INTERNATIONAL JOURNAL IN PHARMACEUTICAL SCIENCES

Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Article

Labetalol For The Treatment Of Pregnancy Induced Hypertension: A Brief Review

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ARTICLE INFO

Received: 28 Nov 2023
Accepted: 01 Dec 2023
Published: 05 Dec 2023
Keywords:
Pregnancy induced hypertension, postsynaptic, labetalol, antagonist, combination
DOI:
10.5281/zenodo.10259558

ABSTRACT

One of the leading causes of maternal morbidity and mortality during pregnancy is pregnancy-induced hypertension. Hypertension that persists complicates between 1% and 5% of pregnancies. A combination of α- and β-adrenoceptor antagonist, labetalol is currently used to treat hypertension. It functions as a competitive antagonist of postsynaptic α-adrenoceptors and a nonselective competitive antagonist at β-adrenoceptors. Comparing it to other β blockers, it can preserve uteroplacental circulation more effectively. Additionally, a comparison was done between labetalol and other medications used for comparable purposes.

INTRODUCTION

In the developed world, hypertensive problems during pregnancy are the second largest cause for immediate maternal death. The most frequent medical issue that arises during pregnancy is hypertension. In order to avoid issues for the mother and the unborn child, it is crucial to manage hypertension during pregnancy as it can be a serious condition.1 A beta-blocker called labetalol lowers blood pressure and heart rate. Because it is widely regarded as safe during pregnancy and has been demonstrated to be effective in decreasing blood pressure, pregnant women frequently use it. To guarantee the best outcome for the mother and the unborn child. As a β-blocker, labetalol works by altering how certain body organs, like the heart, react to nerve impulses. As a result, blood pressure drops and heart rate lowers. The heart receives more blood and oxygen when blood pressure falls.2 It functions as a competitive antagonist of postsynaptic α-adrenoceptors and a nonselective

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

competitive antagonist at β-adrenoceptors. There are oral and intravenous versions available.3 In a similar vein, chronic treatment of angina pectoris can benefit from the early use of β-blockers like labetalol. They work just as well to relieve angina pectoris caused by vasoconstriction in response to a range of both internal and external stimuli, whether or not hypertension is present. Additionally, labetalol improves coronary hemodynamics and reduces elevated coronary vascular resistance in a way that is beneficial for individuals with myocardial ischemia, particularly in stressed people. 4

A common treatment for extreme hypertensive episodes after an acute myocardial infarction, chronic hypertension control (either by itself or in conjunction with other antihypertensive medications), and hypertensive anesthesia is labetalol. Labetalol is administered parenterally to treat hypertensive emergencies (severe hypertension) in order to quickly lower blood pressure. Examples of this include patients with pheochromocytomas and pregnant women experiencing pre-eclampsia. The only β-blocker available for treating postoperative and surgical hypertension as well as parenterally treating hypertensive crises is labetalol. 2

One of the most prevalent medical conditions that pregnant women face and for which medication is recommended is hypertension. 1% to 5% of pregnancies are complicated by chronic hypertension.5 Primigravida have a 10-15% incidence of hypertension, whereas multigravidas have a 2-5% rate. The International Society for the Study of Hypertension in Pregnancy (ISSHP) has classified hypertensive disorders during pregnancy as follows: gestational hypertension (de novo after 20 weeks of gestation), chronic hypertension (predating or diagnosed before 20 weeks of gestation), and (pre)eclampsia (de novo or overlapping on chronic hypertension: hypertension after 20 weeks of gestation combined with proteinuria and/or evidence of maternal acute kidney injury, impaired liver function, neurological features, hemolysis or thrombocytopenia, or fetal growth restriction).6,7

MECHANISM OF ACTION:

Labetalol inhibits adrenergic activation of β-receptors in the heart (β1-receptors), bronchial (β2-receptors), and vascular smooth muscle (α1-receptors) in a competitive manner. By inhibiting β-adrenoceptors, particularly in the heart, and reflex-mediated drive resulting from peripheral vasodilation and systemic vascular resistance, the blockage lowers systemic arterial blood pressure. It also reduces peripheral arteriole α-adrenoceptors. Thus, labetalol given intravenously (IV) or orally lowers blood pressure in patients with hypertension by both its α- and β-blocking effects. Whether used at rest or following moderate exercise, labetalol does not lower cardiac output. Labetalol reduces normally high systolic blood pressure after exercise, but diastolic blood pressure changes unaffected. The drop in diastolic blood pressure caused by isoproterenol was prevented by blocking the β2-receptor. 8

