equal amount of β-adrenoreceptor-blocking doses does not have such an effect.

Clinical uses/Indications

Labetalol is widely used to treat sever hypertension, hypertensive episodes following acute myocardial infraction, general hypertension management (alone or combined with other antihypertensive drugs), as well as for hypertensive anesthesia. In treating hypertensive emergency (sever hypertension), labetalol is parenteral 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. In hypertensive episodes following acute myocardial infraction, the presence of

high blood pressure may increase the risk of heart attack. This problem may be less likely to occur if blood pressure is controlled. Labetalol, a β-blocker, acts through affecting the response to nerve impulse in specific parts of the body such as the heart. Therefore, the heart rate slows and blood pressure decrease. 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 induction and anesthesia.

Adverse effects

Overall, labetalol is usually well tolerated. Most adverse effects are typically mild and transient. As previously described above, symptomatic postural hypotension is a potential occurrence if patients are tilted or allowed to change positions from the supine or seated position to standing too quickly. This is especially important in the post -operative period when managing a hypertensive patient with labetalol who can otherwise ambulate to the bathroom. Increased sweating, as well as flushing, have been reported with the use of labetalol. It seems the incidence of adverse reactions after administering labetalol seems to be dose-dependent.

Labetalol might induce bronchospasm in the respiratory system. In skin and appendages, labetalol might induce rashes of various types such as generalized maculopapular, lichenoid reaction, urticarial, bullous lichen planus, psoriasiform and facial erythema. As with all beta-blockers, labetalol has negative inotropic effects and has the potential to cause acute left ventricular failure if given in sufficiently large enough doses to those patients who have in paid functions of the left ventricle. Sudden withdrawal of beta blockers can results in increased sensitivity to catecholamine's. This up regulation can lead tachyarrhythmia's, acute hypertensive crises, and palpitations, although this is more common with chronic use.

CONTRAINDICATION

Labetalol is contraindicated in people with overt cardiac failure, greater than first degree heart block, severe bradycardia, cardiogenic shock, severe hypotension, anyone with a history of obstructive airway disease including asthma and those with hypersensitivity to the drug.

SIDE EFFECTS

Common

- Neurogenic: Headache (2%), dizziness (11%)
- Gastrointestinal: Nausea (6%), dyspepsia (3%)
- Cholinergic: Nasal congestion (3%), ejaculation failure (2%)
- Respiratory: dyspnea (2%)
- Other: fatigue (5%), vertigo (2%), orthostatic hypotension.

Rare

- Fever
- Muscle cramps
- Dry eyes
- Heart block
- Hyperkalemia
- Hepatotoxicity
- Drug eruption similar to lichen planus.

TOXICITY

Supportive care and close monitoring are the staples of treatment for an overdose of beta blocker with the addition of glucagon for severe refractory hypotension and bradycardia. Glucagon provides several important clinical effects when used for the beta blocker overdose. It provides an increase in the heart rate and improves both myocardial contractility as well as atrio ventricular conduction. Its mechanism of action seems to be independent of the beta-adrenergic bending site allowing it be effective. The recommended initial dose of glucagon to reverse severe symptomatic beta blockade is 50mcg/kg IV as a loading dose, followed by an infusion of 12 to 50 mg/hour IV, titrated to clinical response and improvement.

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

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

Hepatotoxicity: 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 beta-blockers. However, these elevations are often transient, associated with no symptoms, and can be resolved even with continued therapy.

Cardiac failure: Congestive heart failure, intra ventricular conduction delays, and atrio ventricular blocks, can occur with more sever poisoning. Coma and cardiopulmonary arrest can develop secondary to sever hypotension or bradycardia.

COMPARISION WITH OTHER ANTI HYPERTENSIVE DRUGS

Clear pharmacological differences, for e.g., the possession or not of α-receptors- blocking activity, is likely to lead to differing therapeutic response, in particular leading to swifter reduction of raised blood pressure. On other hand comparison between anti-hypertensive drugs is often difficult.

- **LABETALOL VS PROPRANOLOL**

Labetalol and propanol 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. Ventricular arrhythmias are common in patients with mitral valve prolapse. Ten patients with documented ventricular arrhythmia and echocardiographicallly confirmed mitral valve prolapse were included in a particular study with the aim of evaluating the combined alpha and beta blockade (labetalol) value in comparison to beta blockade alone (propranolol) in the treatment of ventricular arrhythmia.

