How full is our antihypertensives pipeline?

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We have a plethora of new antihypertensives coming up with diverse mechanisms of action but if that would drastically change and better the management of hypertension remains to be seen. A review of the newer classes of antihypertensives in the pipeline is presented.

Potassium channel openers: Iptakalim, an ATP-sensitive potassium (KATP) channel opener (KCO), has high selectivity for the cell surface SUR2B/Kir6.1 channels of the vascular smooth muscle and endothelial cells. It causes cellular hyperpolarization via the opening of K^+ channels, decreasing the opening probability of L-type Ca^{2+} channels. It produces arteriolar and small artery vasodilation and has shown protection against hypertension end organ damage endothelial dysfunction.[1] There is lesser incidence of side-effects compared to the non-selective KCOs on central nervous, respiratory, digestive, and endocrine systems. Levcromakalim is shown to have a vasodilatory effect on the umbilical artery similar to that of magnesium sulphate and nifedipine.[2] Another analog rilmakalim is shown to inhibit electrical field stimulated contraction of isolated human internal mammary artery and human saphenous vein.[3] Further studies are warranted to establish the clinical utility of the latter two KCOs.

Direct renin inhibitors: Aliskerin is the only approved direct renin inhibitor (among ciprokiren, ditekiren, enalkiren, remikiren, terlakiren, and zankiren). It blocks the conversion of angiotensinogen to Angiotensin (AT)-I thereby decreasing AT II. As increased plasma renin activity (PRA) could be potentially problematic for ACE inhibitor and angiotensin receptor blocker (ARB) therapy but direct inhibition of renin activity blunts PRA despite the increased concentration (from loss of the negative feedback), which proves clinically advantageous. Addition of aliskiren to an ACE inhibitor (or ARB) and β-blocker had favorable neurohumoral effects in heart failure (lowered plasma NT-proBNP and urinary aldosterone) apart from being well tolerated.[4] Independent of its blood pressure lowering effects, aliskiren (in combination with losartan) is shown to significantly lower mean urinary albumin-to-creatinine ratio.[5] In pediatric age group especially, hypotension, hyperkalemia, and angioedema may rarely complicate.[6]

Vasopeptidase inhibitors (VPIs): Prototypical drugs are omapatrilat, sampatrilat, and fasidotril. They block ACE and neutral endopeptidase (NEP) simultaneously (dual inhibition) resulting in significant lowering of the systemic BP. Triple inhibition inhibits endothelin-converting enzyme (ECE) along with the above two enzymes. Apart from preventing conversion of angiotensin I to angiotensin II, actions of the natriuretic peptides (ANP and BNP) are prolonged resulting in increased urinary sodium excretion, enhanced cyclic GMP (cGMP) excretion and increased kinin and adrenomedullin levels. Proved beneficial in cardiovascular diseases, VPIs have also shown antifibrotic and anti-inflammatory effects, and protection against end-organ damage.[7,8] In experimental diabetes models, VPIs significantly improved the endoneurial blood flow, motor, and sensory nerve conduction velocity, prevented the development of hypoalgesia, and reduced superoxide and nitrotyrosine levels in epineurial arterioles.[9] Adverse effect profile is similar to that of ACE inhibitors (cough, hypotension, hyperkalemia, etc) although angioedema is the most notable.

ARBs and ACE inhibitors: Azilsartan medoxomil is a new

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ARB, which at 80 mg proved superior to both valsartan at 320 mg and olmesartan at 40 mg. With safety and tolerability profile essentially similar to other ARBs, it could provide higher rates of hypertension control within the ARB class.[10] Fimasartan, another ARB, has consistently shown superiority over losartan.[11] Apart from renin angiotensin system (RAS) blockade, the antioxidant properties shown by some ACE inhibitors are postulated to contribute for BP lowering effects. Selenium analogues of captopril are shown to effectively scavenge peroxynitrite, a strong oxidant found *in vivo*.[12]

Mineralocorticoid receptor blockers (MRBs): MRBs like eplerenone have shown beneficial effects independent of RAS inhibition. MRBs heighten the anti-proteinuric properties of RAS inhibitors and have shown impressive results in resistant hypertensive patients whose blood pressure is insufficiently controlled by RAS inhibitors.[13] Eplerenone has shown to reduce the media collagen/elastin ratio. Apart from reducing arterial stiffness, eplerenone is known to decrease circulating concentrations of osteopontin, monocyte chemoattractant protein-1, basic fibroblast growth factor, interleukin-8, and interleukin-10.[14] In diastolic heart failure (DHF), the upregulation of mineralocorticoid receptor is proposed to play a central role thus highlighting the importance of mineralocorticoid receptor blockade for managing DHF.[15] Although hyperkalemia may occur with both spirinolactone and eplerenone, the latter does not sport the former's sexual side effects (like gynecomastia).

