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Review Article

Comparative Study Of Antihypertensive Drug Between Nifedipine, Carvedilol And Methyldopa In Emergency Condition

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ABSTRACT

Throughout the world, hypertension affects billions of individuals. It dramatically raises the risk of heart attacks, heart death, and kidney issues. A number of medication classes are available to assist healthcare providers and their patients in controlling hypertension. Worldwide, more than 1 billion people live with the chronic illness known as hypertension. The Framingham Heart Study revealed that even individuals with normal blood pressure (BP) at age 55 had a 90% lifetime risk of developing hypertension. This is because the likelihood of developing hypertension increases with age. In an emergency involving hypertension, nifedipine, methyldopa, and carvedilol are recommended as first-line treatments for preeclampsia. To determine which drug is the least expensive and has the fewest side effects, more study is needed to assess the effectiveness of various treatments. This study examined the efficacy of different drugs in lowering blood pressure in cases of hypertension.

INTRODUCTION

Preeclampsia, pregnancy, and other emergency conditions are among the most common causes of hypertension. An abrupt, dramatic rise in blood pressure is known as a hypertensive crisis. At least 180/120 millimeters of mercury (mm Hg) is the blood pressure reading. A hypertensive crisis is a medical emergency. A heart attack, stroke, or other potentially lethal medical issues could arise from it. (12)(13). Blood arteries and internal organs, such as the heart, brain, kidneys, and eyes, can sustain harm from extremely high blood pressure. It is possible that the heart cannot pump blood efficiently during a hypertensive crisis.(12)

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There are two types of hypertensive crises.

- A hypertensive emergency. Blood pressure is at least 180/120 mm Hg. No indications of organ damage are present.
- Hypertensive emergency crisis. Blood pressure is at least 180/120 mm Hg. There is life-threatening damage to the body's organs.

Treatment

Antihypertensive drugs fall into several groups; the most commonly used ones are

- Calcium channel blockers (dihydropyridines), such as nifedipine.
- Beta- and alpha-adrenergic blockers (sympathetic inhibitors), such as methyldopa and carvidilol
- Hydralazine, ex of vasodilator.

Therefore, our goal was to evaluate the safety and effectiveness of nifedipine in the treatment of severe hypertension in emergency situations. For the majority of patients, antihypertensives brought their blood pressure down to the reference range. Compared to labetalol or methyldopa, nifedipine retard usage as a single medication led to a higher frequency of primary outcome attainment. In low-resource situations, methyldopa, nifedipine, and carvedilol are all reasonable first choices for treating severe hypertension.(11) Preterm delivery, fetal growth restriction, and increased morbidity and mortality among the mother, fetus, and newborn are among the negative outcomes of hypertension in pregnancy that affect both the mother and the unborn child.(9) (11)

Nifedipine

Studies comparing nifedipine to other antihypertensives have been carried out, particularly after the release of the GITS formulation. Nifedipine may be a better hypertension treatment since it may not be as concerned about reflex SNS activation. In a 10-week, multi-center, double-blind trial with 102 participants, patients received hydrochlorothiazide (HCTZ) 25 or 50 mg daily along with nifedipine GITS 30 or 60 mg daily. In addition, nifedipine and other dihydropyridine CCBs, such as amlodipine, have been compared. In a particular trial, individuals were randomly assigned to receive either daily (1)(4) Only longer acting formulations of this dihydropyridine calcium channel blocker should be used, as short acting formulations have been linked to reflex sympathetic nervous system (SNS) activation, which can cause flushing, tachycardia, worsening myocardial ischemia, and cerebrovascular ischemia. Extended-release formulations are widely accessible and have demonstrated comparable efficacy to other antihypertensives such as ARBs, -blockers, and diuretics in the treatment of hypertension. [8](4)

Bioavailability and half life

Plasma levels show that nifedipine is virtually entirely absorbed from the gastrointestinal tract after sublingual, oral, and rectal dosing. Presystemic metabolism is responsible for between 56 and 77 percent of the bioavailability. After 30 to 60 minutes of oral administration of 10 mg, the mean plasma concentration of nifedipine reaches its highest levels of 160 +/- 49 micrograms/liter. The mean concentration falls to 3.4 +/- 1.2 micrograms/liter after 8 hours.(14) Biphasic elimination takes place following intravenous administration (0.015 mg/kg); in healthy volunteers, the half-lives of the alpha and beta phases are 1.26 +/- 0.55 hours and approximately 13 minutes, respectively.(7) A third phase with a half-life of roughly eight hours can be observed following the oral administration of larger doses (40 mg) and following a continuous infusion over a 24-hour period. The total body clearance is 0.45 +/- 0.1 liter/hr. kg, and the apparent volume of distribution of the central compartment (Vce) is 0.294 +/- 0.1 l/kg. The primary metabolites of nifedipine are 2,6-dimethyl-4-(2-nitrophenyl)-5-methoxycarbonyl-pyridine-3-carboxylic acid (M I) and the

