

ORIGINAL ARTICLE

Effect of nifedipine on DTPA renogram curves

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Abstract

Aims The protective role of calcium channel blockers on renal function has been documented in humans by use of several modalities but renal scintigraphy has however not been used for this purpose. This study was conducted to evaluate the effect of nifedipine a dihydropyridine calcium channel blocker on ^{99m}Tc-DTPA renogram curve.

Methods A total of 43 subjects, 20 normal and 23 hypertensive under went two ^{99m}Tc-DTPA renal scans under same physiological conditions, with a three day interval in between, during which they took oral nifedipine (dose 10 mg twice daily). All the subjects had normal renal function established by routine laboratory investigations. Renograms from each kidney were generated and were used to calculate differential renal uptake and excretory function parameters of the kidneys. Paired student *t*-test was applied to check the statistical significance of the difference observed in the various calculated parameters, taking each kidney as an individual study organ.

Results Quantitative renal function parameters (i.e., GFR, Peak height/mCi and uptake slope) improved significantly after use of nifedipine in both groups. GFR increased by 9.16% in hypertensive group and 6.14% in normal group (p <0.05). Peak height/mCi increased by 6.55% in hypertensive group and 5.8% in normal group (p <0.05). Parenchymal uptake slope increased by 12.6% in hypertensive group and 8.6% in normal group (p <0.05). T_{max} reduced by 10.6% in hypertensive group and 11.95% in normal group (p <0.05). Statistically significant improvement in the renal excretory function parameters was observed only in hypertensive group. $T_{1/2max}$ decreased by 13.4% (p <0.05), Parenchymal retention index 20/3 and 30/3 improved by 9.6% (p <0.05) 21.6% (p <0.05) respectively in hypertensive group. However, no statistically significant change was observed in these parameters in normal group. Target-to-background ratio improved by 10.4 in hypertensive group and 11.5% in normal group (p <0.05).

Conclusion Short-term use of nifedipine, even in a small dose, has significant impact on the different quantitative parameters derived from renogram curves. It improved all the quantitative renal uptake and excretory functional parameters in hypertensive subjects. In the normal group, only the parameters related to the uptake function demonstrated a significant improvement.

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Introduction

^{99m}Tc-DTPA renal scintigraphy is a commonly used technique for evaluating renal function; it has major advantages in its noninvasive nature and its ability to give information about the relative functions of individual kidneys. Many drugs can affect the kidneys so it is possible to have changes in the pattern of renogram curves obtained from renal scintigrpahy in patients taking any systemic medication, especially cardiovascular drugs, and renograms can be used to asses and monitor effect on renal function. Calcium channel blockers are a relatively newer class of drugs and are widely used as anti hypertensive medication. Calcium channel antagonists have been reported to be renoprotective in humans and animals [1-4]. However, most of the reported studies are based on non-scintigraphic methods. In this study, we evaluate the short-term effects of nifedipine, a selective L-type dihydropyridine calcium channel antagonist, on the pattern of ^{99m}Tc-DTPA renogram curve in normal healthy volunteers and hypertensive subjects with normal renal function.

Materials & Methods

This prospective study was carried out at the Punjab Institute of Nuclear Medicine (PINUM), Faisalabad, from September 2007 to March 2008. 43 subjects (24 males and 19 females) participated in the study. These included 20 normal healthy volunteers (13 males and 7 females) and 23 hypertensive patients (11 males and 12 females) with normal renal function. Subjects in both the groups had no history of any systemic disease except for hypertension in the group 2, and their routine lab investigations, especially those related to renal function were normal. They were also screened for medical problems such as diabetes mellitus that might affect renal function. Every subject underwent baseline dynamic renal scintigraphy, which was followed by post nifedipine dynamic renal scintigraphy after 3 days trial of 10 mg BD dose of the drug.

A single-headed gamma camera (Siemens E-CAM) with a rectangular large field-of-view equipped with low-energy all-purpose collimator (LEAP) and an ICON 9.5 Macintosh system were used for data acquisition and analysis. Data was acquired as a dynamic sequential study - 60 frames of 5-sec each followed by 50 0-sec frames. Total study acquisition time was 30 minutes. Sequential composite static images were constructed for visual interpretation of the perfusion, uptake and clearance functions of the kidneys Suitable static image was obtained by summation of frames between 1 to 3 minute and was used for drawing regions of interest (ROI). One pixel thick painted ROIs were drawn around the kidneys and semilunar ROIs were drawn inferolateral to the respective kidney as target and background ROIs respectively. From these regions of interest, time-activity curves were generated and used for calculation of various parameters.

All the processing for calculation of various quantitative parameters from renogram curves and visual interpretation was done by two independent observers. Mean values were calculated and subsequently used for comparison of the baseline and post nifedipine studies. For statistical analysis, data was tabulated in Microsoft Excel work sheet. Each kidney was considered separately. Mean, standard deviation, standard error and range for each parameter were calculated by using Excel functions. For testing null hypothesis, paired student *t*-test was applied by using origin 6.1 statistical software.

