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CHOICE OF ANTIHYPERTENSIVE FOR SPECIAL POPULATIONS

Dr. Mohamed Ashraf*[1] and R. Venugopal[2]

[1]Pharmacist, SEHA- AHS-Abu Dhabi.

[2]JKK Munirajah Medical Research Foundation College of Pharmacy, Komarampalayam, Tamil Nadu -638183.

***Corresponding Author: Dr. Mohamed Ashraf**

Pharmacist, SEHA- AHS-Abu Dhabi.

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ABSTRACT

Hypertension is a multifaceted disease that may present somewhat different in various populations. It is clear that hypertensive treatment reduces cardiovascular, renal and cerebrovascular outcomes for all patients, yet recent clinical trial data suggests that some groups may get benefit more than others from specific drug intervention. This article reviews important features of the presentation, rationale for treatment, and recommendations for the treatment of hypertension in special populations.[1] Early identification of these patients and achieving BP goal could reverse early end organ damage and improve outcomes in these patients. Analysis of the data from Framingham Heart study demonstrate that a 2-mm Hg reduction in blood pressure would result in 14 % reduction in the risk of stroke and transient ischemic attacks, and a 6% reduction in risk of coronary heart disease. The effective management of hypertension is therefore an important primary health care objective in managing cardiovascular and renal disease.

KEYWORDS: Hypertension, Blood pressure, betablockers.

INTRODUCTION

Hypertension is a multifaceted disease that may present somewhat different in various populations. It is clear that hypertensive treatment reduces cardiovascular, renal and cerebrovascular outcomes for all patients, yet recent clinical trial data suggests that some groups may get benefit more than others from specific drug intervention. This article reviews important features of the presentation, rationale for treatment, and recommendations for the treatment of hypertension in special populations.[1] The special populations addressed include diabetic patients, pregnancy and lactation, the elderly and young patients.

CIRCADIAN RHYTHM OF BLOOD PRESSURE

It is commonly known that, in healthy humans, heart rate (HR) and blood pressure (BP) increase during the day and decrease during the night, as a result of sleep-wake or rest-exercise changes.[5,6] In addition, BP, HR, cardiac output, and serum catecholamine levels rise during the day and fall during the night.[1-6] According Guo et al,[3] these changes enable the organism to adapt to the need for higher activity levels while awake. However, the exact relationships of endogenous and exogenous factors to the circadian rhythms of the autonomic neural system are not yet clear.

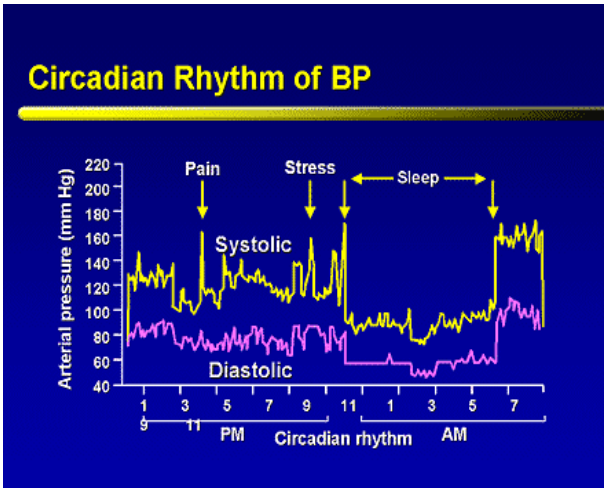

Fig 1: Circadian Rhythm of Blood pressure.

A night time fall is normal and desirable. It correlates with relationship depth but other factors such as sleep quality, age, hypertensive status, marital status, and social network support.[7]Absence of a night time dip is associated with poorer health outcomes, including increased mortality in one recent study.[8] In addition, nocturnal hypertension is associated with end organ damage[9] and is a much better indicator than the daytime blood pressure reading.

