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Hyper-glycaemic effect of calcium channel blockers

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Abstract
New CCBs that inhibit calcium channel subtypes have been developed over the past decade. Treatment of hypertension has been carried out not only using long-acting CCBs but also other CCBs selected on the basis of the characteristics of the calcium channel subtype they block. It is well known that amlodipine acts on L-type calcium channels abundantly expressed on vascular smooth muscle, and cilnidipine acts on N-type calcium channels that abound in the sympathetic nervous system as well as on L-type calcium channels. Therefore, we compared the efficacy of amlodipine with that of cilnidipine using a cross-over study design in hypertensive patients. The two drugs were administered to all patients, irrespective of the presence/absence of diabetes mellitus. Attempts were made to reduce the blood pressure of each patient to the goal of blood pressure control, without modifying the dose of concomitantly used antihypertensive drugs such as beta-blockers. Among the patients in whom the goal blood pressure was attained, the heart rate with cilnidipine did not differ significantly from that with amlodipine. Hoshide *et al.* reported that in a study using amlodipine elevated daytime and nocturnal heart rate, while cilnidipine reduced daytime and nocturnal heart rate. Therefore, the heart rate data collected from the patients of this study have reflected adequately the inhibitory effects of cilnidipine on N-type calcium channels.

Keywords: CCBs, amlodipine., cilnidipine, hypertension, Renin- Angiotensin system

Introduction

Calcium channel blockers (CCBs) are medications, disrupt the movement of calcium (Ca2+) through calcium channels. Calcium channel blockers are used as antihypertensive drugs, i.e., as medications to decrease blood pressure in patients with hypertension. CCBs are particularly effective against large vessel stiffness, one of the common causes of elevated systolic blood pressure in elderly patients. Calcium channel blockers are also frequently used to alter heart rate, to prevent cerebral vasospasm, and to reduce chest pain caused by angina pectoris. N-type, L-type, and T-type voltage-dependent calcium channels are present in the zona glomerulosa of the human adrenal, and CCBs can directly influence the biosynthesis of aldosterone in adrenocortical cells, with consequent impact on the clinical treatment of hypertension with these agents. CCBs have been shown to be slightly more effective than beta blockers at lowering cardiovascular mortality, but they are associated with more side effects. Potential major risks however were mainly found to be associated with short-acting CCBs. Some previous studied showed that these blockers have some effects on serum glucose levels. Dihydropyridine (DHP) calcium channel blockers are derived from the molecule dihydropyridine and often used to reduce systemic vascular resistance and arterial pressure. Sometimes when they are used to treat angina, the vasodilation and hypotension can lead to reflex tachycardia, which can be detrimental for patients with ischemic symptoms because of the resulting increase in myocardial oxygen demand. Dihydropyridine calcium channel blockers can worsen protein-uria in patients with nephropathy.

- Amlodipine (Norvasc)
- Benidipine (Coniel)
- Cilnidipine (Atelec, Cinalong, Siscard)
- Clevidipine (Cleviprex)
- Isradipine (DynaCirc, Prescal)

Phenylalkylamine calcium channel blockers are relatively selective for myocardium, reduce myocardial oxygen demand and reverse coronary vasospasm, and are often used to treat angina. They have minimal vaso-dilating effects compared with dihydropyridines and therefore cause less reflex tachycardia, making it appealing for treatment of angina, where tachycardia can be the most significant contributor to the heart's need for oxygen. Therefore, as vasodilation is minimal with the phenylalkylamines, the major mechanism of action is causing negative inotropy. Phenylalkylamines are thought to access calcium channels from the intracellular side, although the evidence is somewhat mixed. [9]

- Verapamil (Calan, Isoptin)
- Gallopamil
- Fendiline

Benzothiazepine calcium channel blockers belong to the benzothiazepine class of compounds and are an intermediate class between phenylalkylamine and dihydropyridines in their selectivity for vascular calcium channels. By having both cardiac depressant and vasodilator actions, benzothiazepines are able to reduce arterial pressure without producing the same degree of reflex cardiac stimulation caused by dihydropyridines.

Side effects of these drugs may include but are not limited to:

- Dizziness, headache, redness in the face
- Fluid buildup in the legs and ankle edema
- Rapid heart rate
- Slow heart rate
- Constipation
- Gingival overgrowth
- Serum Glucose disturbances?

