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Review Article

Selective Imidazoline Receptor Agonists: redefining the role of centrally acting agents in management of hypertension

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ABSTRACT

Hypertension, often referred to as 'The silent killer', is christened so, as it is seldom preceded by any warning signs or symptoms. With the new ACC/AHA guidelines lowering the Blood Pressure (BP) threshold values, it has resulted in a 140% relative increase in the hypertension prevalence in India, which is 3 times higher than that of in United States. Imidazoline receptor agonists control BP effectively with minimal adverse effects of sedation and mental depression that are usually associated with centrally acting antihypertensives. While having a low affinity to the α2-adrenergic receptors, these new generation centrally acting antihypertensive agents are highly selective for imidazoline receptor. Moxonidine, a second-generation centrally acting antihypertensive drug having selective agonist activity on imidazoline I_1 receptors and minor activity on imidazoline α2 adrenoceptors, reduces the activity of Sympathetic Nervous System (SNS) by activating I_1 imidazoline receptors in Rostral Ventrolateral Medulla (RVLM). Studies of moxonidine have shown equal effectiveness in lowering BP like other well-established antihypertensive drugs such as nifedipine, atenolol or angiotensin-converting enzyme inhibitors, with minimal adverse events. At doses of 0.2-0.6 mg, moxonidine induces satisfactory BP reduction in patients with mild-to-moderate essential hypertension. In patients with mild-to-moderate hypertension, moxonidine (0.2-0.4 mg o.d.) significantly decreased Systolic Blood Pressure/Diastolic Blood Pressure (SBP/DBP), respectively, by 19.5/11.6 mmHg. In obese, non-controlled hypertensive patients, there is a 14% and 13.5% reduction in the mean SBP and DBP, respectively, from the baseline value after moxonidine treatment and during the follow-up with an additional reduction in body weight, plasma leptin levels and Body Mass Index (BMI) ($p<0.01$). Thus, moxonidine could be considered as a therapeutic option in obese patients with metabolic syndrome.

Keywords: Blood pressure, Metabolic syndrome, Moxonidine, Selective Imidazoline Receptor Agonists, Sympathetic activity

INTRODUCTION

Hypertension - a growing epidemic

Hypertension is often referred to as the 'silent killer' in the medical terminology because there are no warning signs or symptoms caused by high Blood Pressure (BP) of its presence.[1] At least 45% of deaths due to heart diseases, 51% of deaths due to stroke, and an estimated 16.5% (9.4 million) of all deaths annually are due to hypertension. BP values vary greatly and tend to increase with age in the people. The risk of vascular complications linearly increases with higher BP values. The hemodynamic factors involved in BP regulation include cardiac output, total peripheral resistance, stroke volume, and heart rate and at least four systems are responsible for direct BP regulation, which include the cardiac system, renal system, and blood vessel tone.[2]

Implications of 2017 ACC/AHA updated guidelines among Indian population

Changes in guidelines

The American Heart Association (AHA) in 2017 updated the hypertension guidelines. According to the latest guidelines, a Systolic Blood Pressure (SBP) of 130 mmHg or more and a diastolic of 80 mmHg or more is considered as hypertension and needs to be controlled, which is said to be the most important modification. Therefore, persons with SBP of 130-140 mmHg and/or diastolic 80-90 mmHg are now classified as hypertensive, while they were earlier classified as prehypertensive by Joint National Committee 7 criteria. This represents a large number of people as having elevated BP and warrants lifestyle modifications. The guidelines also emphasize individualized Cardiovascular (CV) risk assessment and to use 10-year CVD risk calculation to decide on treatment threshold.[3]

Implication in Indian population and challenges

The lowered BP threshold resulted in a 140% relative increase in the hypertension prevalence in India as per the new ACC/AHA guidelines, which is 3 times higher than the 43% relative increase reported in the United States. Such an increase in the hypertension prevalence in India is likely to have significant implications for the Indian health system like greater increase in BP values among younger patients, and those from rural and poorest households may exacerbate the existing access-to-care issues in these high-risk subgroups. Hypertension treatment and control rates are already very low in India.[4]

Sympathetic Nerve Activity in Hypertension

The Sympathetic Nervous System (SNS) constitutes one of the body's main effector systems for maintaining homeostasis at rest, during stress and in disease states. Cannon taught that rapid activation of the SNS preserves the internal environment by producing compensatory and anticipatory adjustments that enhance the likelihood of an individual's survival.