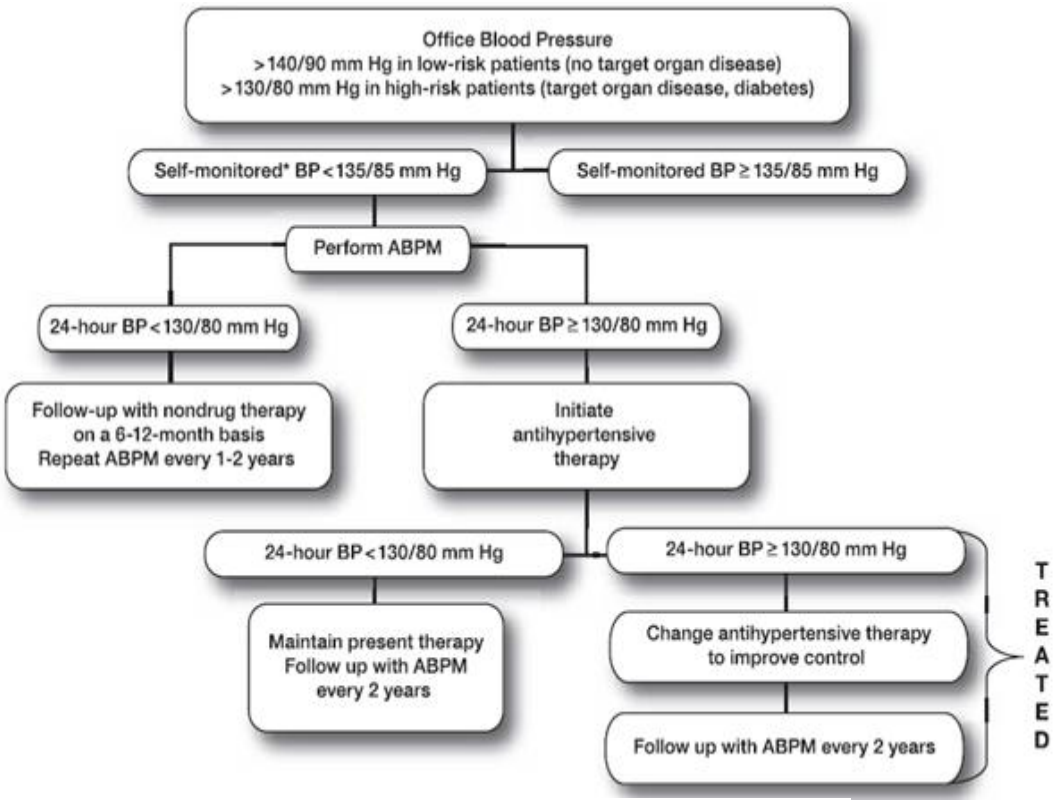

Fig 2: Monitoring, Initiation and rationale for therapy

The average Nocturnal BP is approximately 15% lower than day time value, failure of BP to fall at least 10% during sleep (none dipping) is a stronger predictor of adverse cardio vascular outcome, shifting at least one anti-hypertensive medication from morning to evening may restore normal nocturnal BP dip, (in HOPE and EUROPA trial).

The renin–angiotensin–aldosterone system (RAAS), mainly via production of angiotensin II, is a key regulator of BP. The RAAS is activated in the early morning before arousal as a result of sympathetic neuronal activation.[11,12] In addition, both renin and aldosterone demonstrate significant circadian patterns in both normotensive and hypertensive individuals,[12] with peak values detected early morning then falling to their lowest point in late evening. A similar pattern has been observed for angiotensin II.[11]

People with diabetes are at risk of kidney disease (nephropathy). Microalbuminuria is the earliest sign of kidney damage, whereas diabetic nephropathy is a more severe form of kidney disease.[13] Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists (ARB) are antihypertensive treatments indicated for treating diabetes and kidney disease. The SIGN guideline for diabetes recommends that all people with diabetes and a diagnosis of microalbuminuria are offered ACE inhibitors or ARB treatment, irrespective of blood pressure. This is in agreement with the NICE guidelines[14] for type 1 diabetes and type 2 diabetes, which recommend ACE inhibitors for people with diabetes who have microalbum inuria or confirmed nephropathy, or ARB treatment if ACE inhibitors are not tolerated.