In the body's tissues, the concentration of calcium ion (Ca^{2+}), outside of cells is normally about 10000-fold higher than the concentration inside of cells. Embedded in the membrane of some cells are calcium channels. When these cells receive a certain signal, the channels open, letting calcium rush into the cell. The resulting increase in intracellular calcium has different effects in different types of cells. Calcium channel blockers prevent or reduce the opening of these channels and thereby reduce these effects. Several types of calcium channels occur, with a number of classes of blockers, but almost all of them preferentially or exclusively block the L-type voltage-gated calcium channel. Voltage-dependent calcium channels are responsible for excitation-contraction coupling of skeletal, smooth, and cardiac muscle and for regulating aldosterone and cortisol secretion in endocrine cells of the adrenal cortex. In the heart, they are also involved in the conduction of the pacemaker signals. CCBs used as medications primarily have four effects:

- By acting on vascular smooth muscle, they reduce contraction of the arteries and cause an increase in arterial diameter, a phenomenon called vasodilation (CCBs do not work on venous smooth muscle).
- By acting on cardiac muscles (myocardium), they reduce the force of contraction of the heart.
- By slowing down the conduction of electrical activity within the heart, they slow down the heart beat.
- By blocking the calcium signal on adrenal cortex cells, they directly reduce aldosterone production, which corroborates to lower blood pressure.

Since blood pressure is in intimate feedback with cardiac output and peripheral resistance, with relatively low blood pressure, the after load on the heart decreases; this decreases how hard the heart must work to eject blood into the aorta, so the amount of oxygen required by the heart decreases accordingly. This can help ameliorate symptoms of ischaemic heart disease such as angina pectoris. Reducing the force of contraction of the myocardium is known as the negative inotropic effect of calcium channel blockers. Slowing down the conduction of electrical activity within the heart, by blocking the calcium channel during the plateau phase of the action potential of the heart (see: cardiac action potential), results in a negative chronotropic effect, or a lowering of heart rate. This can increase the potential for heart block. The negative chronotropic effects of CCBs make them a commonly used class of agents in individuals with atrial fibrillation or flutter in whom control of the heart rate is generally a goal. Negative chronotropy can be beneficial when treating a variety of disease processes because lower heart rates represent lower cardiac oxygen requirements. Elevated heart rate can result in significantly higher "cardiac work", which can result in symptoms of angina. The class of CCBs known as dihydropyridines mainly affect arterial vascular smooth muscle and lower blood pressure by causing vasodilation. The phenylalkylamine class of CCBs mainly affect the cells of the heart and have negative inotropic and negative chronotropic effects. The benzothiazepine class of CCBs combine effects of the other two classes. Because of the negative inotropic effects, the nondihydropyridine calcium channel blockers should be avoided in individuals with cardiomyopathy.

Etiopathology

Various theories about the mechanisms of antihypertensive-induced glycemic defects have been postulated. Few of these theories have been confirmed and some are conflicting. In general, postulated mechanisms can be classified into four categories: effects on peripheral blood flow, effects on the insulin receptor, effects on the liver and effects on insulin release. Improved peripheral blood flow to skeletal muscles is thought to facilitate glucose disposal to the tissues. In this way, medications such as alpha-blockers, which promote peripheral vasodilation, may improve insulin sensitivity and glucose uptake. Through the same mechanism, ACEIs or ARBs may improve insulin sensitivity by reducing angiotensin II-mediated vasoconstriction and/or increasing vasodilators such as bradykinin, prostaglandins or nitric oxide. Conversely, medications that reduce peripheral blood flow could direct blood away from sites of glucose uptake, reducing glucose disposal. Nonselective beta-blockers limit peripheral blood flow by reducing cardiac output, a beta-1-mediated effect, and preventing peripheral vasodilation, a beta-2-mediated effect. Beta-blockers with intrinsic sympathomimetic activity are less likely than nonselective agents to reduce peripheral blood flow because of neutral or stimulatory effects on beta-2 receptors. Therefore, these agents may have a reduced impact on glucose disposal and insulin sensitivity compared with nonselective beta-blockers. Cardioselective beta-blockers are also less likely to reduce peripheral blood flow than nonselective agents; however, cardioselective beta-blockers still exhibit some glycemic adverse effects. In support of the blood flow hypothesis is the observation that reduced capillary density in skeletal muscle places individuals at a greater risk for beta-blocker-induced glycemic effects.