Labetalol works by preventing the cardiac muscle and blood arteries from being affected by certain endogenous hormones, like adrenaline. The heart's workload was lessened as a result of this blocking effect, which also caused the blood pressure and heart rate to drop. Because labetalol blocks both β and α, it is used to treat hypertension caused by pheochromocytoma and hypertensive crises. 9 Labetalol antagonises α-1-adrenergic receptors in a selective manner while non-selectively opposing β-adrenergic receptors. When taken orally, the medication has a 3:1 ratio, or three times more β-blocking power than α-blocking power. Following intravenous injection, the ratio rises to 6.9:1, or almost seven times, its original value.4

CLINICAL INDICATIONS:

The two antihypertensive medicines that are most commonly used for managing blood pressure for

pregnant patients with elevated blood pressure diseases are labetalol and methyldopa. Labetalol is frequently used as a therapy option for pregnant women with hypertension and is thought to be safe to take during pregnancy when administered under a doctor's supervision. 1

Pregnancy-related hypertension raises the risk of pre-eclampsia, gestational diabetes, early labour, and delivery problems, such as postpartum hemorrhage and the requirement for a caesarean section. The risk of restricted growth in the uterus and intrauterine death is higher in pregnancies with hypertension. Women who have hypertension throughout pregnancy should be closely watched upon and treated appropriately. The placenta is crossed by labetalol. Babies born to expectant mothers on labetalol may experience respiratory depression, hypotension, bradycardia, and hypoglycemia. It is important to keep an eye out for signs of respiratory depression, bradycardia, hypotension, and low blood sugar in newborns and adjust care accordingly. 4

First 0.25 mg/kg injectable of labetalol HCl given to patients in the reclined posture reduced blood pressure by an average of 11/7 mmHg in clinical research including severe hypertensives. Further dosage-related drops in blood pressure were observed when receiving further injections of 0.5 mg/kg labetalol HCl given at 15-minute intervals, up to a collective dose of 1.75 mg/kg. As to 3.25 mg/kg of cumulative dosages were needed for certain patients. Within five minutes, each dosage level had its maximum effect. When labetalol HCl IV treatment was stopped, most patients' blood pressure increased gradually and steadily until it reached pretreatment baseline values in 16 to 18 hours on average.4

Comparable outcomes were seen when patients with extreme hypertension who needed immediate blood pressure reduction were treated with an initial dose of 20 mg, or 0.25 mg/kg for an 80 kg patient, and additional doses of 40 or 80 mg spaced 10 minutes apart to reach the target, or up to a total of 300 mg.4 Blood pressure was decreased by an average of 60/35 mmHg when labetalol HCl was given as a constant intravenous infusion over a period of 2 to 3 hours (with a mean of 2 hours and 39 minutes). The mean dose of the medication was 136 mg (27 to 300 mg).10 Taking labetalol with meals increases its absolute bioavailability. Depending on how the medication is administered, the hypotensive effect will manifest itself differently. After oral administration, the impact usually manifests itself between 20 minutes to two hours. In contrast, the time after a direct IV injection is much shorter—between 2 and 5 minutes and up to 15 minutes at most. 11

Additionally, it reduces pregnancy-induced hypertension without sacrificing cardiac output thanks to its minor intrinsic sympathomimetic action. Labetalol's unique property keeps the fetal blood supply intact by retaining placental perfusion, which in turn keeps the fetal oxygenation levels high enough for lung development. Numerous studies have demonstrated its extensive application in managing pregnancy-induced hypertension. 12,13

PHARMACOKINETICS OF LABETALOL:

The pharmacokinetics of labetalol in the context of gestational hypertension (high blood pressure during pregnancy) can be affected by various factors, including changes in a pregnant woman's physiology and metabolism. Here are some key points to consider regarding the pharmacokinetics of labetalol in pregnancy:

1. Absorption: Because labetalol is taken orally, alterations in intestinal motility and bioavailability during pregnancy may have an impact on the drug's absorption. Pregnancy can cause variations in the rate of absorption, but these usually don't have a major effect on the overall effectiveness of the medication. Labetalol was rapidly absorbed; 20 minutes after consumption, peak serum concentrations were reached. 14

