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Azelnidipine: A Review on Therapeutic Role in Hypertension

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ABSTRACT

Hypertension is the most common regulating risk factor for cardiovascular disease (CVD) and death; the increased risk associated with blood pressure (BP) elevation can be greatly reduced by treatment with antihypertensive drugs that lower both BP and related tar get organ damage. New Ca2+ channel antagonists have been recently developed, especially in the DHP compounds that have considerable higher vascular selectivity, slower onset and longer duration of hypotensive action. The antihypertensive effect of azelnidipine is primarily based on the inhibition of trans-membrane Ca2+ influx through the voltage-dependent channels of vascular smooth muscles. Ca2+ channels are categorized into several subtypes, including L-type, T-type, N-type, P/Q-type, and R-type Ca2+ channels depend on their electrophysiological properties. Clinical studies have demonstrated that azelnidipine markedly reduced heart rate and proteinuria in hypertensive patients by inhibiting sympathetic nerve activity. Azelnidipine has also been confirmed to have cardio-protective, neuroprotective, and anti-atherosclerotic properties, and has also been found to prevent insulin resistance.

Keywords: calcium channel blocker, hypertension, Azelnidipine, Dihydropyridine, Blood pressure.

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INTRODUCTION

Over the ancient numerous eras, the term "essential hypertension" has become ingrained in our medical vocabulary. We not only use it in our usual medical idiom but the term was actually codified in ICD-9. As a medical community, we do not categorize any other common pathological conditions, such as obesity, NIDDM, or CAD as "essential." Additionally, in order to discriminate the common variety of hypertension from a particular etiology related hypertension so called secondary hypertension the most rational substitute term would have been "primary" hypertension. But why and how did the term "essential hypertension" come approximately? To find the answer, one needs to investigate into the history of the pharmacological treatment of hypertension. The history of hypertension goes back a extensive way. In ancient Chinese and Indian Ayurvedic medicine, the quality of an individual's pulse, as felt by moderate palpation by the trained physician, was a window into the condition of the cardiovascular system. What was called "hard pulse" possibly would qualify for the modern term of hypertension. The history of hypertension, is incomplete without Akbar Mahomed's contribution in developing the modern concept of hypertension. In the late nineteenth century, Frederick Akbar Mahomed (1849–1884), an Irish-Indian physician working at Guy's hospital in London, first described conditions that later originated to be known as "essential hypertension," separating it from the similar vascular changes seen in chronic glomerulonephritis such as Bright's disease. Some of the significant contributions of Akbar Mahomed were the demonstration that high BP could exist in apparently healthy individuals, that high BP was more likely in older populations, and that the heart, kidneys, and brain could be affected by high arterial tension. However, only with the advent of the mercury sphygmomanometer in the early twentieth century and defining of the systolic and diastolic BP by appearance/ disappearance of Korotkoff sounds as heard *via* the stethoscope, the modern quantitative concept of hypertension – broken into systolic and diastolic categories – came into existence. By the middle of the twentieth century, checking BP by sphygmomanometer became part of the routine physical examination in hospitals and clinics. Hypertension, however, was not always considered a disease as we know it now. President Franklin D. Roosevelt was given a clean bill of health by his physician even when his BP

was recorded as ~220/120. A few years later while at Yalta, Winston Churchill's personal physician noted in his diary that President Roosevelt "appeared to be had signs of 'hardening of the arteries disease' and had a few months to live." Subsequent events demonstrated the truth of his diagnosis. President Roosevelt ultimately had a fatal hemorrhagic stroke 2 months later, and his death brought hypertension's potential as a deadly difficulty to the lime light. Three years after Roosevelt's death, the pivotal National Heart Act was signed into law by President Truman. The Act created the track for the study of heart diseases and resulted in several studies including the Framingham Heart Study. The Framingham studies consistently showed that hypertension, such as hyperlipidemia, was associated with many cardiovascular morbidities such as stroke, heart failure, and heart attacks leading to premature deaths and the risk was clearly higher with higher blood pressure (systolic and diastolic).[1]

