

Antihypertensive in Pregnancy-Pharmacotherapy Options

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ABSTRACT

Hypertension during pregnancy is a risk factor for many complications both for the mother and fetus and may lead to mortality of both due to serious complications. Nearly 8% of pregnancies are complicated by hypertensive disorders. Active management of hypertension is necessary to reduce complications of hypertension in pregnancy. Drugs like labetalol, methyldopa are most commonly used oral drugs to treat hypertension. While drugs like hydralazine is mostly preferred for emergency management of hypertension. Low dose aspirin and calcium has showed some benefits in preventing hypertension in pregnancy.

Key words: Antihypertensive, Pregnancy, pharmacotherapy, prevention.

INTRODUCTION

Maternal and neonatal morbidity and mortality is associated with preeclampsia. It has been estimated that nearly 14% of maternal deaths per year is linked to preeclampsia worldwide. All antihypertensive drugs have either shown or assumed to cross placenta. But none of the agents in routine use have been clearly documented to be teratogenic. Even the long feared ACE inhibitors and ARB's has been shown only to be toxic to the foetus, in other words it can be said that they are foeto-toxic and not teratogenic. This comprehensive discussion is an attempt to understand the pharmacotherapy options available in treating the patients.

Hydralazine

It has gained as most important drug for treating acute severe hypertension in pregnancy, so this drug has become the first line therapy¹. Sometimes it can also be used for chronic hypertension in pregnancy although it is not preferred due to tolerance it causes on routine administration, devoid us of drug in emergency. This drug acts by causing vasodilation in peripheral vasculature. Hydralazine activates potassium channel causing

potassium efflux, so decreased potassium prevents calcium mediated smooth muscle constriction. But the vasodilation requires nitric oxide from the endothelium.

This drug is placed in US FDA Pregnancy Category C. The dose needed for acute severe hypertension is 5-10 mg every 20 minutes given in IV bolus over 2 minutes. May be repeated after 30 minutes, then for every 6 hours it can be repeated. But the dose for chronic hypertension is 25 – 50 mg TDS oral there is a very high possibility of development of tolerance, so judicious use is advised. The onset of action is 10-20 minutes with duration of action ranging from 3-8 hours².

The most common side effects limiting the drug use are headache, nausea, flushing, gastrointestinal disturbance including vomiting, diarrhoea, it may also cause maternal hypotension and tachycardia, lupus like syndromes which may have been reported in neonates, low Apgar scores of <7 at 5 minutes also can occur in new-borns. This drug is definitely contraindicated in lupus erythematosus and severe coronary artery disease. Precautionary fluid management with crystalloid

500 ml before or at the same time as first dose is advised since immediate hypotension can occur with hydralazine IV. This has no obvious association with any congenital abnormalities³.

Labetalol

It has a status of second line drug in treating acute hypertension in pregnancy. But recently became the most preferred drug for chronic hypertension in pregnancy. Mechanism of action: It is a mixed alpha/beta adrenergic antagonist. It has a mixed alpha/beta adrenergic competitive antagonist action. The alpha blocking action is selective to α_1 receptor, while the beta action is non-selective. Beta blocking action is more pronounced than alpha action, which even doubles when given parenteral. By blocking adrenergic stimulation of α_1 receptors in myocardium and α_1 receptors of vascular smooth muscles reduces a systemic arterial blood pressure and systemic vascular resistance without reducing resting heart rate, cardiac output or stroke volume, apparently because of its combined alpha and beta adrenergic activity. This is classified under Pregnancy Category C of US FDA

For acute hypertension it is used only as a second line drug, the dose is 20 – 50 mg IV bolus over 2 minutes. This dose may be repeated after 15 to 30 minutes, the maximum IV dose is 300 mg, then switched to oral. Apart from bolus dose, IV infusion at a rate of 2 mg/ min can also be given^[3]. Currently labetalol is the drug of choice for chronic hypertension with dose 100 – 400 mg TDS oral. The onset of action after reaching blood is 5 min with duration ranging from 3 – 6 hours⁴.