USE OF BETA BLOCKERS

The study by Bradley et al[15] studied by comparing other medications with beta-blockers on a category by category basis. This meta-analysis revealed the superiority of calcium channel blockers and inhibitors of the renin-angiotensin system as regards overall mortality and stroke. The British Hypertension Society corroborated these findings and in its new guidelines recommends starting antihypertensive therapy with calcium channel blockers or thiazide diuretics in patients aged over 55 years and with ACE inhibitors in patients aged below 55 years.[16]

The unfavourable effect of beta-blockers on the metabolic profile of patients with certain risk factors (metabolic syndrome, abdominal obesity, glucose intolerance, familial history of diabetes mellitus), as well as their lower efficacy in the regression of left ventricular hypertrophy, must always be taken into account when treating for conditions in coexistent with hypertension. Also evidence are insufficient to prove beta blockers is superior to ACEI, ARBs, CCB and thiazides to prevent stroke as mono therapy.[17]

The LIFE {2002) and ALLHAT (2002) trials have found beta blockers are inferior to low dose of Thiazides or ACE inhibitors/ARB's. Rebound hypertension is also common on sudden discontinuation of beta blockers.[18]

Offer step 1 antihypertensive treatment with a calcium-channel blocker (CCB) to people aged over 55 years and to black people of African or Caribbean family origin of any age. If a CCB is not suitable, for example because of oedema or intolerance, or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic is considered.[19]

CHOICE OF MEDICATION IN PREGNANCY

Teratogenic effect must be considered when choosing anti-hypertensive drugs.

Vasodilators like Hydralazine is one of the preferred anti hypertensive during pregnancy especially preeclampsia because of decades of safety records. Even though Hydralazine is contraindicated in older patients and in those with ischaemic heart diseases, it is occasionally employed in hypertensive emergencies parenterally. Methyldopa is also used to treat hypertension during pregnancy due to safety records, both for mother and foetus.[20]

The National Guideline Clearinghouse,[21] regarding treatment of hypertensive disorders of pregnancy has recommended that the initial antihypertensive therapy should be started with labetalol (IA evidence) or nifedipine, to bring down the target BP to 160 systolic and 110 diastolic. In a Kuwaiti trial[22] involving 104 primigravidas with mild-moderate PIH, the investigators compared alpha-dopa with labetalol for antihypertensive management, and concluded that labetalol is quicker, more efficient and better tolerated. Although it crosses placenta, there is no evidence of intrauterine growth retardation (IUGR), perinatal death and neonatal hypoglycemia. It may ripen the cervix, and reduce the latency of labor in term patients.

In general, alpha agonists (methyldopa) and beta-blockers (acebutolol, atenolol, labetalol, mepindolol, metoprolol, pindolol, oxprenolol, and propranolol) are among the most frequently recommended antihypertensive drugs in pregnancy, although other drugs such as calcium channel blockers (siradipine, nicardipine, nifedipine and verapamil), diuretics (hydrochlorothiazide, etc.), vasodilators (hydralazine and prazozin), ketanserin and glyceryltrinitrate have also been used.[23-26]

BEST OPTION FOR BREAST FEEDING MOTHERS.

Key points about Breastfeeding and Medicines[27,28]

- Many medicines are safe in breastfeeding, however non-essential medicines should be avoided.
- Where possible drugs with short half-lives, high protein binding, low oral bioavailability and high molecular weight are preferred.
- The age and weight of the infant needs to be considered; caution is required for premature infants and neonates.
- Medicines that are safe to use in infants are generally safe to use in breastfeeding women.
- Medicines for which there is long-term experience of use in clinical practice rather than newer medicines are generally preferred.
- Medicines used in the first 3-4 days post-partum generally produce subclinical levels in the neonate due to the limited volume of milk produced during this period.
- Discontinuing breastfeeding for some hours/days may be required for a small number of medicines.