Insulin sensitivity may also be altered through effects on the insulin receptor or downstream signalling. Although few studies have directly examined changes to the insulin receptor, it appears that some antihypertensive agents may modify its activity. Hypokalemia has been linked to reduced insulin-receptor sensitivity, but this theory has not been consistently supported. Various antihypertensive agents could alter glucose transport proteins (GLUT 1 and GLUT 4), tyrosine kinase activity, or insulin receptor binding affinity. However, more information is needed to evaluate these effects. Two other potential sources of altered glucose control include hepatic insulin resistance and impaired insulin release. It has been suggested that thiazide diuretics promote hepatic insulin resistance, resulting in continued hepatic glucose production despite rising serum glucose or insulin levels. Although this effect has been observed with high-dose thiazide diuretics, it is less apparent with lower doses (12.5 mg to 25 mg of hydrochlorothiazide daily) used in current practice. Inhibition of insulin release can lead to hyperglycemia, and beta-blockers have long been considered to inhibit insulin release through pancreatic beta-receptor blockade. Similarly, diuretic therapy has also been associated with impaired insulin release through depletion of serum potassium. However, because insulin levels are higher than normal in most patients with diabetes, this mechanism is unlikely to be of major importance.

Hypertension is associated with impaired glucose tolerance and insulin resistance, resulting in the development of DM in hypertensive patients. If hypertension and DM coexist, the

risk of cardiovascular disease increases by 2- to 3-fold. Therefore, medications for preventing new-onset of DM as well as for treatment of hypertension are important in non-diabetic patients with hypertension. A recent meta-analysis demonstrated the association between types of antihypertensive agents and incidence of new-onset of DM. The findings suggested that the association between anti-hypertensive agents and incident of DM was lowest for angiotensin-converting-enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs). However, the anti-diabetic effect of calcium channel blockers (CCBs) is unclear. It was shown that strict blood glucose control and antihypertensive therapy significantly reduced the incidence of myocardial infarction, sudden death, and cerebral infarction as well as deaths related to these diseases in UKPDS36. Also a sub-analysis of UKPDS38 and HOT studies showed that strict blood pressure control reduced the incidence of cardiovascular disease in patients with both diabetes and hypertension. Thus, the goals of antihypertensive therapy in diabetics with hypertension have been proposed. According to the latest guidelines (ADA2004, JNC-VII, ESH/ESC2007, and JSH2009), the common goal of antihypertensive therapy is to attain a blood pressure of <130/80 mmHg. Currently, dihydropyridine calcium channel blockers (CCBs) are the most frequently used antihypertensive drugs. Because CCBs primarily inhibit L-type calcium channels and thus reduce blood pressure, they stimulate sympathetic nerve activity, leading to a reflective increase of heart rate. Such effects are observed not only with short-acting CCBs but also with long-acting CCBs. Over the past decade, a new type of CCBs, which can inhibit not only L-type calcium channels but also N- or T-type calcium channels, have been developed and used increasingly more frequently for hypertension treatment. In light of the worldwide epidemics of diabetes and hypertension, explorations of the effect of antihypertensive drugs on the incidence of diabetes are of clinical importance. Moreover, they are crucial in the areas of public health, since a modest increase in the risk of diabetes translates into a substantial social burden. These circumstances prompted us to investigate, with greater precision, the effects of CCBs on diabetes prevention by scrutinizing pertinent up-to-date original reports and combining their data in an attempt to obtain meaningful clues for an evaluation of the potential benefits of CCBs.

Hypothesis

Based on some previous studies based the effect of Calcium Channel blockers on serum Glucose levels, we designed a research to assess the effect of Ca channel blockers on serum Glucose levels.

Study Time

November 2016-February 2017 (14 weeks)

Participants

33 subjects using Ca channel blockers as hypertension correction agents, who have no evidence of Diabetes

33 subjects who have Hypertension, using Ca channel blockers as Blood pressure controlling agent, these subjects have frank diabetes also.

Two Calcium channel blockers were using by the both group of subjects – amlodipine and azelnidipine

Azelnidipine dose administered was 16 mg /day and amlodipine dose was 5 mg /day.

Oral glucose tolerance test

(Glucose Feeding)- All the subjects of both the groups were given 100 gms glucose and after 2-3 Hours the serum and urine samples were analyzed for glucose.