Side effects of dizziness, depression, bronchospasm, gastrointestinal disturbance are most common, with chronic administration side effects of raynaud's phenomenon, lipid metabolism disturbance can occur. Sudden withdrawal may precipitate angina so it must be done with caution. Patients with asthma and congestive heart failure are contraindicated for labetalol as they may precipitate those conditions. And precaution must be taken care during labour since neonatal bradycardia may occur.

Labetalol has no obvious association with congenital abnormalities, but in rare occasion it may show mild hypotension in first 24 hours of life and

very rarely hypoglycaemia⁵.

Methyldopa

Earlier it was the drug of choice for controlling chronic hypertension in pregnancy but this crown is now taken by labetalol. It has dual action, one, acting as a competitive inhibitor of DOPA decarboxylase, so reducing dopamine which subsequently reducing adrenaline, resulting in reduced dopaminergic and adrenergic neurotransmission. Two, it is converted to methylnorepinephrine by dopamine beta hydroxylase. This compound is agonist to α_2 receptor in presynaptic neuron. This action reduces sympathetic output in nervous system. Both these actions reduce blood pressure.

It is the only antihypertensive drug with pregnancy category B in FDA. This drug has an excellent record of safety profile than any other drug. But it lost its favour to labetalol for more efficiency and less side effects. The dose preferred is from 250 to 750 mg BD to QID orally. It has slower onset over 24 hours period⁶. Being a centrally acting drug it has many psychological side effects from depression, anxiety, somnolence, impaired attention, memory and cognitive impairment and restlessness. Also the other side effects are vertigo, miosis, xerostomia, gastrointestinal disturbance, migraine, myalgia, restless legs syndrome, parkinsonian symptoms, facial paralysis, bradycardia, hypotension, hepatitis, pancreatitis etc. Also rebound hypertension is known to occur. Precaution must be taken to stop drug within 2 days of birth and any pre pregnancy treatment for hypertension can be started. Neonatal hypotension may occur when the drug is taken during delivery. But there is no obvious association with congenital abnormalities⁷.

Nifedipine

It is widely used for acute treatment of hypertension in pregnancy. But still now FDA has not approved for this indication. It comes under Pregnancy Category C of US FDA. It is calcium channel blocker, primary blocking L-type calcium channels which reduces influx of extracellular calcium for contraction to occur. This cause arterial vasodilatation and decreased peripheral vascular resistance which results in reduced arterial blood pressure. For acute severe hypertension, 10 mg tablet orally, repeat after 30 minutes if response is

inadequate⁸. For chronic hypertension 20 mg BD oral, 60 mg once daily can also be given⁹. Earlier sublingual nifedipine was used for hypertensive emergencies in pregnancy, now this has been abandoned. Its onset is within 5 to 10 minutes and duration from 1 -4 hours. Side effects include tachycardia, flushing, gastrointestinal disturbance, hyperkalemia, edema, and headache. Nifedipine is contraindicated in patients with heart failure, heart block 2 or 3rd degree. But there is no data of any congenital abnormalities.

Sodium Nitroprusside

This is used only in acute severe hypertension. It breaks down to nitric oxide (NO). Nitric oxide reduces total peripheral resistance and venous return by causing vasodilatation. This should be used only when all treatments fail. It is given in the dose of 0.5 µg/kg/min to 5 µg/kg/min [10]. The most serious effect is Foetal cyanide poisoning which occur if used for more than 4 hours. It is labelled under Pregnancy Category C of US FDA
Diazoxide

A potassium channel activator causing relaxation of vascular smooth muscles, causing vasodilatation and reduction of blood pressure. It is used for acute severe hypertension in a dose of 15 to 45 mg rapid IV bolus is given¹¹. This dose may be repeated after 5 minutes. Side effects include inhibition of uterine contraction and profound maternal hypotension. Apart from this neonatal hyperglycemia is reported.

Prazosin

It is alpha blocker. Used in a dose of 0.5 to 5 mg TDS orally. Side effects may include first dose effect – orthostatic hypotension. This drug has shown no obvious congenital anomalies. It comes under Pregnancy Category C of US FDA².

Diuretics

All claims that diuretics prevent hypertension in pregnancy have been proven false. Also they are known for their electrolyte imbalance effect which in pregnancy may prove costly. But drugs like thiazide diuretics are not known to be teratogenic. Any how these drugs have no additional benefits in combination or alone compared with well-established drugs. Diuretics like spirinolactone is not used

because of its antiandrogenic effects on foetus and furosemide provide no added benefit from other drugs¹²⁻¹³.