Both oral and injectable forms of labetalol administration are possible. While giving labetalol orally with food slows down the medicine's gastrointestinal absorption, it also makes the drug more absolutely bioavailable. To prevent hypotension during intravenous administration, patients must remain in a supine position. Patients shouldn't engage in any ambulatory activity until they can tolerate being in an upright position. After a direct IV infusion, labetalol needs to be administered slowly over a 2-minute period at 10-minute intervals; dilution is not required. The blood pressure of the patient is checked prior to, five, and ten minutes following each injection. 15 Elderly patients and elderly people have much higher labetalol bioavailability. 4

2. Distribution: Labetalol reaches the placenta and other parts of the body where it can impact the developing fetus. Since the medication can pass through the placenta, the fetus's exposure to it needs to be carefully watched. It should be taken into account if the mother is nursing because labetalol has been found to infiltrate breast milk. In experiments on animals, very small amounts of the medication passed through the blood-brain barrier. About 50% of labetalol is linked to proteins. Both hemodialysis and peritoneal dialysis fail to eliminate a substantial quantity of labetalol (<1%) from the systemic circulation.10

3. Metabolism: Labetalol undergoes hepatic metabolism primarily via glucuronide conjugation before being excreted by the kidneys. The liver's metabolic capacity can be influenced by hormonal changes during pregnancy, potentially affecting the metabolism of labetalol. However, no major pregnancy-related alterations in labetalol metabolism are typically reported.10

4. Elimination: The kidneys are the main organs responsible for eliminating labetalol, and changes in glomerular filtration rate and renal blood flow during pregnancy can affect renal clearance. Consequently, depending on renal function, the dosage and dosing intervals may need to be changed. After labetalol is infused intravenously, the elimination half-life is roughly 5.5 hours, and the body clears the drug at a rate of about 33 mL/min/kg. Labetalol's steady-state plasma levels on recurrent dosing are attained after 22 to 28 hours of nonstop infusion. Within the first 24 hours after medication, conjugates or unmodified labetalol make up around 55% to 60% of a dose that is detected in the urine. The metabolites are found in plasma and are eliminated by the bile and urine, ending up in the feces.10

Hemodialysis and peritoneal dialysis do not significantly remove labetalol (<1% of a dosage). After intravenous or oral dosing, labetalol has a 6–8hour plasma elimination half-life. When a patient is receiving dialysis and has significant renal impairment (i.e., a creatinine clearance of less than 10ml/min), the drug's elimination half-life seems to remain unaltered. Because liver impairment reduces the medicine's first-pass metabolism, the dosage must be lowered.4

5. Maternal-Fetal Considerations: The growing fetus and the mother may be affected by labetalol. Striking a balance between reducing potential dangers to the infant and efficiently treating maternal hypertension is crucial. It is essential to keep an eye on the fetus's health and to modify the medicine as necessary. In pregnant women with prolonged hypertension, labetalol and nifedipine regulate average systolic and diastolic blood pressure to target.16 The mother and fetus must be closely monitored during labetalol treatment in order to prevent an excessive drop in blood pressure. 17

6. Monitoring: Close blood pressure and medication level monitoring may be required to make sure labetalol is successfully lowering high blood pressure during pregnancy. If the mother's physiology changes as the pregnancy goes on, dosage modifications can be necessary. Labetalol has a broad therapeutic window and a long half-

life. By blocking catecholamine accessibility to both postsynaptic α- and β-adrenergic receptor sites and antagonistically binding different adrenergic receptors, labetalol reduces blood pressure. Vasodilation may be induced by labetalol. Unless they are sensitive of other antihypertensives or do not respond to them, people who are prone to bronchospasms should refrain from taking labetalol. 4

The time it took for the serum levels to peak was 60 minutes after eating. Labetalol was found at amounts of roughly 50% and 16% in fetal cord and amniotic fluid samples, respectively, compared to concurrent maternal venous samples. 14 The absorption of labetalol varies depending on the individual. The suggested range of oral daily dosages, based on patient requirements, is 200–2400 mg/day. Patients with extreme hypertension, for instance, might require 1200–2400 mg of labetalol per day (thiazide diuretics included or not). An intravenous injection of 20 mg should be given over two minutes in the case of a hypertensive emergency. After that, an IV dose of 40–80 mg should be given over ten minutes, for a maximum of 300 mg. As an alternative, the medication may alternatively be continuously infused into the vein at a rate of 1-2 mg/min up to a maximum dose of 300 mg. 4