Imidazoline receptor agonists: Rilmenidine is an oxazoline compound acting on both medullary and peripheral vasomotor structures that shows greater selectivity for imidazoline receptors than for cerebral alpha2-adrenergic receptors (distinguishing it from reference alpha2-agonists). Rilmenidine is effective in minimizing the reflex autonomic disturbances (baroreflex-induced renal sympathetic nerve activity) produced by hypertension and stress.[16] Another compound moxonidine (at low dose) produced sustained and substantial reductions in sympathetic outflow without hemodynamically compromise in ESRD patients.[17]

Selective α1-adrenergic receptor antagonists: Naftopidil a phenylpiperazine derivative, is especially beneficial in hypertensives with benign prostatic hyperplasia. Arylpiperizine compounds are also amongst the most studied α1adrenoceptor antagonists against hypertensive patients with bladder outlet obstruction.[18]

Calcium channel blockers: Cilnidipine is a slow-acting blocker of vascular L-type and N-type calcium channels (without targeting protein kinase C) with appreciable benefit in hypertension.[19] In animal models (uninephrectomized deoxycorticosterone (DOCA)-salt hypertensive rats) cilnidipine inhibited renal dysfunction, sympathetic nerve activity and renal renin–angiotensin–aldosterone system in the DOCA-salt group.[20] In type 2 diabetes, it has demonstrated renoprotective effects through inactivation of intrarenal renin-angiotensin system and suppression of NADPH oxidase-dependent oxidative stress.[21]

Clevidipine is a new lipophilic, short-acting, third-generation dihydropyridine calcium channel blocker has selective arterial vasodilation without effects on the venous circulation and has demonstrated efficacy and safety in acute hypertension and preoperative, perioperative, and postoperative hypertension.[22]

Magnesium replenishment: Magnesium (Mg) supplementation has shown to significantly lower high blood pressure and stems from the understanding that poor Mg status complicates HTN, type 2 diabetes, cardiovascular, and respiratory diseases. A study showed small but consistent ambulatory BP reduction in patients with mild hypertension.[23] Another study on diabetic hypertensives showed that magnesium supplementation showed considerable decrease in both systolic and diastolic blood pressure and a significant increase in high density lipoprotein.[24]

EXPERIMENTAL DRUGS

Ouabain antagonists: Rostafuroxin, with properties like endogenous ouabain antagonism and adducin modulation, normalizes the increased myogenic tone caused by nanomolar ouabain and has high potency and efficacy in reducing BP and preventing organ damage. Rostafuroxin also antagonizes the Src-epidermal growth factor receptor (EGFr)-dependent signaling pathway leading to renal Na+-K+ pump, and ERK/MAPK tyrosine phosphorylation and activation.[25] A population-based study showed that endogenous ouabain might have a trophic effect on the myocardium, independent of blood pressure and other covariables, which may extrapolate the benefits of rostafuroxin beyond BP lowering.[26] Rostafuroxin has demonstrated a high safety ratio and high tolerability.

ACE-2 activation: ACE-2 activator, diminazene aceturate via central regulation of BP and baroreceptor modulation, is shown to reduce mean arterial pressure, heart muscle mass and myocardial fibrosis.[27] A synthetic activator of ACE-2 has shown considerable benefit in lowering pulmonary hypertension.[28] It has also been shown in experimental models that overexpression of transgenic ACE2 protects the heart from hypertension-induced cardiac remodeling and myocardial infarction induced damage by inhibiting both myocardial and perivascular fibrosis.[29]

Renal kallikrein reduction: Renal kallikrein-kinin system prevents sodium accumulation, and reduced levels of renal kallikrein may cause salt-sensitive hypertension. Inhibitors

of carboxypeptidase-Y-like exopeptidase (ebelactone B) and NEP (poststatin) have shown promising antihypertensive effects by increasing urinary kinin levels.[30] Ebelactone B prevents deoxycorticosterone acetate (DOCA)-salt hypertension in rats.[31]

Meiosis activating sterol agonism: A novel Meiosis activating sterol (Mas) agonist peptide is shown to have vasorelaxing and cardioprotective effects probably mediated through endothelium and nitric oxide. An antiarrhythmogenic effect (reduction in the incidence and duration of reperfusion arrhythmias) in addition to dose dependent decrease in mean arterial pressure is noted in animal models.[32]