In the postnatal period some breastfeeding women may require antihypertensive medication. Many of the medications are suitable to use in breastfeeding, however there are some medications which are preferred. Various sources recommend that propranolol, labetolol and metoprolol are the preferred β blockers for breastfeeding women.[29,30,28,31,33,36] Other β blockers such as atenolol which has low protein binding and is primarily renally excreted, have been associated with adverse effects in infants and should be avoided.[29,31,32,34] Monitoring of the infant for hypotension, bradycardia and lethargy is recommended when using β blockers during breastfeeding.[29,28,31] Methyldopa is one of the preferred antihypertensives in breastfeeding women;[28,29,31] low levels of methyldopa are found in breastfed infants and are not expected to cause adverse effects.[28,33,34] Many sources include nifedipine, verapamil and diltiazem as the preferred calcium antagonists to use in mothers of breastfed infants.[28,29,30,31,33,36] Exposed breastfed infants to calcium antagonists should be observed for bradycardia and hypotension.[28] Angiotensin converting enzyme inhibitors (ACEIs): The ACEIs with the most amount of data available on breastfeeding are captopril and enalapril, which are amongst the preferred ACEIs in breastfeeding women.[28,29,31,33,35] They are not recommended however, in the first weeks after delivery due to concerns of profound hypotension, particularly in preterm infants. Infants exposed to ACEIs, should be observed for hypotension.[28] There is insufficient evidence on the safety of angiotensin receptor blockers (ARBs) in breastfeeding women to recommend their use.[30,31,36]

Drugs used in hypertension with Cerebro vascular diseases.

Table 1: Oral drugs for hypertensive urgency.

Drugs	Class	Dose	Onset	Duration
Nifedipine	Calcium Channel blocker	5-10mg S/L or swallowed	5-10min	3-5 hours
Captopril	ACE Inhibitor	12.5-50mg	15min	4-6 hours
Labetolol	Alpha beta blocker	200-400mg	30min -2 hours	8-12 hours
Clonodine	Central alpha agonist	0.2mg stat then 0.1mg/hr (total 0.8mg)	30min – 2 hours	6-8 hours

Table 2: Parentral drugs for treatment of hypertensive emergency in stroke

Drugs	Dosage	Onset of Action	Duration of Action	Side effects
Nitroprusside	0.25-10µg/kg/min as IV	Instant	1-2 min	Nausea, Vomiting, muscle twitching, sweating, cyanide intoxication
Esmolol	200-500µg/kg/min for 4min, then 50-300µg/kg/min as IV	1-2 min	10-20min	Hypotensive nausea
Labetolol	20-80mg IV bolus every 10 min, 2mg/min IV infusion	5-10 min	3-6 hours	Postural hypotension, nausea, vomiting, dizziness, burning in throat
Nitroglycerine	5-100µg/min as infusion	2-5 min	3-5 min	Headache, vomiting, tolerance on prolonged

Table -1 and Table - 2 depict the brief clinical pharmacology of important antihypertensive drugs used inacute stroke patients.[37] Nifedipine[38] is the most popular drug followed by captopril-both sublingually or orally. These agents can be administered repeatedly every 30 minutes till desirable effect is achieved. These agents in different ways, both dilate large cerebral arteries and increase downstream pressure, causing smaller – resistance vessels to constrict, thus during a fall in pressure these vessels provide more autoregulatory dilatory capacity than normal.[39] Medications likely to cause precipitous decline in blood pressure (rapid acting Nifedipine) should be avoided, their use is associated with increased risk of stroke, particularly in older adult patients.

HYPERTENSION WITH PERIPHERAL ARTERY DISEASES (PAD)

PAD is common and sometime painful complication with stenosis of the leg. In PAD, Hypertension has been associated with deficiencies in the synthesis of vasoligating substances, such as prostacyclin, bradykinin, and nitric oxide, by endothelial cells lining the vasculature. Hypertension also increases concentration of vasoconstricting substances, such as angiotensin two.