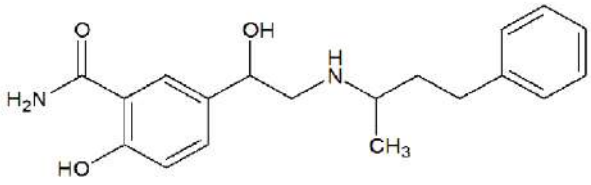
PREGNANCY CATEGORY C:

Oral dosages of labetalol up to roughly 6 and 4 times the maximum indicated human dose (MRHD) have been used in teratogenic investigations in rats and rabbits. There was no consistent evidence of fetal abnormalities found. In both species, increased fetal resorptions were observed at dosages that were close to the MRHD. In a teratology research, labetalol was administered intravenously to rabbits at dosages up to 1.7 times the MRHD. The results showed no signs of drug-related damage to the developing fetus. There aren't enough reliable, well-controlled research on expectant mothers. During pregnancy, labetalol should only be used if the possible benefits outweigh the possible risks to the developing fetus.15

The literature that is currently available indicates that human milk contains trace amounts of labetalol. Regarding the influence on the breastfed newborn and on milk production, no data are available. In addition to the mother's clinical requirement for labetalol and the potential adverse effects of both the drug and the underlying maternal disease on the breastfed newborn, it is important to take into account the cognitive and health benefits of nursing.10

CHEMICAL STRUCTURE:

The molecular chemical composition of labetalol is C19H24N2O3•HCl, and its molecular weight is 364.9 g/mol. Labetalol is also known as 2-hydroxy-5-[1-hydroxy-2-[(1methyl-3-phenylpropyl) amino] ethyl] benzamidemonohydrochloride. The first four isomers, (S,S) and (R,S), are not active, whereas the third and fourth isomers, (S,R) and (R,R) respectively, are strong α1 and β blockers. Divalol, the fourth isomer, consists of a non-selective β blocker and a mixed sensitive α1 blocker. Strong agonist action is produced by labetalol in this combination. However, because they have no intrinsic activity and a receptor affinity, molecules with larger substituents linked to amines are usually found to be antagonists. In nature, labetalol is an off-white or white crystalline powder with a highly polar structure. Thus, labetalol pills need to be stored in a well closed container away from extreme moisture and between 2 and 30°C. Labetalol is most stable at pH 2-4 solutions. 18



Drug ingredient	Labetalol hydrochloride
Proprietary name	Trandate
Drug name	β-adrenergic receptor antagonists

Table no.1 Summary of Labetalol information

COMPARISON WITH ALTERNATIVE MEDICATIONS WITH SIMILAR USES:

Although labetalol is α1-selective, its affinity for α-receptors is lower than that of phentolamine. It has a little lower capacity to inhibit β than propranolol. When hypotension is caused by labetalol, there is less tachycardia than when it is caused by phentolamine and comparable α blockers.[19]When labetalol is used for an extended period of time, it can effectively reduce peripheral vascular resistance, heart rate, blood pressure, and cardiac output while maintaining normal cardiac output. Uncontrolled trials of its use have shown positive outcomes without causing any harm. Although controlled trials have demonstrated that it is even safer, more efficient, and thus superior than methyldopa, it also has the added benefit of promoting fetal lung development.[20]Mothers who take Reserpine may experience a variety of side effects, including sadness, drowsiness, an increased risk of hypothermia, and an increase in the volume of secretions from their respiratory system. However, methyldopa may have a negative impact on the mother and fetus. In addition to having an impact on the fetus's developing neural mechanisms throughout the period in which the mother may have a positive Coomb's titer, it also causes higher salt retention and decreased cardiac output. The two side effects of bethanidine and guanethidine that are known to occur are maternal postural hypotension and diarrhea. Prenatal bradycardia and hypotension have been observed in propranolol trials recently. In the end, these circumstances can exacerbate fetal suffering and obscure the fetal hypoxia diagnostic clinical signs. [21]Additionally, this medication may be to blame for the unusual side effects of raising newborn hypoglycemia.[20]