Function

Because most homeostasis includes the SNS in the range of effectors, alterations in the sympathetic neural outflows accompany virtually all stress responses. Reviewing these alterations requires an integrative understanding of how the processes of norepinephrine synthesis, release, reuptake, vesicular leakage, metabolism, and turnover function together to produce appropriate sympathetic homeostatic responses.[5]

Activity in hypertension

The SNS plays essential role in the regulatory mechanisms of hypertension, sodium balance, and maintenance of homeostatic state and is an arm of the autonomic nervous system.[6] Increased SNS activity has been concerned as a primary precursor of hypertension. Imbalances in several neurotransmitters and neuromodulators are present during the development of hypertension, and these directly and indirectly contribute to increased release of noradrenaline onto the postsynaptic targets of the sympathetic nerves. In sodium chloride-sensitive hypertensive subjects, dietary sodium chloride increases SNS activity both directly and indirectly. Bidirectional interactions among the immune system and the SNS also appear to play a role in the development of hypertension. Studies suggest that insulin-glucose excess and nitric oxide deficiency may increase the SNS's contribution to some forms of hypertension.[7]

Other associated conditions

Increased renal sympathetic nerve activity has the potential to drive increased BP and fluid retention, contributing to the genesis of Cardiovascular Diseases (CVDs), including hypertension and heart failure.[8]

Chronic stimulation of the SNS has the potential to augment risk for the metabolic syndrome through the development of obesity, hyperglycemia, and insulin resistance.

Selective Imidazoline Receptor Agonists (SIRA)

Stimulation of brain α2-adrenergic receptors is one mechanism for sympathoadrenal suppression but comes at the cost of nonspecific depression of Central Nervous System (CNS) function, including sedation and decreased salivary flow. Evidence is accumulating for a second pathway for pharmacological control of sympathoadrenal outflow, mediated by a novel receptor specific for imidazolines.[9] Imidazoline receptor agonists control BP effectively with minimal adverse effects of sedation and mental depression that are usually associated with centrally acting antihypertensives. While having a low affinity to the α2-adrenergic receptors, this new

generation of centrally acting antihypertensive agents is highly selective for the imidazoline receptor.[10]

Mechanism of action

Imidazoline I_1-receptors in the Rostral Ventrolateral Medulla (RVLM) are important for the sympathoinhibitory action of clonidine, rilmenidine, and moxonidine-like antihypertensive drugs. The mechanism by which central antihypertensives lowers BP is a result of activation of both α2-AR and I_1-IRs in the RVLM. The α2-AR agonists directly inhibit pre-sympathetic RVLM neurons, while the I_1-IR agonists increase the release of catecholamines in the RVLM. The catecholamines depress pre-sympathetic RVLM neurons by activating α2-AR.[11]

Moxonidine

Moxonidine is a second-generation centrally acting antihypertensive drug having selective agonist activity at imidazoline I_1 receptors and only minor activity at imidazoline α2 adrenoceptors, reduces the activity of the SNS by activating I_1 imidazoline receptors in the RVLM. This results in the inhibition of peripheral α-adrenergic tone and the decrease of BP due to a fall in Systemic Vascular Resistance (SVR).

