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Review Article

Newer Drug Choices in Hypertension Treatment

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Abstract

Life style alterations and drug therapy are the main stay in the treatment of hypertension (HTN). Five classes of drugs, for example, angiotensin-converting enzyme inhibitor (ACEI), aldosterone receptor blocker (ARB), beta-blocker (BB), calcium channel blocker (CCB), and diuretics have been recommended by various guidelines and these agents are standard of care. This review focusses on certain agents which have become available or new data have emerged with the existing compound. Azilsartan, a recently approved ARB, has been shown to provide sustained and superior antihypertensive effect as compared to existing sartans. Nebivolol, a third-generation long-acting BB with vasodilatory effects, provides excellent hemodynamic and side effect profile. A number of third- and fourth-generation CCB (benidipine, azelnidipine, and cilnidipine) are available in our country. These compounds are highly vascular selective and display organ protection effects. The use of these agents can be individualized depending on the likely benefits. Spironolactone, an old drug with modest blood pressure lowering effects, has proved to be an excellent add-on fourth agent in patients with resistant HTN.

Key words: Azelnidipine, azilsartan, benidipine, hypertension treatment, nebivolol

Introduction

Hypertension (HTN) continues be a major health problem with considerable mortality and morbidity resulting from the resultant vascular complications.[1] There are two well-established strategies to lower blood pressure (BP): Lifestyle alterations and drug treatment. Meta-analysis of randomized controlled trials (RCTs) has shown that a 10 mm reduction in systolic BP (SBP) or a 5 mm reduction in diastolic BP (DBP) is associated with significant reduction in all major cardiovascular (CV) events, all-cause mortality, stoke, coronary events, and heart failure (HF).[1] There are well-established classes of drugs used in the treatment of HTN as per guidelines.[2,3] This review intends to discuss new drugs/choices which are now available for the treatment of HTN in our country. It is not intended to review the well-established compounds.

Five groups of drugs, for example, angiotensin-converting enzyme inhibitors (ACEIs), aldosterone receptor blockers (ARBs), beta-blockers (BBs), calcium channel blockers (CCBs), and diuretics (thiazides and thiazide-like diuretics such as chlorthalidone and indapamide), are recommended based on proven ability to reduce BP, reduce CV events, and overall CV morbidity and mortality. There are some specific differences between various drug groups. BBs cause less stroke prevention, whereas less HF prevention is documented by CCBs. The new drug choices will be discussed in the following sections [Table 1].

1. Blockers of the renin-angiotensin system
2. Newer BBs
3. Third- and fourth-generation CCBs
4. Anti-aldosterone agents (aldosterone antagonists).

Blockers of renin-angiotensin system

Both ACEI and ARBs are among the most widely used classes of antihypertensive drugs. Both groups have similar effectiveness in terms of CV event and mortality reduction. Both ACEI and ARB reduce albuminuria and are effective in preventing chronic kidney disease (CKD). ARBs are associated with significantly lower discontinuation rates for adverse rates than other group Wof drugs. ARBs are extensively used for the treatment of HTN

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Table 1: Newer drug choices in HTN

Class of drug	Compound
ARB	Azilsartan
BB	Nebivolol
CCB	Benidipine, azelnidipine, cilnidipine
Aldosterone antagonist	Spironolactone

ARB: Aldosterone receptor blocker, HTN: Hypertension, CCB: Calcium channel blocker, BB: Beta-blocker

as monotherapy and in combination with other group of drugs. Losartan was the first ARB to be used and many compounds are now available. *Azilsartan medoxomil* is the eight ARB approved by FDA for the treatment of HTN. It is highly selective with a 10,000 times higher affinity for angiotensin (AT) 1 receptor than AT 2 receptor. Azilsartan exerts some of its effects through peroxisome proliferator-activated receptors gamma pathway activation. There are considerable data which have accumulated comparing this compound with ACEI or other ARBs.[4] A meta-analysis of seven RCT including a total of 6152 patients treated with 40 mg azilsartan versus control therapy with other sartans revealed a significant reduction in clinic and 24 h SBP and DBP in the azilsartan group.[5] The initial dose of azilsartan is 40 mg once daily (20 mg for patients >75 years of age) which may be increased to 80 mg once daily with full effect reached by 4 weeks. Adverse effects include dizziness (8.9%), increase in serum creatinine (3.6%), fatigue (2%), diarrhea (2%), hypotension (1.7%), and syncope (0.3%).[4] A fixed-dose combination (FDC) with chlorthalidone has been approved as it reduced 24 h ambulatory SBP more effectively than olmesartan combined with hydrochlorothiazide.[6] ARBs have an excellent patient safety profile as assessed by low discontinuation rates.[7] Any ARB including azilsartan has been recommended in ACC guidelines for the treatment of HTN.[1]