A-methyldopa vs. Labetalol: Labetalol is recommended as the first-line treatment for pre-eclampsia, or high blood pressure in pregnancy due to its advantages over other β-blockers. This has been demonstrated by a specific study (Labetalol vs. methyldopa in the management of hypertension produced by pregnancy) where pregnant women with diastolic blood pressures recorded above 100 mmHg were given both labetalol and α-methyldopa. Comparing labetalol to methyldopa, the former is safer and more effective. Labetalol is more well-tolerated, controls blood pressure more well, and may cause the uterine cervix to mature.[22]The study's findings indicated that labetalol is a safe and effective medication for treating pregnancy-related hypertension. This is due to the fact that labetalol has certain advantages over α-methyldopa. There are no adverse effects of constipation, postpartum depression, galactorrhea, α-receptor blockage, disturbed sleep patterns, or postural hypotension. It avoids tachycardia and promotes appropriate and long-term blood pressure regulation. The blood flow in the utero placenta is unaffected by labetalol. α-methyldopa creates incorrectly non-reassuring fetal cardiac rhythms on electronic fetal monitoring in antepartum fetal surveillance. α-methyldopa builds up in renal failure and can occasionally make pre-eclampsia more difficult. Lastly, it seems that labetalol prevents fetal developmental retardation with greater effectiveness.[2]

Atenolol vs. Labetalol: Labetalol reduces the chance of triggering asthma attacks. This is demonstrated by a placebo-controlled double-blind trial that examined the effects of 300 mg and 100 mg single doses of labetalol and atenolol in 11 patients with hypertension and asthma. Labetalol dramatically reduced the effect of inhaled salbutamol on forced expiratory volume in one second (FEV1) as compared to atenolol. Contrary to the effects of non-selective β-adrenoceptor

blockers, which did not achieve baseline values following isoprenaline, β-adrenoceptor blocking medications cannot be suggested in patients with airway obstruction. If these variations were verified through direct comparison, they would bolster the theory that α-adrenergic receptors play a role in regulating bronchial muscle tone in asthmatic patients. In comparison, labetalol is less dangerous than pure, non-selective β-adrenoceptor blockers.[24]The conclusion is that labetalol and atenolol are generally safe and effective in controlling hypertension that complicates pregnancy. However, it seems that labetalol is more effective at preventing the onset of fetal growth retardation.[20]

Metoprolol vs. Labetalol: Both labetalol and metoprolol are equally effective and safe when used to treat patients with medium to moderate HF. In a double-blind, parallel-group, multicenter clinical trial, the antihypertensive impact of oral metoprolol and labetalol was evaluated in 91 patients with mild moderate to severe hypertension (diastolic blood pressure of 90-115 mmHg). While both medications lowered heart rate, metoprolol had a noticeably greater effect. Whereas bradycardia was more common with metoprolol, nausea, dyspepsia, and fatigue was more common with labetalol. By the conclusion of this time, the blood pressure in both therapy groups was at baseline, but the metoprolol-treated patients' heart rates were higher than baseline. Moreover, two of the patients reported a symptomatic recurrence in their high blood pressure that needed to be treated; none of the individuals receiving labetalol had this rebound. This suggests that labetalol may have a safety benefit. It has been noted that stopping labetalol does not cause any negative withdrawal symptoms in people with chest pain and hypertension. At the time, labetalol's combination α- and β-adrenergic suppressing ability was heralded as a pharmacological breakthrough that offered a revolutionary conceptual approach to treating patients with hypertension.[25]

Propranolol vs. Labetalol: Patients with prolapsed mitral valves frequently experience ventricular arrhythmias. In one study, 10 patients with mitral valve prolapse confirmed by echocardiography and documented ventricular arrhythmia were included in order to compare the efficacy of β- and β-blockade (labetalol) versus β-blockade alone (propranolol) in treating ventricular arrhythmia. Symptomatic premature contractions of the ventricular and no triggered ventricular tachycardia in a patient with mitral valve prolapse.