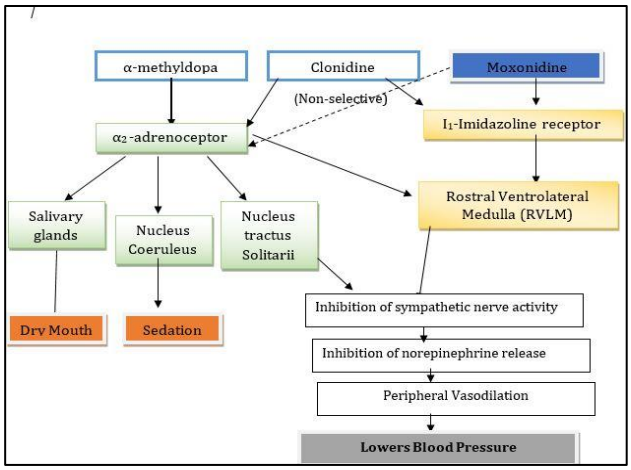

Figure 1: Mechanism of actions of centrally acting agent and moxonidine[14]

Evidences from the larger studies demonstrated that moxonidine acts on heart, a target organ. This effect is achieved through the activation of cardiac I_1 imidazoline receptors. Through this mechanism, moxonidine produces clinically relevant sympatholysis, with beneficial effects on overall hemodynamics, and neurohumoral parameters.[12] Moxonidine produces a pronounced reduction in peripheral vascular resistance without reflex tachycardia, accompanied by reduced plasma norepinephrine concentration and plasma renin activity. Comparisons have shown moxonidine has equal effectiveness in lowering BP like other well-established antihypertensive drugs such as nifedipine, atenolol, or Angiotensin-converting Enzyme inhibitors, with minimal adverse events. Considering its efficacy, safety, and specific effects (e.g., its ability to reduce Left Ventricular Hypertrophy [LVH]), moxonidine meets the criteria satisfied by other currently prescribed antihypertensive drugs. Moxonidine can be recommended as one of the first-line treatment of hypertension in certain situations because of its favourable benefit-to-risk ratio.[13]

Hypertensive efficacy of moxonidine

Effects of moxonidine in essential hypertension

A daily dose of 0.2-0.6 mg induces satisfactory BP reduction in patients with mild-to-moderate essential hypertension. In a placebo-controlled, 6-week study of patients with mild-to-moderate hypertension, moxonidine (0.2-0.4 mg o.d.) significantly decreased BP by 19.5/11.6 mmHg (SBP/DBP, respectively). In elderly patients with resistant hypertension of 60-80 years with poorly controlled BP, moxonidine decreased the mean daytime SBP from 169.2 to 153.8 mmHg, and Diastolic Blood Pressure (DBP) from 91.6 to 84. 2 mmHg. The 24-hr BP readings showed a reduction in the mean SBP from 163.0 to 148.6 mmHg and the mean DBP from 87.2 to 80. 2 mmHg significantly ($p=0.013$).[19,20]

In obese, non-controlled hypertensive patients

Abellan J, et al, in an interventional study, added moxonidine to non-controlled, hypertensive, obese subjects totaling 112 patients (61 males and 51 females). The reduction in the mean SBP after moxonidine treatment and during the 6-month duration was 23.01 mmHg (14% of the baseline value). The decrease in DBP was 12.9 mmHg (13.5% of the baseline value). For the whole group, the mean systolic and diastolic pressures were 158.5±10.6 and 95.1±9 mmHg, respectively, at baseline vs. 135.5±11.6 and 82.2±5.8 mmHg at the end of the study. In terms of BP control, 96 patients (86%) achieved DBP control at the end of the study; 70 (63%) of them had SBP adequately controlled, and 54 (48%) were seen to have adequately controlled the 2 BP components after 6 months.

Body weight decreased from 88.19±12.09 kg (baseline) to 84.9±11.5 kg (6-month) ($p<0.01$). The Body Mass Index (BMI) was also seen to decrease from 33.6 to 32.3 kg/m^2($p<0.01$).

