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Use of Anti-Hypertension Drug Safety (Labetalol and Nifedipine) During Pregnancy

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Abstract: Efforts to manage hypertension in pregnancy, on *evidence based medicine* using pharmacological therapy lower blood pressure, so it can reduce morbidity and mortality in the maternal and prinatal. Therefore, prior to administration of anti-hypertensive drugs, the need to consider pharmacodynamic and pharmacokinetics that occur in the mother and fetus. Labetalol and nifedipine are category C (FDA) antihypertensive drugs that can be used as an option in the treatment of hypertension during pregnancy, because they do not have teratogenic risks for both pregnant women and the fetus. The making of this article is intended to determine the safety of the use of antihypertensive drugs, labetalol and nifedipine during pregnancy.

Keywords: Antihypertensive Drug, Labetalol, Nifedipine, Pregnancy

BACKGROUND

Hypertensive disorder is a complication in pregnancy that is common and includes one of 3 lethal types, along with bleeding and infection. Hypertension is widely recognized as a cardiovascular disease, when the patient has a blood pressure above normal. It is hypertension in pregnancy if it found systolic / diastolic blood pressure exceeds 140/90 mmHg (normally 120/80 mmHg) at the time of pregnancy.[3] Hypertension in pregnancy such as preeclampsia, chronic hypertension, and gestational hypertension with different diagnostic criteria, and This disease is estimated to have caused a global morbidity increase of 4.5%. In Indonesia, hypertension in pregnancy shows an increasing trend, 20% in 2007 and in 2011 up to 30%.[7.15] Hypertension in pregnancy is at risk for cerebrovascular disorders, cerebral edema, liver disorders, renal failure, heart failure, and maternal death. In the fetus will be at risk of complications such as premature birth, growth disorders and stillbirth.[3] The disease, often called the *silent killer* because of the absence of symptoms and without realizing the patient experiencing complications in vital organs.[7]

Based on the results of the study showed that pregnant women who were exposed to hypertension caused by age > 35 years, primigravida parity, hormonal use of contraception for more than 2 years and family history of hypertension.[14] Multivariate analysis of logistic regression hypertension risk factor

Risk Factor	β	OR adjusted	95%CI	P
Age	1,86	2,1	3,2-12,8	0,005
Parity	1,06	3,0	1,3-6,1	0,003
Hereditary hypertension	1,52	6,6	1,9-10,7	0,001
Hormonal Contraception time of use	-3,17	0,42	0,01-0,10	0,001

Source: Mardianingsih, 2017.

Katsung, et al. 2014 said, The mechanism of absorption, distribution and elimination of drugs in the body, is a pharmacokinetic process that an important role in determining the selection and administration of drugs in patients. In pregnant patients, pharmacokinetic changes of the drug used during pregnancy require special attention, especially in drug selection, drug dose regulation and drug delivery intervals. So the pharmacokinetic process, capable of providing therapeutic effects and minimize the risk of exposure to drugs, both for maternal and fetal.[6]

This article discusses the safety of the use of antihypertensive drugs Labetalol and nifedipine in pregnant conditions. Labetalol is a sympathgersgic drug that works to lower blood pressure, by reducing peripheral vascular resistance, inhibiting cardiac function, and increasing venous blood in vessel capacitance, with classification as a drug of the adrenoceptor □. While Nifedipine is a direct Vasodilator that works to lower blood pressure by reducing and inhibiting calcium influx to the smooth muscle cells of the arteries.

DISCUSSION

LABETALOL

Profile:

Labetalol is the latest third generation of β-adrenoceptoror antagonists or β-blockers, it is have a different affinity for β_1- and β_2-adrenoceptor, is *lipid soluble* and pass through the central nervous system, has a sympatholimetik activity intrinsic agonist partial *(partia lagonist activity*) that mediate stimulation of β_2-adrenoceptor can activate vasodilatori effect in lowering blood pressure with the result of a decrease in cardiac output.[10, 17, 25]

The α1 or α1-adrenoceptor receptors are mostly present in the blood vessels (vascular smooth muscle). Activation at this receptor, causes vasoconstriction of arteries and veins. While β receptors are present in the heart, if there is stimulation increases the cardiac output thus increasing contractility, immediate activation of sinus nodes in increased heart rate and increased calcium influence in heart cells. There is a type of receptor β_1 and β_2,where β_1 receptor

stimulation can increase the strength and speed of contraction and increase spending renin, whereas stimulation of β_2-receptors induce relaxation of smooth muscle. [14]