Hypertension is the most common regulating risk factor for cardiovascular disease (CVD) and death; the increased risk associated with blood pressure (BP) elevation can be greatly reduced by treatment with antihypertensive drugs that lower both BP and related target organ damage. A total of 69 drugs in 15 different classes are available and many of them are also available in single pill combinations, have been approved for the treatment of hypertension in the United States. Irrespective of this superfluity of retreatment options, an estimated 10% to 15% of the general hypertensive population has resistant hypertension, defined as uncontrolled BP on ≥3 antihypertensive drugs of different classes, including a non-potassium sparing diuretic, at optimal doses, or requiring ≥4 drugs to achieve control. In addition, ≈0.5% of hypertensive patients has refractory hypertension, defined as uncontrolled BP on ≥5 drugs. Numerous additional hypertensive patients are uncontrolled because of nonadherence or intolerance to available antihypertensive agents. Recent drug monitoring studies have revealed non-adherence to BP lowering therapy in 25% to 65% of patients with apparent treatment resistant hypertension (TRH). In 24% to 34.5% of these individuals, who were prescribed 3–5+ antihypertensive medications, no antihypertensive medication was detected in blood or urine samples. The unmet need of controlling BP in these high-risk patients may be addressed, in part, by the development of new drugs and devices and procedures that are designed to treat hypertension and comorbidities, such as heart failure (HF), chronic kidney disease, and diabetes mellitus.[2,3]

ETIOLOGY

Etiological factors correlated with hypertension in adults have also been associated with blood pressure elevations in youth. Intrauterine malnutrition, family history of hypertension ,obesity, particularly excess abdominal fat, insulin resistance, high dietary sodium intakes, low dietary intakes of calcium, potassium and magnesium, physical inactivity, high alcohol intakes, tobacco use, drug use (e.g., cocaine, ecstasy, anabolic steroids), emotional stress, diet pill use, oral contraceptives are the factors associated with development of hypertension. An inadequate supply of nutrients may program changes in fetal structure and metabolism, increasing the risk of hypertension and other diseases in later life. Hyperinsulineamia and insulin resistance are also associated with the development of hypertension which leads to many problems. The prominent plasma insulin levels may cause sodium sensitivity. Adequate dietary potassium, calcium, and magnesium intakes have been associated with lower blood pressure in youth. Potassium and calcium intakes are below recommended levels, particularly in adolescent females, while median intakes of phosphorus and protein, which promote calcium loss, are high. Lack of physical activity may increase the risk of developing hypertension by 20-50%.[4]

CALCIUM CHANNEL BLOCKER:

Voltage-gated Ca2+ channel:

In excitable cells such as cardiac myocytes, smooth muscle cells and neurons the Voltage-gated Ca2+ channels play important roles in excitement-contraction, excitement-transmission, and/or excitement-transcription couplings. High voltage-gated Ca2+ channels are pharmacologically classified into five different subclasses (L-, N-, P-, Q-, and R-type), the characteristics of which are determined by the pore-forming α1 subunit. New Ca2+ channel antagonists have been recently developed, especially in the DHP compounds that have considerable higher vascular selectivity, slower onset and longer duration of hypotensive action. Those more lipophilic Dihydropyridine Calciun channel blockers may reach their receptor, the L-type Ca2+ channel, via a membrane pathway with a two-step process: first, these drugs bind and accumulate in the membrane lipid bilayer, and Then diffuse within the membrane to its receptor site.[5]

Dual L/N-type Ca2+ channel blockers:

N-type Ca2+ channels are abundantly found in the nervous system particularly in peripheral and central sympathetic nerve endings and deeply involved in the fast release of norepinephrine and other neurotransmitters. Inhibition of N-type Ca2+ channels in both peripheral and central nervous systems may provide a new strategy for the treatment of hypertension and other cardiovascular diseases. To ensure efficient coupling of Ca2+ influx to rapid vesicle release,

N-type Ca2+ channels must be localized with the active zones of presynaptic nerve terminals. Pharmacologically, N-type Ca2+ channels are typically inhibited by the selective peptidergic blocker ω-conotoxin GIVA.[5]