Antihypertensive efficacy and safety of moxonidine as a combination therapy

The use of the combination of both moxonidine and hydrochlorothiazide for 8 weeks led to a 27/16 mmHg fall in BP.[22] In patients with metabolic syndrome presenting with moderate hypertension, ramipril+moxonidine combination therapy after 12 weeks normalized BP in 88% of the patients compared to BP normalization in 40% and 44% on monotherapies with ramipril or moxonidine, respectively.[23]

Table 1: Dose range and pharmacokinetics of central sympatholytic drugs.[15-18]

Drug	Total dose Range, (mg/d)	Doses Per day	T-max, (hrs)	Half-life (hrs)	Renal Elimination (%)	Volume of Distribution (l/kg)[16]	Absorption (%)[16]	Metabolic Effects[17]	Adverse Effects[18]
Clonidine	0.2-1.2	2-3	1-4	6-16	40-60	2.0	75-100	No	Drowsiness, Sedation, Lethargy, Dry mouth
Methyldopa	250-2000	2	2-4	1-2	70	0.6	25	-	Restlessness, Sweating, Anxiety, tremor, Palpitations, And headache
Moxonidine	0.2-0.6	1-2	1.0-1.5	2-3	50-75	3.0	80-90	Yes	Dry mouth Is the only adverse effect
Rilmenidine	1-2	1	1.7	8.5	52-93	315-325	100	No	Dry mouth

Pleiotropic benefits of moxonidine

Influence of moxonidine on target organ protection and metabolism

Sanjuliani, et al., showed that after 24 weeks of moxonidine treatment, plasma arterial adrenaline and noradrenaline were significantly reduced. This fact confirms the decrease of plasma catecholamines, and moreover, proves the action of the drug in conditions of sympathetic overactivity.[24] A double-blind, placebo-controlled, crossover study demonstrated that moxonidine reduces exercise and mental stress-induced SNS activation and seems to be considered as an alternative to b-adrenoceptor blockers in combination therapy, when patients are bothered by the exercise limitations of b-adrenoceptor blockers.[25]

The study of Krespi, et al., suggests that in hypertensive patients with microalbuminuria, moxonidine reduces urine albumin excretion, thrombomodulin, and Plasminogen Activator Inhibitor-1 (PAI-1) levels. These results demonstrate an effect on renal function and endothelial homeostatic mechanisms.[26] Also, a 3-year trial showed that treatment with standard antihypertensive therapy and adjunctive moxonidine in patients with advanced renal failure was predicted to reduce the number of new end-stage renal disease cases compared to adjunctive nitrendipine. The model showed that adjunctive moxonidine seems to increase life-years lived.[27]

Metabolic syndrome

Metabolic syndrome is a cluster of metabolic abnormalities that includes hypertension, central obesity, insulin resistance, and atherogenic dyslipidemia and strongly associated with a greater risk of developing ASCVD.[28] Currently, global estimate of metabolic syndrome among the adult population is around 20-25% with a rapid increasing rate in South Asian countries particularly in India leading to increased morbidity and mortality due to CVD and Type 2 Diabetes Mellitus (T2DM).[29] Metabolic syndrome confers a 5-fold increase in the risk of T2DM and 2-fold the risk of developing CVD over the next 5-10 years with a 2-to 4-fold increased risk of stroke and 3-to 4-fold increased risk of MI.[30]

Pathophysiology of metabolic syndrome

AT2 =Angiotensin II type 2 receptor; CRP = C-reactive protein; IL-6 =Interleukin 6; LOX =Lectin-like oxidized low-density lipoprotein; RAAS=Renin-angiotensin-aldosterone system; ROS =Reactive oxygen species; TNF =Tumor necrosis factor.[28]