The α1 receptor antagonist drug causes decreased peripheral vascular resistance and blood pressure.[14] While β-blocker drugs occupy β-receptors, the receptor binding of these drugs does not cause the activation of receptors. Most of the β-blocker drugs are pure anthony, but some are also partial agonists. A partial agonist will inhibit the activation of the β-respetor when there is high concentrations of ketokolamine but will activate the receptor if, there is no endogenous agonist. The β_1-blocker drug decreases peripheral resistance and cardiac output by decreasing heart rate, blood pressure, myocaridum contractility, and myocardium oxygen consumption. In labetalol, partial agonists apply to the activation of β_2 receptors there by promoting smooth muscle relaxation.[17]

Mechanism of Action:

Labetalol role in vasodilation action, mediated by the stimulation of β_2-adrenoceptor. The mechanism of action is to reduce peripheral vascular resistance without being followed by significant changes in heart rate or cardiac output.[5] Effect of labetalol hypotensive generated through vasodilation, played by α1-adrenoceptor-blockade and activation of β_2-adrenoceptor on vascular smooth muscle. The of $\beta_1$blockade-adrenoceptors in the heart also contributes to hypotensive effects, by reducing the reflexes that impact on increased cardiac output.[11]

Labetalol is one of the main choices of treatments for the hypertension during pregnancy and is the of therapy *first line* in some countries, especially in cases of mild hypertension and hypertension in pregnancy. Labetalol affinity for the receptor α are known to be small compared to fentolamin, but labetalol have selective properties of α_1. The ability of labetalol in inhibiting β-receptors is known to be lower than that of propranolol. However, the hypotensive effects induced by labetatalol are less commonly accompanied by tachycardia than if given fentolamine therapy or a similar α-blocker.[14]

Labetalol is able to lower blood pressure through the mechanism of decreased peripheral vascular resistance, with little or no lowered speed, cardiac output, without causing a change in maternal heart rate and without endangering uteroplacental blood flow.[20]

THE NIFEDIPIN

Profile:

Nifedipine is a *calcium channel blockers* (CCB) / calcium antagonist, including mild to moderate drugs *second line*, and is a prototype of the family / class of dihydropyridine, which inhibits calcium flow into the cell membrane across the L-type , thus supporting smooth muscle relaxation. In addition, nifedipine belongs to the vasodilator group, which has a strong vasodilation effect on arterioles that can decrease peripheral resistance and blood pressure.[2, 26]

Giannubilo et.al (2012), stated nifedipine is available in 3 formulas, including:

1. Very short-acting capsule (immediate release), with a peak effect of 30 minutes after administration, is used for severe hypertension therapy. This class contains dihydropyridine which increases reflexes in *sympathetic tone* (strength or sympathetic tone) and is associated with ischemic events in individuals with coronary artery disease or DM is therefore not recommended for use during pregnancy.
2. PA tablets, peaking effects about 1 hour post-administration, used for the treatment of moderate to severe hypertension.
3. Slow-release formulation (XL), which secretes nifedipine effects about 24 hours after administration, is usually given once per day for mild hypertensive therapy. [17]

Work Mechanism:

Nifedipineas a vasodilator means as a class of antihypertensive drugs that work to reduce blood pressure by relaxing the smooth muscle of blood vessels, resulting in dilation of blood vessels. As *calcium channel blockers* (CCBs) work by inhibiting calcium influx into arterial smooth muscle cells through an L-type channel.[14] Negative effects of nifedipine cause *myocardial inotropy*, reduced stimulation of nodal cells and peripheral vasodilation.[2]

Nifedipine is also classified in calcium antagonists in anti-hypertensive drugs by its mechanism of action inhibiting calcium influx into the arterial smooth muscle and widen the peripheral arteries so as to reduce blood pressure. Side effects caused by the use of this drug are headache, red face occurs due to vasodilatation of the meningeal arteries and in the face, peripheral oedem mainly due to dilatation of arterioles that exceed dilatation of the veins, thus increasing the hydrostatic pressure that pushed fluid out interstitial space without any fluid retention and salt.[14]

Nifedipine is a second-line anti-hypertensive drug on the treatment level of hypertension, can decrease peripheral resistance, decrease systolic and diastolic blood pressure, increase per minute volume and heart rate, decrease coronary resistance and increase coronary flow and decrease heart oxygen consumption. Nifedipine belongs to potent anti hypertensives, because the response is more beneficial to high blood pressure, and at normotensive blood pressure will not go down. In single oral doses the anti-hypertensive effect is within 15-30 minutes and lasts for 6-12 hours. Treatment of mild hypertension can work well and has no side effects.[21]