corresponding 2-hydroxymethyl-pyridine-carboxylic acid (M II), which are produced by the liver during the metabolism of the drug. Techniques have been developed for the quantitative detection of the main metabolites in plasma and urine (GLC) and unchanged nifedipine in plasma (HPLC) in the presence of the pyridine analog. HPTLC, a straightforward semiquantitative technique for identifying metabolites in urine, can be used to track patient adherence.[7] [14] In a crossover design, the kinetics and pharmacologic effects of three nifedipine formulations were investigated in six young, healthy menEach individual received 20 mg of nifedipine in pill form, 20 mg of nifedipine in slow-release tablet form, or 0.015 mg/kg body weight intravenously. Changes in heart rate (HR), blood pressure, heart size, and plasma norepinephrine levels (PNE) were all examined repeatedly. Urine metabolites and nifedipine (Cp) concentrations in plasma were determined by liquid chromatography. After the intravenous injection, the distribution volume was 0.8 ± 0.2 l/kg, the elimination t½ was 1.7 ± 0.4 hr, and the systemic clearance was 26.7 ± 5.4 l/hr. Following the capsule, Cp grew swiftly, reaching a maximum time (Tmax) of 1.4 ± 0.5 hours and a maximum concentration (Cmax) of 117 ± 15 ng/ml. The Cmax was 26 ± 10 ng/ml and the tmax was 4.2 ± 0.7 hours after the sustained release pill. After investigation, the bioavailability of nifedipine varied significantly between individuals: 56% ± 25% for the capsule and 52% ± 13% for the tablet. Urine excretion was 58% ± 13% 24 hours after the intravenous injection, 55% ± 13% after the capsules, and 32% ± 8% after the tablets 32 hours later. HR increased briefly (15–20 bpm) with the intravenous injection and the capsules, but not significantly following the tablets. After consuming the pills (8 to 10 mm Hg), there was a brief drop in diastolic blood pressure (DBP). ; however, the effect persisted after taking tablets. Cardiac measurements did not change. In all three trials, PNE levels correlated with drug plasma levels .The changes in DBP and nifedipineCp showed a hyperbolic correlation (r2 = 0.86), with a minimal effective concentration of roughly 15 ng/ml. The effect on blood pressure and heart rate is directly correlated with nifedipine kinetics, it is concluded. With the tablet, side effects from a high Cmax can be avoided. Dosing twice a day is probably going to have a long-lasting effect.(14) (6)

Pharmacology

By operating as an arterial vasodilator, nifedipine treats angina and hypertension. Smooth muscle contractions are regulated by calcium ions, which contribute to the heart's inotropic and chronotropic activity. In vascular smooth muscle, the L-type channels allow calcium ions to enter, intensifying a contraction. Dihidropyridine CCBs, like nifedipine, attach to the L-type channel in arterial tissue, especially coronary arteries, blocking calcium ion inflow, which promotes vasodilation and increases oxygen delivery to the heart. Peripheral vascular resistance declines in tandem with a decrease in cardiac oxygen demand. Systolic blood pressure drops, which is indicative of a reduction in afterload caused by CCBs.A patient's blood pressure will drop depending on their baseline value; patients with higher baseline values will see a more notable drop. Dihydropyridine CCBs have also been linked in several studies to a reduction in the formation of new atherosclerotic lesions; this reduction is believed to be a result of their vascular protective properties. Research on female subjects indicates that there is little danger to the baby if this drug is taken while nursing.(7) (3) (9)

MECHANISM OF ACTION

Through the blockage of voltage-dependent L-type calcium channels, nifedipine prevents the entrance of calcium ions

It causes the intracellular fluid's calcium ion concentration to drop, which lowers peripheral artery resistance.

Cause the coronary arteries to dilate, the blood pressure in the system to drop, and the oxygen supply to the heart to rise.

Administration

Both immediate and prolonged release preparations are offered for them. Rapid vasodilation is caused by this preparation, and reflex sympathetic activity follows. Compared to the immediate-release formulation, the bioavailability of extended-release formulations can reach up to 89%.