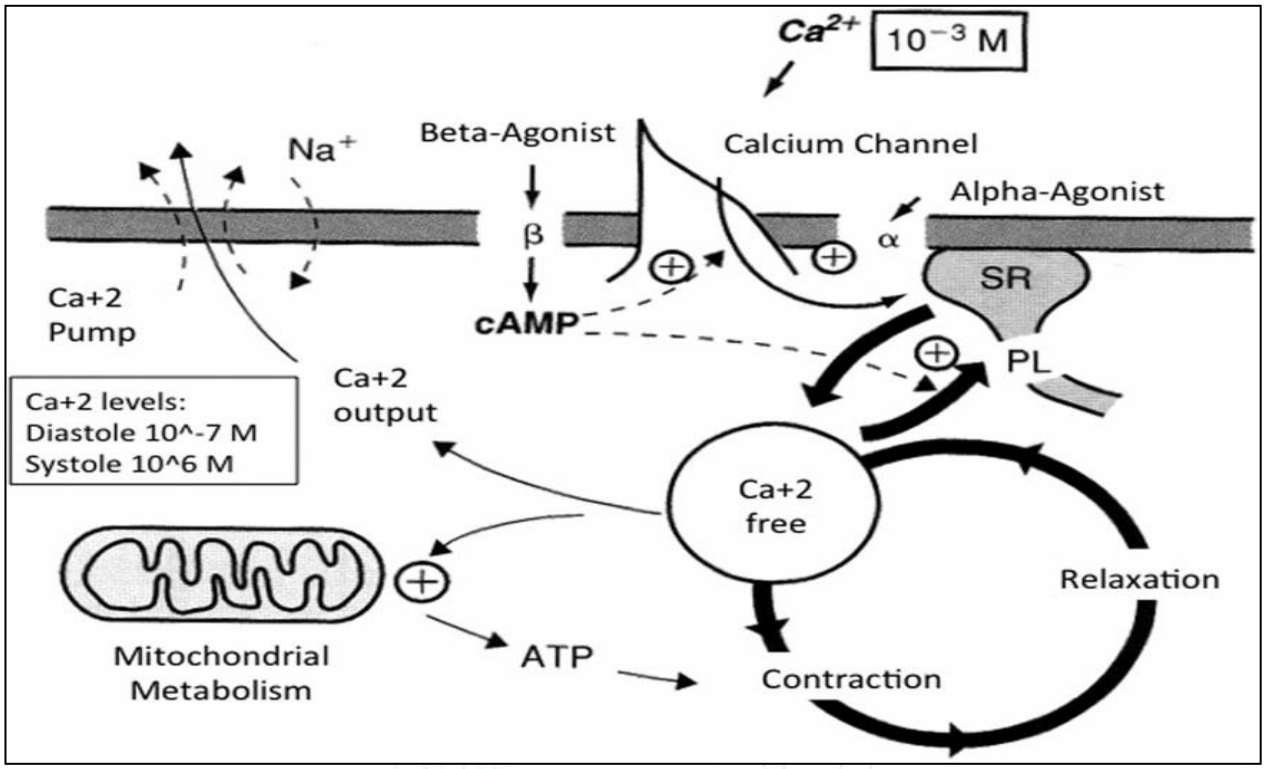

Figure 1: Schematic representation to explain the molecular mechanisms of actions of calcium channel blockers (CCBs).[6]

AZELNIDIPINE AS CALCIUM CHANNEL BLOCKER:

IUPAC name of the Azelnidipine is (±)-(3)-(1- diphenyl methyl azetidin- 3-yl)-5-isopropyl-2-amino-1, 4-dihydro-6-methyl-4-(3- nitrophenyl)-3, 5-pyridine dicarboxylate, is a new dihydropyridine derivative with calcium antagonistic activity. Although all the existing dihydropyridine calcium blockers have two methyl groups located at the 2- and 6-positions of the dihydropyridine ring, one methyl group at the 2-position is substituted by an amino group in the azelnidipine molecule. Consequently a conduct of a series of preclinical and clinical studies, this drug was launched into the market as CALBLOCK® in Japan in 2003. Azelnidipine occurs as two enantiomers due to an asymmetric carbon at the 4-position of the 1,4 dihydropyridine ring.[7]