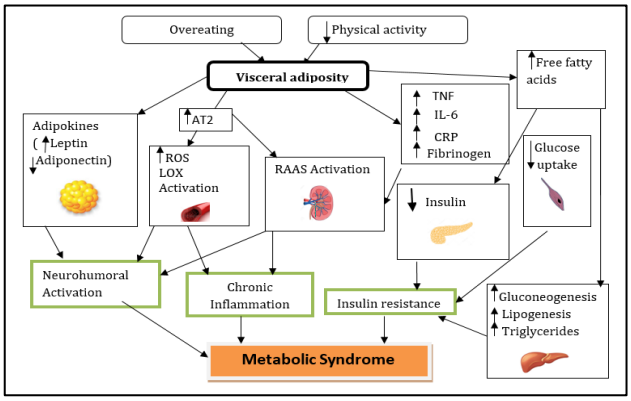

Figure 2: Pathophysiological mechanisms in metabolic syndrome.

Importance of hypertension management in metabolic syndrome

A very high prevalence of metabolic syndrome in the hypertensive population is observed in study of more than 19,000 hypertensive patients attending primary care centers in Spain, where, more than 40% of people were present with metabolic syndrome using the original ATP-III definition. The presence of metabolic syndrome is accompanied by a 3-to 6-fold increase in the risk of developing T2D and also enhances the risk of developing chronic kidney disease (albuminuria and/or a diminished estimated Glomerular Filtration Rate [GFR]. Hypertension associated with metabolic syndrome has pathophysiologic characteristics that provide clinical challenges as well as opportunities for successful therapeutic interventions. [31]

Challenges in management of hypertension in metabolic syndrome

- The syndrome is not a discrete entity known to be caused by a single factor. Moreover, it shows considerable variation in the components among different individuals. This variation is even greater among different racial and ethnic groups.[32]
- In hypertensive patients with metabolic syndrome, procedures to diagnose hypertension should be more extensive than usual because of the higher prevalence of multiple organ damage and increased levels of inflammatory markers.
- Lack of specific intervention trials in metabolic syndrome prevents any firm recommendation to be given on whether lifestyle modifications should be associated with antihypertensive drug treatment in non-hypertensive and non-diabetic patients with MS.[33]

Role of centrally acting antihypertensive drugs in patients with hypertension with metabolic syndrome

Antihypertensive treatment with a centrally acting sympatholytic agent that targets common underlying pathophysiologic pathways is a safe and effective treatment strategy with potential additional benefits in regard to metabolic disturbances frequently encountered in hypertensive populations.[34]

Traditional centrally acting antihypertensives have been associated with a high incidence of adverse effects and are no longer recommended as first-line therapy. With methyldopa, a centrally acting alpha (2)-agonist, although unpredictable idiosyncratic or hypersensitivity reactions are uncommon, these include hepatitis, myocarditis, and haemolytic anemia. Less serious problems such as abnormal liver function tests, positive Coombs test, drug-induced fever, and pancreatitis also occur. Central side-effects include drowsiness, fatigue, lethargy, sedation, depression, psychotic reactions, nasal stuffiness, impotence, and exacerbation of parkinsonism. Clonidine acts primarily as an alpha (2)-agonist but also acts as an agonist at imidazoline receptors in the RVLM but is considerably less well-tolerated in comparative trials. The principal adverse effects of clonidine are drowsiness, sedation, lethargy, and dry mouth. Reserpine acts primarily by depleting central catecholamine neurotransmitter stores; its central side-effects of sedation, nasal stuffiness, and severe depression are now considered so undesirable that the drug is seldom prescribed. Rilmenidine acts selectively and has very little central alpha (2)-agonist activity.[18]

Moxonidine in the management of hypertension and metabolic syndrome

Moxonidine reduces BP in patients with metabolic syndrome while simultaneously reducing body weight in obese patients, as it has been shown in the postmarketing surveillance study CAMUS.35 Furthermore, moxonidine is used in the treatment of obese patients with metabolic syndrome because this antihypertensive agent reduces leptin levels in plasma and reduces weight in obese patients through the action of the SNS.[12]