Recommended doses-

Extend release – 30 or 60 mg daily

Hypertensive condition in pregnancy :-

Immediate release – 10 mg in 20 min

Pharmacokinetics

a. Absorption

Nefidipne exhibits zero order kinetics within the 30 mg to 180 mg dosage range .Nefidipine's bioavailability ranges from 56% to 77%.formulations with extended release for use in long-term therapeutic activation .Although it is nearly entirely absorbed in the digestive system, first pass metabolism contributes to its 45–68% bioavailability.(14).(7)

b. Distribution

Nifedipine's steady state volume of distribution is 0.62-0.77L/kg, while the central compartment's volume of distribution is 0.25-0.29L/kg. 90% to 95% of proteins bound. (1)(7)

c. Metabolism

CYP3A4 is primarily involved in the metabolism of nifedipine. 2,6-dimethyl-4-(2-nitrophenyl)-5-methoxycarbonyl-pyridine-3-carboxylic acid is the main product of nifedipine metabolism. 2-hydroxymethyl-pyridine carboxylic acid is the end product of additional metabolism. A little metabolism of nifedipine results in dehydronifedipine. It was discovered that the maximal mean plasma concentration of nifedipine was 160 +/- 50 mg/liter after 30 to 60 minutes of oral treatment of 10 mg. After 8 hours, the concentration drops to 3.4 +/- 1.2 mg/liter.

After injecting the emulsion, the alpha phase has a half-life of 13 minutes and the beta phase has a half-life of 1.2 +/- 0.5 hours . The estimated elimination half-life is 1.7 hours. Urine contains 90% to 60% excited inactive metabolites.(14)(7)

d. Elimination

The majority of the nifedipine is excreted in the feces as metabolites, with the remaining 60–80% being recovered in the urine as inactive water soluble metabolites.

Interaction

- Specific guidelines for using food, drink, or tobacco.
- Juice of grapefruits
- Because grapefruits and grapefruit juice increase the amount of nifedipine in your body, they may intensify its effects. When taking this medication, avoid consuming grapefruits or grapefruit juice.(14)(1)(3)

Methyldopa

Methyldopa is a drug that is used to treat and manage hypertension. This medication belongs to the class of centrally acting anti-hypertensive drugs. This exercise goes over the uses, side effects, and precautions of methyldopa, a useful medication for treating hypertensionThis session will emphasize the mechanism of action, adverse event profile, and other pertinent information that interprofessional team members need to know when managing patients with hypertension and

related disorders(4)(5)(9)One centrally acting sympatholytic medication used to treat hypertension is methyldopa. The medication was first introduced in 1960 and soon rose to prominence as an antihypertensive; however, due to the availability of more tolerable substitutes, its use has significantly declined. Because of its low cost, it is still in use in developing nations. Because this medication has no teratogenic effects, it is also beneficial during pregnancy.(11) An increased risk of myocardial infarction, stroke, and congestive heart failure is linked to hypertension. Throughout the 1970s and 1980s, methyldopa, a centrally acting antihypertensive medication, was widely used to regulate blood pressure. Due to its low cost, it is still used in developing countries even though antihypertensive drug classes with fewer side effects have largely replaced its use in medicine today. If you are allergic to methyldopa or have any other allergies, let your doctor or pharmacist know before taking it. Inactive ingredients in this product have the potential to trigger allergic reactions or other issues.(4)(5)

MECHANISM OF ACTION

Alpha-methyldopa is converted to methyl norepinephrine centrally to decrease the adrenergic outflow by alpha-2 agonistic action from the central nervous system

Decreasing systemic blood pressure and total peripheral resistance as a result.

This medication is helpful for hypertensive patients with renal insufficiency since alpha-2 agonistic activity has no effect on cardiac output or renal blood flow.

Administration

125, 250, or 500 mg tablets containing a single ingredient of methyldopa are generically available. There are also fixed-dose thiazide combinations available. For adults, a daily dosage of 500 mg to 2 g is advised. Methyldopa hydrochloride is available for IV infusion. After diluting the medication with 5% dextrose, the required dosage is added to 100 milliliters of 5% dextrose in water injection, which is then gradually given over a period of 30 to 60 minutes. It is not advised to administer intramuscularly (IM) or subcutaneously because of variable absorption.(5)(11)

Pharmacokinetics

a. Absorption

In about three to six hours, peak plasma concentrations are reached at 50% of the absorbed dose . . .After oral administration, blood pressure drops to its maximum in 4–6 hours. Hypotensive episodes last for roughly 10 to 16 hours after IV therapy. The active L-isomer is more readily absorbed in healthy individuals than the inactive D-isomer Methyldopa has a mean bioavailability of 25%, with a range of eight to 62%.(5)(4)

b. Distribution

The medication is lipid soluble and binds weakly to plasma proteins to cross the blood-brain barrier. When compared to the medication, its primary metabolite exhibits higher plasma protein binding .The distribution's total volume spans 0.41 to 0.72L/kg, while its aspparent volume falls between 0.19 and 0.32L/kg.(5)

c. Metabolism

The active metabolite of methyldopa is alpha-methylnorepinephrine. Additionally, the drug undergoes extensive liver metabolism to produce its sulfate conjugate.(4)(5)

d. Elimination

Seventy percent of the drug is excreted in urine as parent drug and metabolite. Unabsorbed medication is eliminated unaltered in feces. Patients with renal failure have sluggish excretion, which causes the medication and its metabolites to build up.