Biochemical Estimations Done

- The demographic data of all the Non Diabetics and Diabetics were collected.
- To access the effect of Ca Channel Blockers estimation of Serum Calcium was done by OCPC (Ortho-Cresolphthalein Complexone) method by using the kit of "Lab Care" in auto analyzer, model no-Star 21 Plus. 1 ml vial of reagent was mixed with 0.5 ml serum. The calcium in the patient serum/plasma reacts with OCPC to form a purple colored complex. The intensity of the color is directly proportional to the concentration of calcium in the sample. The concentration is measured colorimetrically at a wavelength of 578nm (550 – 590nm) and compared with that of a standard.
- C–reactive protein is indicator of inner damage and inflammation in chronic hypertensive stage. C-reactive protein was assessed by using kit of Span Diagnostics, reagent kit, Surat [code 25934] used for in vitro detection of C - reactive protein (CRP) in human sera in auto-analyser by agglutination method.50 micro ml serum was mixed with 1 ml reagent, clumping was indication of positive test.
- Hemoglobin gm % values was assessed by using Hemoglobinometer, to access the general health condition of the participants. also other parameters were assessed by using by using 5 Part Hematology Analyser, BC-5000 of Minray company.
- The HbA1c values for all participants were estimated, as higher Serum Glucose is strong etiological factor for diabetes.
- Those blood samples, which were found positive for C-reactive protein were sent to Ranbaxy Lab, Bombay via local sample collecting centre and were again qualitatively analysed. About 11 samples were sent outside, we analysed remaining samples ourselves and compare the results. We also got the same trend of serum values. The results were compared with the normal serum values. Qualitative and semi quantitative rapid latex slide test was used. We used kit of Span diagnostics, mixed 50 micro ml serum with 1 drop of reagent and within 6 seconds the result was read.
- As Serum Creatine Kinase is bio-indicator of cardiac damage-so quaitative analysis of this enzyme is done to assess the severity of the cardiac damage. For analysis Kit of Tecko Diagnosis was used, for assessment kinetic method was adopted. Sample value of 50 micro ml serum was mixed with reconstituted reagent with buffer, at 37 Ç, and the absorbance was read at 340nm, the time interval was 30 seconds.
- Estimation of lipid profile- Chema Diagnostica Qualigens fine chemicals A division of Glaxo India Ltd.

2. Span diagnostic limited, Surat, India

a. Cholesterol Estimation Kit (one step method of Wybenga and Plleggi) (Catalog No. – 25924)
b. HDL Estimation Kit (One step method of Wybenga and Plleggi) (Catalog No.–25924)
c. Triglyceride Estimation Kit (Enzymatic colorimetric method GPO–PAP liquid stable single regent) (Catalog No. 77034 (6×250 ml)).

- The intervention dosage for Azelnidipine dose administered was 12 mg /day and amlodipine dose was 6 mg /day in an average as prescribed by physicians
- Analyzing serum C- Peptide levels. Measuring C-peptide can help to access the effect of administered hypotensive agents on Insulin status in the body, because some studies said that these Ca channel blockers have effect of Insulin status. C-peptide is indirect estimation of Insulin, as this molecule binds two molecules of Insulin, by Akita Abay method the estimation of C-peptide was done.
- Oral Blood Glucose Testing- the al subjects and controls were given 100 gms of glucose (Glucose Loading) and after 3 hours of incubation, their serum glucose level was assessed to know the glucose managing capacity of the persons.
- Heart rate was assessed by counting pulse, because due to pulsus paradoxus in High BP, measuring heart rate is important.
- The Blood tests were done to assess the serum level of the following enzymes-
- Troponin T.
- Troponin I.
- Myoglobin.
- Creatine phosphokinase (CK).
- Lactic dehydrogenase (LDH).
- Aspartate aminotransferase (AST)

These cardiac Biomarkers (cardiac enzymes) were estimated by using Biochemical autoanalyser Star 201, by using kits of Span Diagnostics.

- Platelet count was done, because in chronic use of hpotensives precipitates diminution of platelet factors specially Platelet I & III the count decreases.
- Blood Pressure –The periodic estimation of all the participants was estimated by Auscultatory method.