Also, a multicentric, prospective, randomized, open-label study showed that moxonidine improves insulin sensitivity in response to glucose challenge in patients with evidence of metabolic syndrome.[34]

DISCUSSION

While BP reduction is the primary goal of antihypertensive therapy, potential effects on metabolic parameters also need to be taken into account. [34]

Although centrally acting antihypertensive drugs have a proven efficacy in controlling or decreasing BP, they are no longer widely used because of the relative high incidence of adverse effects. Most central side-effects occurring with these drugs are mediated by the α2-receptor. Moxonidine is an imidazoline receptor agonist that is highly selective for the I_1-imidazoline receptor with little effect at the central α2-receptor. Moxonidine has been shown to diminish sympathetic activity, as measured by norepinephrine, epinephrine, and plasma renin activity. Clinical studies have documented efficacy of moxonidine as an antihypertensive agent. Most patients' BP was satisfactorily controlled with a dose between 0.2 and 0.4 mg per day. Comparative studies with most other antihypertensive drug classes such as clonidine, diuretics, alpha-blockers, beta-blockers, calcium antagonists, and ACE inhibitors document similar BP control with moxonidine as with other agents. Specifically, by using 24-hr ambulatory BP monitoring, BP control was found to be similar with moxonidine and enalapril.[36] Moxonidine (0.2-0.4 mg once daily) for 6 months, either as monotherapy or as adjunctive therapy to current antihypertensive treatment in patients with uncontrolled essential hypertension meeting criteria for metabolic syndrome, was associated with: (i) improvement in control of BP, (ii) neutral or beneficial trends in a range of metabolic indices including lipid fractions and fasting plasma glucose

and weight loss which has clearly been associated with improved CV and other outcomes, suggesting that moxonidine may have additional beneficial effects beyond BP reduction, particularly in overweight or obese hypertensive subjects or those with the metabolic syndrome. In this context, the average reduction in body weight of 2.1 kg in patients treated with moxonidine replicates that early treatment of moxonidine has benefits in population with metabolic syndrome.[34]

The use of antihypertensive, for an aggressive BP control, in addition to a healthy lifestyle in patients with stage 2 hypertension and individualization of the treatment for a reduction of BP are the requirements of the hour. Treatment aim to achieve the target BP need not be very strict, it should be a less stringent one. There is no sufficient clinical data to set the target BP in diabetic hypertensives as 130/80 mmHg, as even the current ADA 2018 guidelines suggest 140/90 mmHg as the suggested target.

Metabolic syndrome is a very common disease with repercussion on sympathetic overactivity. Metabolic syndrome is going to rise as major problem of our country with its increase in the affluence, changes in lifestyle, and less physical activity. Sympathetic overstimulation is chiefly responsible for causation of obesity, insulin resistance, and hypertension, thereby resulting in the constellation of metabolic syndrome.

In clinical practice, there is lot more experience about the use of moxonidine as there are a number of trials comparing moxonidine and clonidine, which showed that moxonidine is as effective as clonidine. Additionally, moxonidine causes less dryness of mouth (about 30-40% patients in current clinical practice) and less incidence of postural hypotension compared to clonidine. Moxonidine, besides alpha and beta-blocking, has got another 4 actions - action on leptin, metabolic syndrome, satiety center, and liver. Edema, which is commonly seen in most of the renal patients, makes it often confounding whether it is due to renal deterioration or due to the Calcium Channel Blocker (CCB). If there is a rise in creatinine, moxonidine is a very good add-on therapy (recommended if the rise in creatinine is by more than 25% from the baseline) to either an ACE inhibitor or an ARB in diabetic or non-diabetic. In addition, moxonidine is also a good add-on to a diuretic if the patient's BP is not controlled and if it is refractory. Moxonidine has favourable benefit as opposed to beta-blockers which causes worsening of lipid profile.

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