Nifedipine which is a *calcium channel blockers* (blocker antagonist) blocks the flow of calcium ion transmitter through the voltage at the L-Type gate on the smooth muscle channel (slowly disable).[26] Drug binding reduces the opening frequency in response to depolarization, resulting in a dramatic decrease in transmembrane calcium currents in smooth muscle that induces prolonged relaxation. *Calcium channel blockers* (CCB) also reduce systemic vascular resistance and increase urine production by increasing renal blood flow and inhibiting the release of ADH. Because nifedipine causes vascular relaxation especially in the arteries, uterine relaxation and relaxation of smooth muscle in the bladder, nifedipine is usually also prescribed for both hypertension and tocolytics. [14]

PHARMACOKINETIC LABETALOL AND NIFEDIPIN IN PREGNANCY

LABETALOL

Absorbtion:

During pregnancy the absorption of the drug may be delayed due to delayed emptying of the stomach and intestines. As a study conducted by Saotome et.al (1993) in 7 pregnant women of 3rd trimester with moderate to severe hypertension who received oral labetalol therapy at a dose of 150-450mg twice daily, it was known that peak plasma concentration (C_{max}) of labetalol occurred 60 minutes post oral administration, this condition indicates that labetalol is absorbed rapidly in pregnant women with hypertension, and when compared with C_{max} labetalol in nonpregnant women, physiological changes of pregnancy alone have no significant effect on labetalol absorption rate. Thetime range *half-life(elimination half-life)* 4.3 to 6.9 hours ofappears shorter than non-pregnant. Under conditions of pregnancy, there is variability in both inter- and intra- individuals in terms of bioavailability, clearance, and dosing requirements in which variability is 3 to 5 times greater in the individual inter- face.[8]

Distribution:

Labetalol widely distributed into tissues.[8] The volume of labetalol distribution during pregnancy did not change significantly.[24]

Metabolism:

In pregnancy there is a decrease in albumin and α-1 acid glycoprotein which can affect the reduction of bond between the drug and plasma protein. Known fractions of free labetalol in second trimester pregnancy 38%, third trimester 42%, and postpartum 41%.[8] Labetalol has a high extraction ratio, with elimination in *hepatic metabolism*, its metabolism involving UGTenzymes *(urindine diphosphate-glucuronosyltransferase*) 1A1 and 2B7that are largely responsible for *hepatic metabolic pathways* via phase II (reactions*glucoronidation*). Increased progesterone hormone during pregnancy also increases activation of UGT 1A1, whereas for UGT 2B7 its activation is not directly affected by estrogen and progesterone hormones.[8]

Excretion:

In pregnant women clearance of labetalol increases from 31.9 to 73.3 mL / min / kg, it is also representative with increased *hepatic intrinsic clearance*and increased *first pass metabolism*. Research conducted by Fischer et.al (2014) observed pharmacokinetics from oral labetalol during pregnancy and post-pregnancy, where respondents were 57 women who were treated for hypertension during 12 weeks gestation until 12 weeks postpartum. In this study it was found that *lean body weight* (LBW) and gestational age significantly affects the clearance of oral labetalol, obtained by clearance (for 50 kg LBW in women), at 12 weeks gestation was 258L / h, 40 weeks' gestation was 296L / hour and postpartum is 188L / hr. Oral clearance in 12 weeks 'gestation was 1.4 times higher than in the post partum, and in 40 weeks' gestation 1.6 times greater than in postpartum. In this study also found that in pregnancy, the dose of labetalol based on *lean body weight* (LBW) is better than the dose based on *total body weight* with the aim of reducing the possibility or risk of exposure to maternal or fetal drugs.[8]

NIFEDIPINS IN PREGNANCY

Absorption:

Post oral administration, CCB is rapidly and completely absorbed in the gastrointestinal tract, with *first-passmetabolism* liverresulting in 40% of drug convertion into inactive products via oxidative pathways (cytochrome P450 CYP3A), low bioavailability about 50%, with significant individual variation.[26] In pregnancy, nifedipine has a decrease in plasma peak concentration (Foster et.al, 1983), which is about 38.6 ± 18 ng / mL achieved in 40 minutes post-administration of 10 mg of oral nifedipine. This decrease in plasma peak concentration occurs because of pregnancy conditions increased *first pass elimination* and increased hepatic blood flow due to arterial vasodilatation.[23]

Metabolism:

Oral clearance in the use of nifedipine during pregnancy increased 108% as a sign of increased CYP3A activity during pregnancy.[13] Prevost et.al (1992) study of 15 women with hypertension in pregnancy, oral nifedipine clearance was increased during pregnancy at 2.0 ± 0.8 L / hr / kg compared with non-pregnant women of 0.49 ± 0.09 L / hr / kg. The clearance is increased, and the *terminal elimination half-life* is shorter than the nonpregnant condition. This is associated with the presence of the CYP3A enzyme in which the regulation increases in pregnant conditions (high expression for CYP3A5). This increase in clearance affects the dose interval of nifedipine, in which the clinician suggests giving the dose interval more intensively from 8 hours to 6 hours. With their differences, making the *duration of action* is shorter gestation nifedipinselama ie 6 hours.[23]

Excretion:

In pregnant women, elimination clearance becomes faster compared to nonpregnant women ie 2.0± 0.8 L / hr / kg.[9] Nifedipine was found in cord blood samples and amniotic fluid with about 93% and 53% of the simultaneous maternal vein samples.

The information proves that the use of nifedipine in pregnant women with hypertension shows shorter half-life characteristics, faster clearance, and lower serum concentrations. So it was concluded that nifedipine would work as well as antihypertensive in pregnant women if given at shorter intervals.[23]

SECURITY USE DURING PREGNANCY

LABETALOL

Safety:

According to the FDA (*Food and Drug Administration*), labetalol is classified as a C-class drug in its use during pregnancy, meaning that this class of drugs may be given if the therapeutic benefits outweigh the risks to fetal. The use of β-blockers during pregnancy has no bearing on teratogenic effects. This is stated in one study conducted by Yakoob et. al (2013) who conducted a meta-analysis study to see the teratogenic effects of β-blocker use in early

pregnancy. In this study it was found that the use of oral β-blockers in the first trimester showed no increase in the incidence of major or minor congenital defects (OR = 1.00, 95% CI: 0.91-1.10, 5 studies). However, in this study also observed the incidence of malformations of specific organs and found results in an increased risk of occurrence in:

a) Cardiovascular defects (OR = 2.01; 95% CI: 1.18-3.42, 4 studies)
b) Labioskisis / palatoskisis (cleft lip / palate) (OR = 3.11; 95% CI: 1.79-5.43, 2 studies)
c) Neural tube defect (OR = 3.56; 95% CI: 1.19-10.67, 2 studies)

Although the researchers present such data, but the mechanism explanation is still difficult to interpret . Thus, further research is needed to confirm the management of hypertension in pregnant women, especially about the teratogenic effects that can be raised by labetalol.[27]

The effects of giving β-blockers at the end of pregnancy are also feared to affect the fetus, such as bradycardia, increased risk of respiratory distress syndrome, endocrine and metabolic disorders such as hypoglycemia, jaundice, gastrointestinal disorders and nutritional intake, but the effect is not significant.[1] In addition, β-blockers were also found to have no significant effect on the occurrence of LBW when compared with methyldopa.[11]

In a study conducted by Giannubilo et.al (2012), a retrospective study of the effects of hypertension treatments using nifedipine compared with labetalol to maternal and fetal outcomes, it was found that the labetalol matured had the potential to disrupt *fetal growth* in women with mild hypertensive disorder during pregnancy. This effect occurs because of the adverse pharmacological effects of labetalol affecting metabolism through the feto-placental unit, affecting the transfer of nutrients through the placenta or reducing the perfusion pressure on the intravili. [11]

General and Pregnancy Dose Arrangements Dose settings are:

Highly dependent on individual individuals. Under nonpregnant conditions, the dose of oral labetalol for mild to moderate hypertension therapy is 100 mg with administration every 8 hours, or a dose of 300 mg with 12 hours administration, and the maximum dose is 1200 mg / day.[4]

As a therapy of mild to moderate hypertension in pregnancy, the dosage of labetalol adala 200-1200mg / day, divided into 2-3 feedings. However, basically there is no consensus on the dosage of twice daily labetalol for the optimal treatment of hypertension during pregnancy, thus giving oral labetalol at doses 3 times per day also allows for women who have not received an optimal treatment on administration twice daily.[4]

In this study also found that in pregnancy, the dosage of labetalol based on LBW is better than dosing based on *total body weight* in order to reduce the possibility or risk of exposure to maternal or fetal drugs.[8]

NIFEDIPIN

Safety:

According to the FDA (*Food and Drug Administration*), nifedipine is categorized as class C drug in its use during pregnancy meaning that this class of drugs may be given if the therapeutic benefits outweigh the risks that will occur to the fetal.[14]

Groups of *calcium channel blockers* (CCB) including nifedipine are able to cross the placenta and are found in the umbilical cord, fetal blood and amniotic fluid. However, no data suggest an increased risk of teratogenic, potentially fetal hypotension and uteroplacental flow disorders from nifedipine use during pregnancy. [26]

Fornifedipine *short-acting* (*immediate release*) in severe hypertension therapy is known to cause acute hypotension in maternal and cause fetal distress, so this class is not recommended for use during pregnancy.