Other Calcium channel blockers

There is no evidence of benefits reported for amlodipine also the safety profile in pregnancy is still incomplete. While verapamil showed no obvious congenital abnormalities but its efficacy is still surpassed by other drugs given for hypertension in pregnancy¹⁴.

Beta blockers

Atenolol should never be considered a drug for hypertension in pregnancy since it may cause low birth weight and placental weight. Also causes neonatal bradycardia¹⁵. For this reason it is kept under Pregnancy Category D in US FDA. Other beta blocker like metoprolol, oxprenolol, pindolol has no obvious association with congenital abnormalities but not used since better proven alternatives exist¹⁴.

Angiotensin converting inhibitors and Angiotensin receptor blocker's

Even though these drugs have been omitted permanently as an option for hypertension during pregnancy till now there is no conclusive evidence that these drugs are teratogenic exist. So all women can be assured that they can get pregnant while taking these drugs, of which data for ACE inhibitors are strong. But these women must be informed to discontinue the drugs within two days of identification of pregnancy. Oligohydramnios, Intra Uterine Growth Retardation (IUGR), joint contractures, pulmonary hypoplasia, hypocalvaria, foetal renal tubular dysplasia and neonatal renal failure are the malformations reported for these drugs¹⁶⁻¹⁷.

Prevention of Preeclampsia

Low dose Aspirin

Low dose Aspirin results in a small decrease in preeclampsia. Intravascular production of prostacyclin, a vasodilator, and excessive production of thromboxane, a vasoconstrictor and stimulant of platelet aggregation becomes deficient in preeclampsia. So anti-platelet may be helpful in preventing preeclampsia. Aspirin also partially corrects the pathologic increase in angiotensin

II sensitivity which precedes preeclampsia. No evidence of short or long term adverse effects on mother or new born. It does not increase miscarriage risk. The dose used is 75 mg/ day; even 100 mg/day may affect foetal prostacyclin synthesis. Also it has been found that bedtime aspirin resulted in more blood pressure control than in morning. It may be continued till delivery¹⁸.

Calcium

It is understood that inverse relation between dietary calcium intake and blood pressure exists. Since low calcium causes vasoconstriction by either increasing magnesium levels or by stimulating release of parathyroid hormone or renin. It is proposed that Calcium supplement may prove beneficial. Evidence substantiating the finding is also present [19]. So oral calcium supplement of at least 1g/day is recommended²⁰.

Antihypertensive therapy

Antihypertensive therapy does not prevent preeclampsia. But decreased incidence of severe hypertension among women has been seen.

Drugs not recommended for prevention of pregnancy induced hypertension (PIH)

Diuretics²¹, Nitric oxide donors²², Progesterone²³, Low molecular weight heparin²⁴ is not recommended for prevention of pregnancy induced hypertension because of its potential risk it possess to the foetus.

Drugs showing no additional benefit in PIH prevention

Magnesium, folic acid²⁵, antioxidants (Vitamin C and E)²⁶, fish oils (Omega 3 fatty acids)²⁷ shows no added benefit in preventing hypertension in pregnancy.

Breast feeding

The drugs with no known adverse events on babies are labetalol, nifedipine, metoprolol, atenolol, enalapril, captopril, angiotensin converting enzyme inhibitors (except Enalapril and Captopril), angiotensin receptor blocker's and amlodipine there is no sufficient data to be given during breast feeding²⁸. But diuretics is usually avoided during lactation since it may cause increased thirst²⁹.

CONCLUSION

The most acceptable antihypertensive agents are labetalol, methyldopa, nifedipine and for emergency management hydralazine followed by labetalol is most preferred. Low dose aspirin and calcium supplement can be tried for women holding higher risk of developing PIH. Even though pregnancy induced hypertension can be prevented, the options for prevention with medications and lifestyle modification are very minimal and too difficult. Proper management of the condition during pregnancy helps to prevent teratogenicity and fetotoxic effects due to hypertension and its complications. Good knowledge about the various medications available, their mechanism of action and the sideeffects is of utmost importance for the treating physician for best therapeutic effects both for the mother and the child.

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