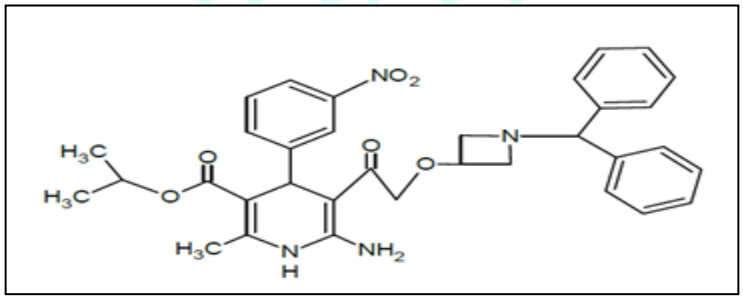

Figure 2: Structure of azelnidipine

Azelnidipine was synthesized by Ube Industries, Ltd. and developed by Sankyo Co., Ltd. (currently known as Daiichi Sankyo Co., Ltd., Tokyo, Japan). Azelnidipine has a potent and sustained Blood pressure -lowering effect in various animal models of hypertension . It was confirmed that azelnidipine has renoprotective effects (such as reducing proteinuria by dilating efferent arterioles), as well as cardioprotective, insulin resistance-improving, cerebroprotective, and anti-atherosclerotic effects.[8]

The antihypertensive effect of azelnidipine is primarily based on the inhibition of trans-membrane Ca2+ influx through the voltage-dependent channels of vascular smooth muscles. Ca2+ channels are categorized into several subtypes, including L-type, T-type, N-type, P/Q-type, and R-type Ca2+ channels depend on their electrophysiological properties. Azelnidipine is selective for L-type Ca2+ channels. It has strong lipophilicity and affinity to membranes of vascular smooth muscle cells. A preclinical study showed that azelnidipine could not be removed from the blood vessels, even by washing. It is retained in the vascular wall after clearance from the blood and continues to stimulate a hypotensive effect. Unlike other dihydropyridine Calciun

Channel Blockers, azelnidipine does not induce reflex tachycardia, probably since it elicits a gradual fall in BP. In addition, clinical studies have demonstrated that azelnidipine considerably reduced heart rate and proteinuria in hypertensive patients by suppressing sympathetic nerve activity. Azelnidipine has also been confirmed to have cardio-protective, cerebro-protective, and anti-atherosclerotic effects, and improves insulin resistance. Azelnidipine is used in the treatment of patients with hypertension, and the recommended dosage is 8–16 mg orally once daily. Oral administration of azelnidipine shows rapid, dose-dependent absorption.[9]

Calcium channel blockers (CCBs) are not recommended for routine treatment in patients with heart failure with reduced ejection fraction, because they might reduce the myocardial contractility. Conversely, their effects on LV diastolic function are still not fully elucidated. A combination of CCB and an angiotensin receptor blocker could improve LV relaxation effectively in hypertensive patients. On the other hand, dihydropyridine CCBs might have unfavourable effects on diastolic function due to reflex tachycardia. Azelnidipine is a unique dihydropyridine CCB that lowers BP without increasing heart rate, and even slightly decreasing it. We previously demonstrated that azelnidipine improved LV relaxation in hypertensive patients with LV diastolic dysfunction in the prospective multicentre, Clinical impact of Azelnidipine on Left VentricuLar diastolic function and Outcomes in patients with hypertension (CALVLOC) trial.[10]

Two or more antihypertensive agents to reach their target blood pressure (BP) are require to most of hypertensive patients. Currently the best therapy for preventing cardiovascular disease is a combination of angiotensin II type 1 receptor blockers (ARB)/CCB. Such combinations include many kinds of ARB and CCBs. Thus, differences in safety and efficacy among ARB/CCBs depend on the kind of ARB or CCB. Recent studies have shown that not all ARBs have the same effects, and some benefits conferred by ARBs may not be class (or common) effects, but rather molecular (or differential) effects. Furthermore, CCBs also have molecular effects independent of BP-lowering.[11]

PHARMACODYNAMIC:

Azelnidipine is a vasodilator that induces a gradual decrease in blood pressure in hypertensive patients. Different other member of its drug class, azelnidipine does not induce reflex tachycardia due to vasodilation. This is probable due to the fact that it elicits a gradual fall in blood pressure.It also exhibits a prolonged hypotensive effect and has been shown to have a strong anti-arteriosclerotic action in vessels due to its high affinity for vascular tissue and antioxidative activity.