But there have been reports of potentially fatal arrhythmias that could result in abrupt death. These findings demonstrated the role of α-adrenergic receptors in the pathophysiology of ventricular arrhythmias in mitral valve prolapse syndrome and suggested labetalol as a viable substitute for solitary β-blockade that should be taken into account while managing this condition.[4]

ADVERSE OUTCOMES DUE TO LABETALOL:

Generally, labetalol is well tolerated. Although they are rare, minor side effects can include depression, impotence, lethargy, and dizziness as well as postural hypotension and fever. The majority of side effects happen early in the course of treatment and are minor and temporary. The most common adverse effects include weariness (1–11%), tingling in the scalp (4–12%), nausea (≤19%), dizziness (1-20%), and lightheadedness (1-20%).[26]There have been reports of a few more, less frequent negative effects in various bodily systems, though. If the patient is tilted or permitted to assume an upright position within three hours of administering labetalol, symptomatic postural hypotension could develop in the cardiovascular system.[15]It is important to consider the potential effects of α- and β-adrenoceptor blockage in both neonates and fetus due to the placental barrier

being crossed by labetalol. Rare reports have been made of neonatal and perinatal discomfort (hypothermia, hypoglycemia, breathing difficulties, low blood pressure, bradycardia). These signs may appear after one to two days following delivery. Although there is normally a quick response to supportive therapy (IV fluids and glucose), there is a chance of severe pre-eclampsia, particularly with extended supportive treatment. In neonates, recovery from labetalol side effects may take longer. Premature babies' decreased liver metabolism may be linked to this. There have been reports of labetalol-related deaths in utero and to babies, although there may also be other medications (vasodilators, respiratory depressants) as well as the effects of preterm, premature development, and pre-eclampsia.[27]Patients with asthma, atrioventricular block (2nd and 3rd degree), and uncontrolled heart failure with bradycardia should not use labetalol. A few side effects include dyspnea, limb swelling, chest rigidity, wheezing, blurred vision, sweating, breathing difficulties, dizziness, and lightheadedness while standing up from a seated or lying down position. Tremors and tachycardia, two early warning signs of hypoglycemia, can be concealed by labetalol. In order to avoid unintentional hypoglycemia, patients using insulin and oral hypoglycemic drugs may need to raise their dosage. Liver poisoning could result from labetalol. This side effect of hemolysis, increased liver enzymes, and low platelet levels syndrome must be acknowledged. Once therapy is stopped, the labetalol-induced liver function abnormality progressively goes away.[28,29]Miscarriage was not caused by labetalol. Compared to other beta blockers, it can also preserve uteroplacental circulation more effectively. As opposed to methyldopa, it operates more quickly. Patients with myocardial infarction, renal disorders linked to pregnancy induced hypertension, and reflex tachycardia benefited from labetalol.[30]Labetalol may cause wheezing, or bronchospasm, in the respiratory system. Labetalol may cause a variety of rashes on the skin and appendages, including psoriasiform, urticaria, bullous lichen planus, generalised maculopapular, lichenoid response, and facial erythema. After taking labetalol, reversible alopecia and Peyronie's disease may also manifest. The urinary system has also been linked to acute urinary tract retention and difficulties with micturition. Rare reports of anaphylactoid responses and hypersensitivity (breakouts, rashes, pruritus, angioedema, dyspnea) have been made.[27]

Hepatic necrosis and the initial indication of liver malfunction, including right upper quadrant pain, jaundice, chronic hunger, dark urine, and itching, have been documented in relation to the hepatic system. Elevated liver function tests are a sign of cholestatic jaundice and hepatitis. In the musculoskeletal system, pregnant women taken labetalol for hypertension have been shown to experience tremors, muscle cramps, and toxic myopathy.[31]In spite of these adverse effects, labetalol was found to be more successful in successfully controlling HTN caused by pregnancy induced hypertension. The small dangers are surpassed by the benefits. With very few side effects, labetalol is safe for usage by the mother, fetus, and infant.[32]

CONCLUSION:

For individuals with preeclampsia and eclampsia, labetalol is a safer and more effective medication for managing hypertension. When compared to other medications on the market, it acts more quickly through both oral and intravenous modes. With labetalol, adverse effects are less common. Because of this, labetalol may be the medication of choice for treating pregnancy induced hypertension in clinical practice. The simultaneous blockage of α1-adrenergic and β-adrenergic receptors is the mechanism of action of labetalol, with β-receptors being more affected than α-

receptors. Oral administration of labetalol is possible as a bolus or as a continuous infusion

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HOW TO CITE: A. R. Shabaraya, Lathika A. Nayak, Labetalol For The Treatment Of Pregnancy Induced Hypertension: A Brief Review, Int. J. in Pharm. Sci., 2023, Vol 1, Issue 12, 78-87. https://doi.org/10.5281/zenodo.10259558