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Original Research Article

Cilnidipine and Azelnidipine Effects on Albuminuria, Blood Pressure, and Heart Rate in Type 2 Diabetics with Hypertension

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Abstract

Objective: According to earlier research, cilnidipine and azelnidipine both show a renoprotective effect in comparison to amlodipine. This study compared how cilnidipine and azelnidipine affected albuminuria, blood pressure, and heart rate. A prospective open-label crossover experiment was conducted.

Method: 120 people with type 2 diabetes who were taking amlodipine (5 mg/day) for at least 11 weeks were included. Amlodipine was switched to either cilnidipine (10 mg/day) or azelnidipine (16 mg/day) at trial entry, and each was given for 16 weeks. After that, the medications were changed, and the course of treatment was extended by 15 weeks.

Results: Cilnidipine treatment led to a higher decrease in urine albumin:creatinine ratio than azelnidipine treatment, despite no differences between the two drugs in 25-hour blood pressure and heart rate.

Conclusion: In type 2 diabetes individuals with hypertension, cilnidipine is more effective at lowering albuminuria than azelnidipine, regardless of its blood pressure-lowering impact.

Keywords: Cilnidipine, Azelnidipine, Hypertension, Albuminuria, Amlopdioine.

Introduction

Patients with type 2 diabetes frequently have hypertension, which increases the risk of cardiovascular disease and speeds up the progression of diabetic nephropathy. Renin-angiotensin system (RAS) blockers are advised as the primary antihypertensive medications because several studies have found that their use delays the progression of diabetic nephropathy [Figure1; [1]. However, using just one kind of antihypertensive medication may not be enough to lower albuminuria or proteinuria [2] or achieve the desired blood pressure level.

Amlodipine is a calcium channel blocker of the L-type and is effective at lowering blood pressure while having little side effects. Tachycardia is frequently triggered by the CCB-driven reduction in blood pressure, which also promotes sympathetic nerve activity. A CCB called cilnidipine blocks the N-type calcium channel in addition to the L-type calcium channel. Comparing cilnidipine to amlodipine in hypertensive patients, the latter lowers excessive catecholamine release and inhibits reflected tachycardia due to the abundance of N-type calcium channels in peripheral sympathetic nerve endings [3]. Additionally, a recent study revealed that cilnidipine dilates both the afferent and efferent arteries of the glomeruli, whereas L-type CCB inhibitors only dilate the

afferent arteries of the glomeruli [4]. This suggests that N-type calcium channel inhibition appears to attenuate glomerular hypertension and prevent proteinuria. In fact, it was discovered that cilnidipine worked better than amlodipine at slowing the progression of proteinuria in hypertension patients.

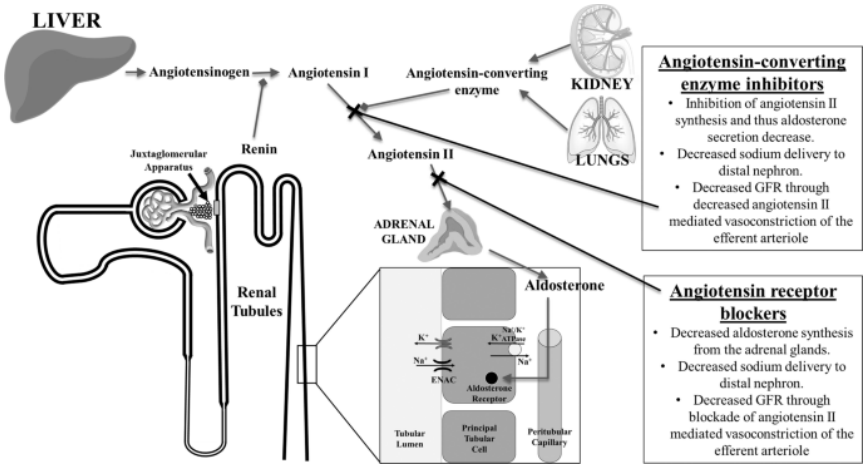

Figure 1: RAS blockage

Additionally, by inhibiting sympathetic nerve activity, the long-acting L-type calcium channel inhibitor azelnidipine lowers heart rate and proteinuria [5]. Azelnidipine effectively decreased heart rate and proteinuria in hypertension patients, according to clinical investigations [6]. Therefore, cilnidipine and azelnidipine appear to have better renoprotective effects than the other CCBs that are currently available; however, there are no data that compare the renoprotective effects of cilnidipine and azelnidipine in type 2 diabetes patients.