Catestatin: Catestatin/Human chromogranin A 352–372, is found to be elevated in essential hypertension. It is proposed as a novel cardiac modulator owing to its cardioinhibitory influence exerted on basal mechanical performance and the counterregulatory action against beta-adrenergic and endothelin-1 stimulations.[33] With such properties it is able to protect the heart against excessive sympathochromaffin overactivation (hypertensive cardiomyopathy, etc). In myocardial ischemia catestatin reduced post-ischemic rise of diastolic left ventricular pressure (LVP, an index of contracture), and significantly improved post-ischemic recovery of developed LVP. In isolated cardiomyocytes, catestatin increased the cell viability rate by about 65% after simulated ischemia/reperfusion.[34]

Soluble guanylate cyclase activators: Drugs that directly target soluble guanylate cyclase (sGC) (bypassing NO) of vascular smooth muscle cells, in increasing intracellular cyclic guanosine monophosphate levels, which in turn leads to contractile relaxation and vasodilation overcome the limitations like tolerance associated with NO donors. Heme-independent sGC activators exhibit a higher affinity for the oxidized enzyme and may be of benefit in treating cardiovascular diseases and systemic and pulmonary hypertension, especially in advanced cases and in the elderly.[35]

Drugs acting via epoxyeicosatrienoic acids (EETs): Epoxyeicosatrienoic acids released from endothelial cells and vascular smooth muscle cells are vasodilators and contribute to blood pressure regulation. They have protective actions against hypertension-related end organ remodeling and damage as well and drugs that mimic EETs or block their breakdown by inhibiting soluble epoxide hydrolase have shown promising benefits against hypertension.[36] Caution needs to be excised when used in lung disorders because EETs potentiate hypoxia-induced vasoconstriction, and are implicated in vascular remodeling associated with chronic hypoxia and pulmonary hypertension.[37]

Drugs acting via 20-hydroxyeicosatetraenoic acid: Several new agonists and antagonists of 20-hydroxyeicosatetraenoic acid (20-HETE) are being developed which in conjunction with peroxisome proliferator-activated receptor-α agonists induce the renal formation of 20-HETE helping combat sodium retention, some salt sensitive forms of hypertension and the effects of transforming growth factor β in promoting proteinuria and renal end organ damage in hypertension. In a mouse model, selective inhibition of 20-HETE formation together with a soluble epoxide hydrolase inhibitor, so as to elevate ETTs, attenuated hypertension and associated end organ damage in angiotensin II-dependent hypertension.[38]

HMG-CoA reductase inhibitors: Although PHYLLIS trial[39] has not shown any blood pressure lowering effects by statins, there are conflicting reports in different studies. There is growing evidence that statins may be useful in hypertensives with high serum total cholesterol, in those whose hypertension is not well controlled with antihypertensive agents (even without high serum total cholesterol), in hypertensive subjects well controlled with antihypertensives without high serum cholesterol when they have high polymerase chain reaction levels, in those who require preventive measures because of other concomitant cardiovascular risk factors, or when they require secondary prevention. The pleiotropic effects of statins might explain such benefits.[40]

Vaccine: CYT006-AngQb, a conjugate vaccine composed of modified angiotensin II covalently linked to recombinant virus-like particles derived from the RNA bacteriophage Q-beta, is shown to mount an angiotensin II-specific antibody response which resulted in significant lowering of blood pressure. Apart from having no serious side effects the vaccine induced a reduction from baseline in mean ambulatory daytime blood pressure at week 14 by 9mm of Hg (systolic) and 4 mm (diastolic). It also reduced the early morning blood-pressure surge compared with placebo.[41]

Genetic regulators: Phosducin (Pdc) is a G-protein regulator/ a novel candidate gene for stress-induced hypertension and is found to regulate sympathetic activity in postsynaptic ganglia. Several single nucleotide polymorphisms (SNPs) in the Pdc gene are known to be associated with stress-dependent blood pressure phenotypes. It is a novel target for newer treatment modalities and has implications for both the treatment of hypertension and kidney disease.[42]

Others: The antialdosterone as well as antiandrogenic effects of Drospirenone (DRSP) and 17-β estradiol were studied in post-menopausal women with hypertension, which showed significant reductions in early morning systolic BP implying a potential role in reducing cardiac and cerebrovascular events.[43] Renal sympathetic denervation (catheter-based radiofrequency ablation of renal nerves) is a promising approach especially in refractory hypertension.[44]

CONCLUSIONS

There is a myriad of antihypertensive agents available and more coming up but early diagnosis and prompt and aggressive approach (treating the cause in case of secondary hypertension) remain the cornerstones of hypertension management. Also, clinicians need to embrace the latest developments targeting hypertension.

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