- **LABETALOL VS ATENALOL**

Labetalol lowers the risk of precipitating the asthmatic attacks. This is proved from a placebo controlled doubled blind study, which the effects of dose of labetalol (3mg) 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 force expiratory volume in 1sec. Labetalol has been compared with other β-adrenoceptor-blocking drugs.

- **LABETALO 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 in a double- blind parallel- group multicenter clinical trial. Both drugs decreased heart rate but metoprolol affected better. Nausea, dyspepsia, and dizziness were more prevalent with labetalol, and bradycardia was more familiar with metoprolol.

- **LABETALOL AND BETA-BLOCKERS PLUS HYDRALLAZINE**

A double-blind comparative study in mild to moderately hypertensive found labetalol 600mg twice daily was approximately equivalent to pindolol 15mg twice daily plus hydralazine 50mg three times daily. In a further fixed dose randomized study in 12 patients with mild hypertension, who received methylclothiazide 5mg throughout, labetalol 300mg twice daily, was equally effective as propranolol 80mg twice daily, better than hydralazine 50mg twice daily; but although labetalol was similar to the combination of propranolol plus hydralazine in the standing position, the combination was more effective. The decreases in blood pressure were greater with propranolol plus dihydralazine, with the exception of the standing systolic blood pressure.

LABETALOL IN PREGNANCY INDUCED HYPERTENSION

Labetalol is important to treat high blood pressure during pregnancy. This will help you and your baby to stay healthy. You can take labetalol while you are pregnant. Labetalol can effect the baby's growth in the womb so you may be offered extra scans to check that your baby is growing ok. There is also a small chance that labetalol can affect a baby blood sugar levels just after birth. For this reason your baby may have their blood sugar levels monitored in hospitals for the first 24 hours to make sure everything is ok before you go home.

As well as taking any prescribed medicines, you can help high blood pressure in pregnancy by making some key life style changes;

- Stop smoking in pregnancy
- Avoid alcohol during pregnancy
- Exercise in pregnancy regularly
- Have healthy diet throughout pregnancy
- Try to avoid stress

We prospectively studied the effects of oral labetalol therapy in patients with moderate to severe pregnancy induced hypertension. The outcome variables were blood pressure control, effect on umbilical artery flow velocity wave forms (UAFVW) and fetal outcome. 42 patients

were recruited, all had moderate to severe PIH. The mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) on entry were 154±7mmHg and 104±5mmHg, respectively. All had significant proteinuria. After one week on labetalol therapy, 85% of patients had their blood pressure controlled. The reduction in both SBP and DBP was statistically significant. There were no significant changes in UAFVW, resistance index (RI), uric acid or platelets. The mean fetal age on entry was 246±10 days while gestation and delivery is 258±17 days. The mean birth weight was 2712±609g. No perinatal mortality occurred in the study. Labetalol is an effective drug in controlling blood pressure and does not adversely affect the UAFVW. No neonatal problems were attributed directly to the drug. Labetalol allows safe prolongation of pregnancies complicated by PIH.

CONCLUSION

Labetalol mechanism of action is result of combined α1 adrenergic and β adrenergic receptor blockade, with a greater effect on beta receptor as compared to α receptor. Labetalol can be administered orally, as bolus or continues infusion. Labetalol administration has been reported to produce negative inotropic and Chrono tropic impacts, thus making labetalol one of the suitable agents in the management of serious side effects that have been reported include hepatotoxicity, hypotension, cardiac failure, renal failure, bronchospasm and hypoglycemia. Labetalol has been endorsed for its superiority over other β blocker as a first line drug for hypertension in pregnancy.