Clinical studies have demonstrated that azelnidipine markedly reduced heart rate and proteinuria in hypertensive patients by inhibiting sympathetic nerve activity. Azelnidipine has also been confirmed to have cardio-protective, neuroprotective, and anti-atherosclerotic properties, and has also been found to prevent insulin resistance.

MECHANISM OF ACTION:

Azelnidipine inhibits trans-membrane Ca2+ influx through the voltage-dependent channels of smooth muscles in vascular walls. Ca2+ channels are classified into various categories, including L-type, T-type, N-type, P/Q-type, and R-type Ca2+ channels. The L-type Ca2+ channels. Normally, calcium induces smooth muscle contraction, contributing to hypertension. When calcium channels are blocked, the vascular smooth muscle does not contract, resulting in relaxation of vascular smooth muscle walls and decreased bood pressure

METABOLISM

Like most members of its class, azelnidipine primarily undergoes first-pass hepatic metabolism. Azelnidipine is metabolized by hepatic cytochrome P450 (CYP) 3A4 and has no active metabolite product. It may interact with other drugs or compounds that are substrates for this enzyme. Azelnidipine is lipophilic and has a potent affinity for membranes of vascular smooth muscle cells.[9, 12, 13]

REFERENCES

1. Mohammad g. Saklayen and neeraj v. Deshpande,timeline of history of hypertension treatment, frontiers in cardiovascular medicine, february 2016: 3(3).
2. Suzanne oparil, roland e. Schmieder, new approaches in the treatment of hypertension, circulation research,2015: 1074-1095.
3. Food and drug administration and the department of health and human services. Notice. Guidance for industry on hypertension indication: drug labeling for cardiovascular outcome claims; availability. 15 march 2011;76 fr 14024:1–12. (accessible at http://www.fda.gov/downloads/ drugs/.../guidances/ucm075072.pdf).
4. Nandhini.s, essential hypertension –a review, article journal of pharmaceutical science and research, 2014: vol. 6(9), 305-307.
5. Angela swang, costantino iadecola, gang wang, new generations of dihydropyridines for treatment of hypertension, journal of geriatric cardiology (2017) 14: 67-72.
6. Giuliano tocci, allegra battistoni, jasmine passerini, maria beatrice musumeci, pietro francia, andrea ferrucci and massimo volpe, calcium channel blockers and hypertension, journal of cardiovascular pharmacology and therapeutics,2014: 1-10.
7. G. Suneetha, p. Venkateswarlu and p.s.s. prasad, sensitive analysis of azelnidipine and related derivative in human plasma by ultra-performance liquid chromatography-tandam mass spectrometry, asian journal of chemistry; 2013: 25(18): 10319-1032.
8. Kazuomi kario, yuki sato, masayuki shirayama, megumi takahashi, kazuhito shiosakai, katsutoshi hiramatsu, masahiro komiya, kazuyuki shimada, inhibitory effects of azelnidipine tablets on morning hypertension, drugs r d: 2013; 13; 63–73
9. Bi-lian chen1, yin-zhuang zhang, jian-quan luo, wei zhang, clinical use of azelnidipine in the treatment of hypertension in chinese patients, therapeutics and clinical risk management; 2015; 309–318.
10. Katsuomi iwakura, hiroshi ito, katsuhisa ishii, motoo date, fumiaki nakamura, toshihiko nagano, shin takiuchi, changes in left ventricular relaxation after azelnidipine treatment in hypertensive patients with diabetes: subanalysis of a prospective single-arm multicentre study, bmj open; 2014;4.
11. Akira kawamuraa, shin-ichiro miura, yoshino matsuoa, hiroyuki tanigawaa, keijiro sakua, azelnidipine, not amlodipine, induces secretion of vascular endothelial growth factor from smooth muscle cells and promotes endothelial tube formation cardiol res. 2014;5(5):145-150
12. Nada t, nomura m, koshiba k, kawano t, mikawa j, ito s, clinical study with azelnidipine in patients with essential hypertension. Antiarteriosclerotic and cardiac hypertrophy-inhibitory effects and influence on autonomic nervous activity; s2007; 57 (11): 698-704.
13. Pubmed