Newer BBs (BBs)

Some years ago, BBs were relegated to the 2nd or 3rd line positions by HTN societies. Current RCTs and meta-analyses demonstrate that when compared with placebo, BBs significantly reduce the risk of HF and major CV events in hypertensive patients. When compared with other BP lowering groups, BBs are equivalent in preventing major CV events, except for less effective control of stroke.[3] BBs are not a homogenous class. In recent years, the use of vasodilating BB such as labetalol, nebivolol, celiprolol, and carvedilol has increased. Nebivolol is a third generation, long-acting and highly selective B1 adrenoreceptor antagonist that also exhibits nitric oxide-mediated vasodilatory effects. It is an effective anti-HTN agent with long duration of action. *Nebivolol* has a unique pharmacological profile, despite showing similar BP lowering effects, and has certain advantages in the treatment of HTN compared to previous generation of BBs. It has favorable effects on endothelial function, central BP, and aortic stiffness. The side effect profile is favorable with negligible risk of new-onset diabetes mellitus and less risk of erectile dysfunction.[8,9] Nebivolol at doses of 1.25 mg–40 mg/day has been evaluated for the treatment of HTN both as monotherapy and in combination of other drugs. The usual initial is 5 mg daily. The compound is beneficial and widely prescribed for sexually active man and in those with comorbidities such as type 2 diabetes mellitus, metabolic syndrome, and chronic obstructive lung disease. Nebivolol has been approved by FDA as monotherapy and also a FDC of nebivolol and valsartan (5/80 mg). ESC guidelines recommend use of nebivolol for the treatment of HTN although long-term outcome data in HTN are not available.[3]

Third- and fourth-generation CCBs

Based on chemical structure, CCBs are categorized into three subgroups; benzothiazepines, phenylalkylamines, and dihydropyridines (DHPs). The first two groups have negative chronotropic and inotropic effects and are used for the treatment of stable coronary artery disease and in certain arrhythmias. Main action of DHP group of CCBs is peripheral vasodilatation and these drugs are used for the treatment of HTN. The CCBs, a diverse group of CV drugs, exert their effect by inhibiting the L-type (or other type T, N, and L/N) calcium channel and cause vasodilatation in the heart and the smooth muscles. Although the CCBs have common antihypertensive action, they have vast difference in their pharmacological actions, pharmacokinetic profile, and adverse reactions. The CCBs have evolved from first to fourth generation.[10] The first-generation CCBs have a rapid onset of action, need frequent dosing, and cause significant tachycardia by baroreceptor reflex mechanism. These drugs reduce both myocardial contractility and conduction of electrical impulses to the heart. Nifedipine is the first-generation DHP specifically blocking L-type calcium channel in heart and blood vessels. The second generation of drugs has a better pharmacokinetic profile and also reduced baroreceptor activation. This group has less negative inotropic effect and reduced effect on atrioventricular conduction system. Nifedipine extended release is prototype of this group and benidipine is an intermediate compound between generation two and three. The third-generation drugs with slow and prolonged action limit reflux tachycardia. They are lipophilic, inhibit L-type calcium channel, have stable pharmacokinetic, and are well tolerated in HF and CKD. Amlodipine, azelnidipine, and lercanidipine represent this group. The fourth-generation CCBs possess both L- and N-type calcium channel blocking action and are highly lipophilic. These drugs can completely attenuate the activation of sympathetic system. Cilnidipine represents this generation. Clinical application of CCBs is dependent on antihypertensive and vasodilatory actions, duration of benefits, profile of end-organ protective effects, and incidence of adverse events. CCBs are a heterogeneous class of agents. Most RCTs demonstrating the benefits of CCBs on outcomes have used DHP, especially amlodipine. CCBs are widely used for the treatment of HTN and have similar effectiveness as other major drug classes on BP, major CV events and mortality outcomes. CCBs have a