Observations

Table 1: Baseline characteristics of patients

Male/female	19/14 (Non diabetics) 16/17 (Diabetics)
Age, years	43 ± 15
Body mass index, kg/m 2	25.2 ± 3.8
Impaired glucose tolerance (%)	11 (Non diabetics) 16 (Diabetics)
Dyslipidemia (%)	9 (Non diabetics) 13 (Diabetics)
Serum Ca mg %	6.9 (Non diabetics 6.3 (Diabetics)
Current smoker (%)	13 (Non diabetics) 8 (Diabetics)
History of CHD (%)	3(Non diabetics) 5 (Diabetics)
Hemoglobin gm %	9.5 ± 3.1(Non diabetics) (Diabetics (10.2 ± 1.1)
Fasting blood sugar, mg/dL	99 ± 3(Non diabetics) 116 ± 9 (Diabetics)
Serum Glucose after Glucose loading	106.9 ± 4.2 (Non diabetics) 162 ± 9 (Diabetics)
Blood Pressure	161/97 (Non diabetics) 166 /99 (Diabetics)
Heart Rate	66 (Non diabetics) 71 (Diabetics)
Platelet count	44,000 (Non diabetics) 464000 (Diabetics)

Table 2: Comparison of blood pressure and heart rate between treatment with azelnidipine and amlodipine

Blood Pressure	Baseline	Total =33	
		Azelnidipine N = 16	Amlodipine N = 17
SBP (mmHg)	121.3 ± 9.5	121.4 ± 11.5	131.3 ± 9.6
DBP (mmHg)	73.1± 9.6	68.4 ± 6.2	72.1 ± 9.1
Heart rate	66.9 ± 3.9	63.3 ± 7.1	62.1 ± 6.6
TC, mg/dL	195 ± 19	190 ± 20	191 ± 23
LDL-C, mg/L	119 ± 14	115 ± 21	121 ± 11
HDL-C, mg/dL	49 ± 11	51 ± 19	59 ± 22
Triglyceride, mg/dL	127 ± 36	116± 59	116 ± 67
HbA1c, %	5.4 ± 2.3	5.3 ± 0.4	5.3± 0.1

Data are mean ± SD. SBP; systolic blood pressure, DPB; diastolic blood pressure.

Table 3: Comparison of 75 g oral glucose tolerance test between treatment with azelnidipine and amlodipine

	Baseline	Azelnidipine N = 16	Amlodipine N = 17
Glucose 0, mg/dL	97 ± 2	93 ± 8	92 ± 3
Glucose 30, mg/dL	169 ± 44	164 ± 32	171 ± 22
Glucose 60, mg/dL	167 ± 55	185 ± 39	174 ± 44
Glucose 120, mg/dL	128 ± 22	128 ± 33	143 ± 32

Data are mean ± SD.

Discussion

The adverse impact of new-onset DM in treated patients with essential hypertension is well established. It is well known that renin-angiotensin system-related agents such as ACE inhibitors and ARBs have potential for preventing new-onset of DM [7, 20]. However, the effect of CCBs on glucose tolerance and insulin sensitivity has not been clearly elucidated, particularly in the clinical setting. The present study demonstrated that azelnidipine administration rather than amlodipine administration significantly ameliorated

glucose intolerance and the inflammatory state in non-diabetic patients with essential hypertension. In addition, the number of circulating HPCs was significantly higher after azelnidipine administration than those after amlodipine administration. This study is, to the best our knowledge, a first report that demonstrates the beneficial effects of azelnidipine on glucose tolerance and insulin sensitivity in non-diabetic patients with essential hypertension. Increased heart rate is a sign of the increased sympathetic activity. Increased heart rate is associated not only with multiple coronary risk factors, but also morbidity and mortality of cardiovascular diseases. Indeed, enhanced sympathetic tone could cause insulin resistance by β-adrenergic stimulation. It has been reported that dihydropiridine CCBs, even third generation CCB, such as amlodipine, increase plasma norepinephrine levels and the ambulatory heart rate. However, azelnidipine has been reported to prevent an increase in heart rate by inhibition of the sympathetic nerve center, rostral ventrolateral medulla. After azelnidipine administration, the heart rate was significantly reduced and was significantly lower than that after amlodipine administration in the present study. Therefore, the anti-sympathetic nervous system effect of azelnidipine may contribute to a favorable effect on glucose tolerance.

Conclusions

These results suggest that azelnidipine treatment may have beneficial effects against glucose intolerance, insulin sensitivity, the inflammatory state, and circulating numbers of progenitor cells in non-diabetic patients with essential hypertension. Further prospective investigations in a large population are required to confirm these findings.

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