REFERENCES

1. McCarthy EP, Bloomfield SS. Labetalol: a review of its pharmacology, pharmacokinetics, clinical uses and adverse effects. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, Jul. 8, 1983; 3(4): 193-217.
2. Yuen PH. Taddei CR, Wyka BE, Chaudry IA. Compatibility and stability of labetalol hydrochloride in commonly used intravenous solutions. American journal of hospital pharmacy. 1983 Jun 1; 40(6): 1007-9.
3. Kanto JH. Labetalol in the treatment of angina pectoris. International journal of clinical pharmacology, therapy, and toxicology, Mar., 1987; 25(3): 166-74.
4. Katz Ung BG. Basic and clinical pharmacology. McGraw-Hill Education, 2017; 1203.
5. McEvoy GK. AHFS Drug Information 93. Bethesda: American Society of Hospital Pharmacists, 1993; (Plas Supplements. 1993), 1063.

6. Labetalol hydrochloride drug summary. https://www.pdr.net/drug-summary/Labetalol-Hydrochloride-Injection- labetalol-hydrochloride-1568. Accessed August 16, 2019.
7. McNeil JJ, Louis WJ. Clinical pharmacokinetics of labetalol. Clinical pharmacokinetics, Apr 1, 1984; 9(2): 157-67.
8. LABETALOL National Library of Medicine HSDB Database. https://toxnet.nlm.nih.gov/cgi- bin/sis/search/a?dbs+hsdb:@term+DOCNO+653 Accessed August 19, 2019.
9. Presolol (Labetalol hydrochloride) Product Information. https://gp2u.com.au/static/pdf/P/PRESOLOL-PL.pdf. Accessed August 19, 2019.
10. Labetalol Hydrochloride Injection, USP. https://dailymed.nlm.nih.gov/dailymed/Ida/fdaDrugXal.cfm?setid=17bb21ce- 9bb1-4603-6168-abea7fc85d17&type=display. Accessed August 22, 2019.
11. Hoffman BB. In: Brunton LL, Chabner BA, Knollmann BC, editors. Goodman and Gilman's pharmacological basis of Mansoor GA, Frishman WH. Comprehensive management of hypertensive emergencies and urgencies. Heart disease (Hagerstown, Md.), 2002; 4(6): 358-71.
12. Salem AE, Hagras AM, Abo-Ragab HM. Labetalol Hypotensive Anesthetic Protocol Paves the Way to Safe Open Abdominal Myomectomy. J Anest & Intern Care Med., 2017; 3(2): 555606, DOI: 10.19080/JAICM.2017.03.555606. .
13. Ågesen FN, Weeke PE, Tfelt-Hansen P, Tfelt-Hansen J., for ESCAPE-NET. Pharmacokinetic variability of beta-adrenergic blocking agents used in cardiology. Pharmacol Res Perspect, Aug., 2019; 7(4): e00496. [PMC free article] [PubMed]
14. Facchini E, Degiovanni A, Cavallino C, Lupi A, Rognoni A, Bongo AS. Beta- blockers and Nitrates: Pharmacotherapy and Indications. Cardiovasc Hematol Agents Med Chem., 2015; 13(1): 25-30. (PubMed).
15. Labetalol [package insert]. Spring Valley, NY: Par Pharmaceutical; 2011" (PDF). Archived from the original (PDF) on 2015-12-10. Retrieved 2015-11-03.
16. "Trandate" (PDF). Prometheus Laboratories Inc. November 2010. Retrieved 3 November 2015.
17. Shiohara T, Kano Y. "Lichen planus and lichenoid dermatoses". In Bolognia JL (ed.). Dermatology. St. Louis: Mosby, 2007; 161.
18. Bailey B. Glucagon in beta-blocker and calcium channel blocker overdoses: a systematic review. J Toxicol Clin Toxicol, 2003; 41(5): 595-602. [PubMed].

19. Labetalol. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet). https://www.ncbi.nlm.nih.gov/books/NBK547846/. Accessed September 27, 2019.
20. Trandate (Labetalol hydrochloride), https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/018716s026lbl.pdf. Accessed August 22, 2019.
21. Mahmoud Alalfy, E.Eltaieb, Mahmoud Soliman, Labetalol in Comparison to Methyl Dopa in Treatment of Gestational Hypertension, A Randomized Trial. Journal of Gynecology Research, 2018; 4(1): 101. doi: 10.15744/2454-3284.4.101
22. Jackson SH. Beevers DG. Comparison of the effects of single doses of atenolol and labetalol on airways obstruction in patients with hypertension and asthma. British journal of clinical pharmacology, May, 1983; 15(5): 553-6.