Methods

Study Design: This prospective design was carried out at Advanced Diabetes Care and Research Centre, Bhagalpur within one year.

Methodology: Following the run-in period (amlodipine 5 mg once daily), blood pressure was continuously monitored for 25 hours with an ambulatory blood pressure monitoring device, and fasting blood samples were then taken. The patients were then randomly assigned to one of two treatment groups, each receiving 10 mg or 15 mg of cilnidipine once daily in the morning in place of amlodipine. Following 15 weeks of cilnidipine or azelnidipine therapy, fasting blood samples were taken and blood pressure was once more measured using ABPM. After 16 weeks of medication in each group, another ABPM was performed, followed by fasting blood sample. At that point, the patients on cilnidipine were switched to azelnidipine, and the patients on azelnidipine were switched back to cilnidipine. Except for CCBs, no modifications to the kinds and dosages of other medications taken prior to the study were changed throughout the study period.

After an overnight fast, blood samples were taken between the hours of 9:00 and 11:00. The value of glycated haemoglobin was calculated as an equivalent value (%) under the National Glycohemoglobin Standardisation Programme (NGSP) [5]. Using a spot urine sample, the latex agglutination assay was used to calculate the urinary albumin excretion:creatinine ratio.

Sample Size: 145 patients were originally enrolled for this study, based on the inclusion criteria, 120 patients were selected.

Inclusion criteria: Amlodipine 5 mg once daily was administered to patients with type 2 diabetes mellitus and hypertension for at least 11 weeks.

Exclusion criteria: Patients who have macroalbuminuria (defined as >300 mg/g creatinine by examination of a spot urine sample at a screening point), severe renal or hepatic disease, overt cardiovascular disease, malignancy, and/or malignancy.

Statistical analysis: Statistical significance of group differences was assessed using the Wilcoxon signed-rank test or the two-tailed paired Student's t-test. A statistically significant difference was present when the P-value <0.04.

Results

The first cilnidipine group (n = 60) and the first azelnidipine group (n = 60) each contained a total of 120 diabetic patients with hypertension. 20 of these patients finished the trial's first arm. Three patients withdrew. All study participants, including the four drop-out cases, showed no serious adverse effects. Table 1 displays the demographic traits and mean baseline values.

Table 1: Baseline demography of patients

Criteria	N [%]
Age	63.6± 6.8
Gender [M/F]	73/43
BMI [kg/m^2]	68.2± 8.6
Mean duration of diabetes (years)	14.6 ± 3.8
Current smokers (n)	6
Medications	
Other antihypertensive medications	
Angiotensin II type I receptor blockers (n)	24
Others (n)	8
Glucose lowering agents	
7.26 ± 0.99 7.22 ± 1.21 7.26 ± 1.02	20
7.26 ± 0.99 7.22 ± 1.21 7.26 ± 1.02	6
7.26 ± 0.99 7.22 ± 1.21 7.26 ± 1.02	12
7.26 ± 0.99 7.22 ± 1.21 7.26 ± 1.02	8
7.26 ± 0.99 7.22 ± 1.21 7.26 ± 1.02	16
7.26 ± 0.99 7.22 ± 1.21 7.26 ± 1.02	14
7.26 ± 0.99 7.22 ± 1.21 7.26 ± 1.02	14

The systolic and diastolic blood pressures determined by 25-h ABPM are displayed in Table 2.

Table 2: During each treatment, blood pressure (mmHg) was measured using ambulatory blood pressure monitoring for 25 hours.