Research conducted by Khan et al (2010) aims to evaluate the effect of CCB use in certain doses during pregnancy to fetal-maternal. Performed in 5607 pregnant women with hypertension who received oral nifedipine therapy with a total dose> 60 mg. There was an unfavorable effect on the mother through the manifestation of dizziness 19%, flushing 51%, first 9% and vomiting 18%, tachycardia 33%, and 39% hypotension. In this study did not explain the total duration of CCB therapy. Data on the safety and efficacy of CCB use for hypertension during pregnancy are in fact still low, thus proper monitoring and consideration in the use of CCB as a choice of hypertension therapy in pregnancynecessary[16 are]. Sublingual use of nifedipine should be avoided as it may cause sudden hypotension to the mother and fetal distress caused by placental hipoperfusion. Similarly, if used in conjunction with magnesium as a treatment or prophylaxis against eclamptic seizures or severe preeclampsia, hypotension may occur suddenly.[12]

General and Pregnancy Arrangements The:

Dosedosage of nifedipine under nonpregnant conditions or in general is 30mg / day for initial recommended doses, and 30-60mg / day as the usual range of maintenance doses.[8]

From the previously described pharmacokinetic changes in pregnancy, the recommendation to provide nifedipine during pregnancy is given at shorter intervals,[23] ieeach every 8 hours to every 6 hours at the same dose to obtain a therapeutic effect equivalent to nifedipine when not pregnant.[22] Nifedipine pharmacokinetic changes during pregnancy (shorter half-lives and faster clearances) make the *duration of action* nifedipin during pregnancy to be shorter ie 6 hours.[23]

Other references mentioned, based on the type of nifedipine preparations, the recommended dose for pregnant women for this type of PA tablet is 10-20 mg orally 2 to 3 times per day, a maximum of 180 mg / day, and the XL formulation is 30-60 mg per oral once per day, maximum 120mg / day.[17]

The generic names for nifedipine are Adalat CC and Procardia XL (Katzung et al, 2015). Adalat Oros®

(Osmotic-controlled Release Oral Delivery System), which is a long acting nifedipine whose drug-release mechanism is slowly being used for a dose of 1 tablet per day.[3]

Pregnant women who have preeclampsia, will result in edema of the legs and legs. While one of the side effects of the use of nifedipine is the presence of edema, which will worsen the condition of pregnant women. Considering the presence of edema in preeclampsia, for hypertensive cases due to preeclampsia is recommended to choose alternative drug therapy other than nifedipine.

CONCLUSION

Pharmacokinetics Labetalol in general in pregnant women namely; Absorbtion process in pregnant women Absorbsinya not changed significantly, Cmax achieved 60 minutes and t ½ ie 4.3-6.9 hours. Distribution Process in pregnant women The volume of distribution during pregnancy did not change significantly, the free fraction at 2 trimester 38%, 3% trimester 42% and 41% postpartum. Metabolic processes in pregnant women are metabolized in the liver, with the same process of glucoronidation with its metabolite form 7 Glucuronides metabolites, which is different ie an increase in activity of UGT 1A1 due to the influence of progresterone hormone during pregnancy. The process of excretion in pregnant women Clearance (C) increased 31.9-73.3 ml / min / Kg

Nifedipine pharmacokinetics in general in pregnant women namely; Absorbtion process in pregnant women The same absorbance in GI tract (oral route), decreased Cmax (10 mg) 38.6-18 ng / ml in 40 min and t ½ became shorter. Distribution Process in Pregnant Women The volume of distribution during pregnancy did not change significantly. Metabolic processes in pregnant women are equally metabolic processes unless CYP3A regulation increases during pregnancy. The process of excretion in pregnant women Clearance (C) 2.0 +/- 0.8 ml / min / kg (faster in pregnant condition) and increased clearance leads to shorter duration of action.

Labetalol and nifedipine are category C (FDA) antihypertensive drugs that can be used in hypertension therapy during pregnancy due to no teratogenic risk.

SUGGESTIONS

By knowing the symptoms and risk factors of hypertension, it is expected that the general public is able to anticipate and prevent the risk of hypertension with the implementation of dietary modification or a healthy lifestyle. Health workers in particular are expected to be able to manage hypertension management with safe medicines, especially in pregnant women, so that complications can be minimized. A review of the administration of antihypertensive medications during pregnancy is required, adjusting the variation between individuals and pharmacokinetic changes of the drug when administered under the conditions of pregnancy.

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