Lifestyle measures are effective in preventing development and reducing progression of hypertension.[40] In the absence of specific studies in PAD, it would be pragmatic to advise patients to adopt a multiple life style approach to management of hypertension in the context of overall cardiovascular risk. Reducing sodium intake below 100mmol/day, combined with the Dietary Approaches to Stopping Hypertension (DASH) diet, is more effective than either approach alone in reducing both onset of hypertension and blood pressure in patients with milder hypertension.[40] The DASH diet includes increased intake of fruits, vegetables, low-fat dairy foods, potassium, calcium, magnesium, dietary fibre and protein and includes whole grains, poultry, fish, and nuts. It also includes less red meat, sweets, and sugar-containing drinks than a typical Western diet.[40]

Mild distal tubular diuretics in younger and elder populations with uncomplicated hypertension reduce a wide range of CVD endpoints.[41] A thiazide was used within the INVEST Trial (see below) as add-on treatment, with evidence of overall endpoint benefit from intensive blood pressure lowering.[42] In patients taking thiazide treatment it is important to monitor blood glucose, uric acid, potassium and sodium levels to anticipate possible metabolic cardiovascular effects of treatment.

Although beta-blockers would be expected to worsen PAD by reducing muscle blood flow, there is no clear evidence of long-term disadvantage of beta-blocker treatment in PAD and some evidence that patients with concomitant coronary artery disease have better cardiovascular outcomes when treated with a beta-blocker. A meta-analysis of randomised controlled trials in PAD treated with beta-blockers reported no significant worsening of intermittent claudication or walking distance.[43] However when combined, atenolol and nifedipine reduced maximum walking distance by 9%, indicating the importance of context of beta-blocker treatment.[44] A capillary microscopy study[45] reported no microcirculatory or symptom differences between measurements obtained before and during withdrawal of beta-blocking therapy, and again 2 weeks after re-introduction of beta-blocker treatment in patients with intermittent claudication or ischaemic rest pain and mild-moderate hypertension. Beta-blocking drugs appear to be cardioprotective in patients with PAD however evidence is largely from observational or unblinded randomised studies. Poldemans *et al*[21] studied patients with abnormal stress echocardiography who were undergoing elective abdominal aortic or infra-inguinal arterial reconstruction.

Major options are dihydropyridines, which vasodilate and increase renal sodium and water excretion and the cardioselective CCBs diltiazem and phenylalkalamine verapamil, which vasodilate, and reduce cardiac output by reducing heart rate and force of cardiac contraction. In the VALUE Trial the primary outcomes were cardiac morbidity and mortality[46] with a primary intention to assess response to treatment with the angiotensin receptor blocker valsartan compared to the dihydropyridine CCB amlodipine in the subgroup of patients with PAD. The Invest Trial (International Trandolapril Study) included 2699 PAD patients.[47] The ACE inhibitor trandolapril and diuretic hydrochlorothiazide were added to verapamil sustained

release or beta-blocker (atenolol-based) initial treatment. Achieving a pressure <140 systolic or <90 diastolic reduced adverse cardiovascular outcomes [Hazard Ratio (HR): 0.82 or 0.70].

A prospective observational study noted that ACEi-based PAD treatment was associated with reduced renal failure progression;[48] since this was not a randomised study, results should be treated with caution. Effects of ACEi and angiotensin receptor blockers may lead to clinical benefits independent of blood pressure lowering. These effects include attenuating the pleiotropic effects of angiotensin II such as stimulation of oxidant stress, cardiovascular fibrosis, vascular and cardiac muscle hypertrophy.[49] However, 24 hour ambulatory blood pressure monitoring suggested blood pressure decrease with ramipril could have explained cardiovascular benefits.

Selective blockade of the Type 2 receptor for angiotensin II inhibits angiotensin II mediated vasoconstriction, aldosterone secretion, cardiovascular hypertrophy and fibrosis and salt and water retention. The VALUE study included specified sub-group analyses of the primary endpoint according to history of peripheral artery disease.[46]

CONCLUSION

Early identification of these patients and achieving BP goal could reverse early end organ damage and improve outcomes in these patients. Analysis of the data from Framingham Heart study demonstrate that a 2-mm Hg reduction in blood pressure would result in 14 % reduction in the risk of stroke and transient ischemic attacks, and a 6% reduction in risk of coronary heart disease. The effective management of hypertension is therefore an important primary health care objective in managing cardiovascular and renal disease.

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