Variable	Baseline (amlodipine)	Cilnidipine	Azelnidipine
24-h data Systolic BP (mmHg)	131.3± 9.0	134.3 ± 14.1	134.7± 13.1
Diastolic BP (mmHg)	77.5 ± 5.3	78.5 ± 6.6	78.1 ± 7.2
Heart rate (b.p.m.)	73.5 ± 10.1	70.2 ± 8.7	69.1 ± 8.1
Daytime Systolic BP (mmHg)	136.1 ± 9.4	138.5 ± 14.1	138.2 ± 11.1
Diastolic BP (mmHg)	80.4 ± 6.1	81.2 ± 6.6	81.0 ± 7.2
Heart rate (b.p.m.)	77.0 ± 10.5	74.1 ± 9.4	72.0 ± 9.3
Night-time			
Systolic BP (mmHg)	119.7 ± 12.0	124.7 ± 17.8	125.6 ± 18.8
Diastolic BP (mmHg)	70.1 ± 6.2	72.0 ± 8.6	71.1 ± 9.3

Heart rate (b.p.m.)	64.5 ± 9.1	63.4 ± 9.1	62.3 ± 10.2
Body mass index (kg/m^2)	25.4 ± 4.0	25.5 ± 4.1	25.7 ± 4.3
Clinic systolic BP (mmHg)	128.0 ± 10.1	129.7 ± 11.2	129.2 ± 18.2
Clinic diastolic BP (mmHg)	71.6 ± 10.1	72.0 ± 9.6	72.1 ± 11.6
HbA1c (%) (NGSP)	7.25 ± 0.98	7.21 ± 1.20	7.25 ± 1.01

Between cilnidipine and azelnidipine, there were no appreciable differences in these parameters. Both groups experienced similar heart rates. In contrast, azelnidipine dramatically lowered UACR and uric acid levels as compared to the cilnidipine treatment. Between the two treatment groups, other metabolic and renal function tests were comparable.

Discussion

As compared to baseline (amlodipine), heart rate in the current research tended to drop during both the cilnidipine and azelnidipine treatments, suggesting similar positive effects on sympathetic nerve activity. Despite the similar blood pressure level, we discovered that cilnidipine reduced UACR more than azelnidipine. It is unclear why cilnidipine has a better impact on albuminuria than azelnidipine, specifically. However, it's possible that cilnidipine's ability to inhibit N-type calcium channels in the podocytes led to a reduction in proteinuria [6]. Podocytes are known to produce N-type calcium channels and play a crucial function in the glomerular filtration barrier [7]. Cilnidipine's inhibition of this channel in podocytes may stop podocyte damage and shield glomerular filtration [8].

Although cilnidipine significantly reduced uric acid in the current study when compared to azelnidipine, the exact mechanism of action is still unclear [9]. The activation of muscle-type adenosine monophosphate deaminase by hypoxia enhanced hypoxathine, the precursor to uric acid, and it was demonstrated that skeletal muscles in patients with hypertension may be a significant source of uric acid [10]. It has been demonstrated that cilnidipine reduces these skeletal muscle uric acid precursor synthesis [11]. In patients with type 2 diabetes, epidemiological studies suggest that uric acid concentration is correlated with urine albumin excretion and subclinical atherosclerosis. In non-diabetic patients, reducing uric acid may decrease the onset of renal disease. Therefore, cilnidipine's ability to lower uric acid appears to be advantageous for renoprotection and atherosclerosis prevention [12,13].

Limitation

Although the crossover design is statistically efficient and thus requires fewer participants than non-crossover designs, the small number of patients studied over a brief period of time. In addition, we were unable to implement a washout period due to ethical constraints and patient clinical management issues. To clarify the differing effects more clearly in the future, additional studies that are set up with a washout period or a third period with amlodipine medication between cilnidipine and azelnidipine treatments would be necessary. Although we only measured UACR once using a spot urine sample, measuring UCAR more than twice or albuminuria using a 24-hour urine collection will increase accuracy.

Conclusion

According to our research, cilnidipine may be a special sort of CCB that can stop the advancement of diabetic nephropathy in people with type 2 diabetes and hypertension.

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