greater effect on stroke reduction than expected for the BP reduction, but may also be less effective for preventing HF with preserved ejection fraction. Based on large data, amlodipine remains a safe and effective drug of choice in the treatment of chronic HTN owing to its slow, prolonged duration of action and lesser incidence of reflux tachycardia. The newer CCBs, although similar to amlodipine in BP lowering effect, have several pharmacological advantages. However, it is important to understand that there is lack of robust data with the newer agents and head-to-head comparative data with amlodipine are lacking. Three compounds, benidipine, azelnidipine, and cilnidipine, will be discussed briefly and are already in use in our country. *Benidipine*: This agent was marketed in Japan 15 years back and has highest affinity for binding sites among all CCBs, blocks N, L, and T calcium channels, and has vascular selectivity 20 times more that of amlodipine.[11] The blockage of N- and T-type calcium channels inhibits the catecholamine with resultant reduction in tachycardia. This agent is renoprotective as it promotes natriuresis, reduces apoptosis of renal tubule and proteinuria. Anti-atherosclerotic properties have also been demonstrated. The dose is 2–4 mg daily and maximum dose being 8 mg daily. Side effects include palpitations, headache, rash, itching, gynecomastia, and photosensitivity. Three benidipine-based regimens, benidipine + ARB, benidipine +BB, and benidipine + thiazide, were equally effective in lowering BP and preventing cardiac events in a substudy of COPE trial.[12] Benidipine-thiazide regimen provided better CV outcomes, BP control, and stroke reduction than the benidipine-BB combination in another subanalysis.[13] *Azelnidipine*: The compound is lipophilic and inhibits both L- and T-type calcium channels. The drug has high affinity to vascular tissues resembling nifedipine except for being long acting with slow onset and no tachycardia. Like benidipine, it displays anti-atherosclerosis, anti-oxidative properties and reduces proteinuria. A meta-analysis of 19 studies (1482 patients) revealed similar efficacy and safety of both azelnidipine and amlodipine for reducing BP in mild-to-moderate HTN.[14] In an open-labeled randomized short-time study, a combination of olmesartan with azelnidipine was superior to combination of candesartan and amlodipine and provided better morning BP, heart rate, and glycemic control.[15] The dose is 8 mg once a day and can be increased up to 16 mg. Adverse effects include headache, hot flashes. and nausea. Cilnidipine: The drug belongs to the fourth generation of the DHP-CCB and is a dual L/N type CCB. *Cilnidipine* reduces excessive excitation of the sympathetic nervous system and the release of norepinephrine from sympathetic nerve endings and consequently suppresses reflective tachycardia and stress-induced BP elevation more efficiently than amlodipine.[16] In white coat and morning HTN, there is excessive sympathetic activity and cilnidipine can be a preferred choice. It is postulated that cilnidipine provides superior renal protection attributable to reduced activation of renin-angiotensin-aldosterone system. In a short-term study, lower incidence of edema was observed with cilnidipine as compared to amlodipine.[17] Anti- ischemic, pleiotropic, and favorable glycemic effects have been reported. The dose is 5–10 mg daily and can be increased to 20 mg a day. The side effects include fever, rashes, gastric reflux, flushing, myalgia, and increased urination.

Anti-aldosterone agents (aldosterone antagonist)

Aldosterone is a mineralocorticoid that regulates electrolyte and volume homeostasis in normal subjects when elevated can contribute to the development of HTN. There is a strong postulate that sodium retention plays a dominant role in resistant HTN. Mineralocorticoid receptor antagonist (MRA), spironolactone which has modest BP lowering efficacy has been used in resistant HTN.[18] There is a growing evidence to suggest that the fourth-line treatment in HTN should involve a blockade of the biological effects of aldosterone through the use of MRAs. PATHWAY-2 is the first RCT to compare different BP lowering treatments in patients with resistant HTN.[19] The patients enrolled in this trial had uncontrolled BP despite being on triple drug therapy involving an ACEI/ARB, CCB, and a diuretic. In the study, spironolactone was compared with alternate fourth-line treatments targeting different pathogenetic mechanism: The alpha-1 adrenoreceptor blocker, doxazosin, acting to reduce peripheral resistance and the beta-1 adrenoreceptor blocker, bisoprolol, which inhibits the release of renin and reduces cardiac output. The 25–50 mg daily dose of spironolactone in PATHWAY-2 was well tolerated and was superior to other groups in achieving BP control within 3 months. The use of spironolactone should be restricted to patients with eGFR above 45 ml/min and plasma potassium concentration of ≤4.5 mmol/l. Guidelines recommend the use of spironolactone as add-on treatment for resistant HTN.[3]

The equivalence and efficacy of all five groups of drugs are well established as monotherapy and in certain combinations. The drugs discussed above can be used judiciously by the clinician as an alternative to the existing compounds. A number of new BP lowering drugs (nitric oxide donors, vasopressin antagonists, aldosterone synthase inhibitors, and endothelin antagonists) are investigational and have not been discussed.

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