Half-life

Methyldopa has a plasma half-life of 105 minutes. Methyldopa has a plasma half-life of 90 to 127 minutes after intravenous injection.

Interaction

Products containing iron (such as ferrous sulfate and ferrous gluconate) and lithium are a few examples of items that may interact with this medication. There could be a major (potentially fatal) drug interaction if MAO inhibitors are taken with this medication. (11)

Carvedilol

A non-selective adrenergic blocker, carvedilol is prescribed for the long-term treatment of hypertension, left ventricular dysfunction, and heart failure with reduced ejection fraction (HFrEF) in patients who are clinically stable after myocardial infarction (MI). Beta-blockers are used to treat hypertension; whichever beta-blocker a doctor chooses, anti-anginal therapy targets a heart rate of 60 or lower. It is possible to achieve rate control therapy with almost any beta-blocker when treating atrial fibrillation. While some studies have indicated that carvedilol may be more effective than other beta-blockers in lowering hepatic venous pressure or preventing variceal bleeding, it should be noted that specific beta-blockers other than carvedilol are preferred for preventing esophageal variceal bleeding.(2)(6)

MECHANISM OF ACTION

As said, carvedilol is a non-selective adrenergic blocker; more precisely, it is a non-selective beta-blocker that possesses antagonistic effects on alpha1-adrenergic receptors

It Is a peripheral vasodilator and non-selective cardiac beta-blocker.

Carvedilol's alpha1-blocking effects reduce arterial vascular resistance, which lowers blood pressure primarily via lowering afterload

Administration

Oral therapy doses of twice-daily immediate-release or once-daily controlled-release carvedilol are administered. The dose is customized according to response to heart rate and blood pressure. For blood pressure control, start at 6.25 mg twice daily and work your way up to 12.5 mg and finally 25 mg twice daily over the course of one to two weeks.(2)(3)

Pharmacokinetics

a. Absorption

After administration, carvedilol is quickly absorbed, reaching its peak plasma concentration (Cmax) in one to two hours. When carvedilol is taken with food, the rate of absorption decreases but the bioavailability remains unchanged. Despite being well absorbed, carvedilol has a low 25% systemic bioavailability because of significant first-pass metabolism.(2)(6)

b. Distribution

Carvedilol is a medication that is widely absorbed by tissues and is very lipophilic. With an approximate volume of distribution of 1.5 L/kg, it is high.

c. Metabolism

Oxidation is the liver's method of breaking down Carvedilol. CYP2D6 and CYP2C9 are the two main cytochromes P450 that mediate metabolism.

d. Elimination

Mostly excreted into the bile and removed through feces only sixteen percent are eliminated through urine.(2)(6) Half-life of carvedilol is generally of 6- 7 hours.

Table 1 Pharmacokinetics of all three drugs:-

	Nifedipine	Methyldopa	Carvedilol
Administration	Dose(adult) 10 mg - 120mg Daily	Dose(adult) 500mg – 2g Daily	Dose(adult)10 – 80 mg daily
Absorption	Completely absorb in GTI	Completely absorb in GTI	Completely absorb in GTI
Bioavailability	56%-77%	Oral –50% Mean-25%-65%	25% - 35%
Distribution	Distribution volume 0.62 – 0.77 lit/ kg	Distribution volume 0.19 –0.33 lit / kg	Distribution volume 1.5 lit / kg
Protein Binding	Protein binding 92% - 98% (Serum) 97% in solution	Protein binding Less than 15% 50 in plasma	Protein binding 95 % in (serum albumin)
Elimination	Enzyme CYP3A4	Unabsorbed drug (feces) requires 36 hrs	Enzyme CYP2D6 , CYPE4
Metabolism	60%- 90% in urine	Only 70% in urine	Only 16% In urine
Half-life	120 min	I.V – 150 min	7- 8 hrs
Adverse effects	Dizziness, Lightshades, Fainting .	Bind to Alpha 2 receptor as agonist.	Allergy, Chest pain, dizziness, Fainting.
Interaction	Must be avoided taking with grapefruit or juice , may be induce action of medication .	Should be avoid taking with drug containing iron product (feSo2). Also should not take with MOA inhibitor	Carvedilol can interact with heart rhythm medication, digoxin and certain antidepressant.

CONCLUSION

When taken as a single dose, nifedipine is the medication that decreases blood pressure the greatest; however, successive doses are needed to further drop blood pressure. For the majority of pregnant women, all oral antihypertensives brought blood pressure down to the reference range. Compared to carvedilol or methyldopa, nifedipine administration as a single medication led to a higher frequency of primary outcome attainment. The key conclusion drawn from the foregoing discussion is that nifedipine is the best medication to treat hypertension in emergency situations like pregnancy and preeclampsia when taken as a single dosage.

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