Results

No statistically significant drop in mean arterial pressure after nifedipine trial was observed in either group. Quantitative renal function parameters, i.e. glomerular filtration rate (GFR), Peak height/mCi, uptake slope and T_{max} improved significantly after use of

Table 1 Hypertensive group

		Average	Standard deviation	Standard error	*p*
GFR	Baseline	42.6	11.20	1.68	0.0002
	Post nifedipine	46.4	11.14	1.76	
T_{max} (sec)	Baseline	232	91.2	14.4	0.049
	Post nifedipine	208	50.5	7.99	
$T_{1/2\ max}$ (sec)	Baseline	1106	368.2	58.2	0.01
	Post nifedipine	956	378.6	59.8	
20/3 ratio	Baseline	0.62	0.14	0.02	0.01
	Post nifedipine	0.56	0.14	0.02	
30/3 ratio	Baseline	0.46	0.15	0.025	$1e^{-05}$
	Post nifedipine	0.35	0.14	0.023	
Peak height/mci	Baseline	55.6	13.4	2.11	0.03
	Post nifedipine	59.3	16.5	2.60	
Uptake slope (counts/sec^2)	Baseline	13.2	7.41	1.17	0.025
	Post nifedipine	15.4	8.82	1.39	
Target-to-background ratio	Baseline	3.71	0.88	0.14	0.003
	Post nifedipine	4.06	1.004	0.15	

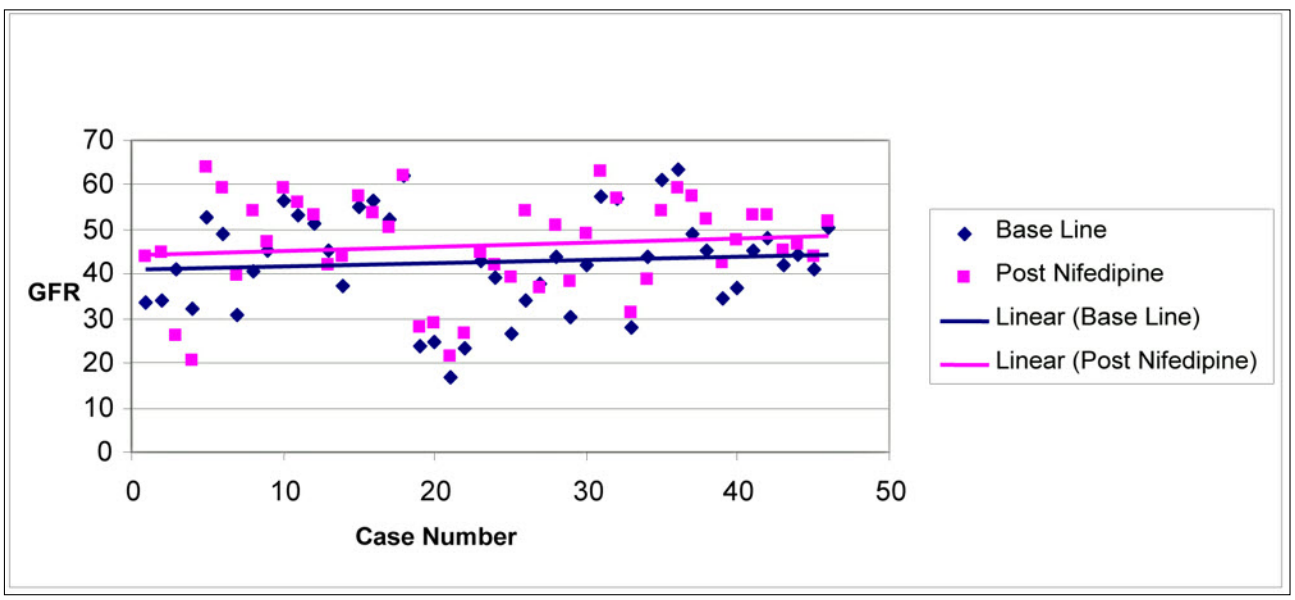

Figure 1 *GFR changes in hypertensives*

Table 2 Normal group

		Average	Standard deviation	Standard error	*p*
GFR	Baseline	50.18	7.24	1.14	0.016
	Post nifedipine	53.13	6.22	0.98	
T_{max} (sec)	Baseline	244.5	98.2	15.54	0.012
	Post nifedipine	212.4	50.8	8.03	
$T_{1/2\ max}$ (sec)	Baseline	693	316	50	0.57
	Post nifedipine	662	247	39	
20/3 ratio	Baseline	0.54	0.15	0.025	0.098
	Post nifedipine	0.50	0.10	0.017	
30/3 ratio	Baseline	0.32	0.17	0.028	0.11
	Post nifedipine	0.28	0.11	0.017	
Peak height/mci	Baseline	68.4	14.4	2.28	0.006
	Post nifedipine	72.4	14.04	2.22	
Uptake slope (counts/sec²)	Baseline	17.5	5.55	0.87	0.026
	Post nifedipine	19.2	5.37	0.84	
Target-to-background ratio	Baseline	3.54	0.95	0.15	0.038
	Post nifedipine	3.92	1.09	0.17	

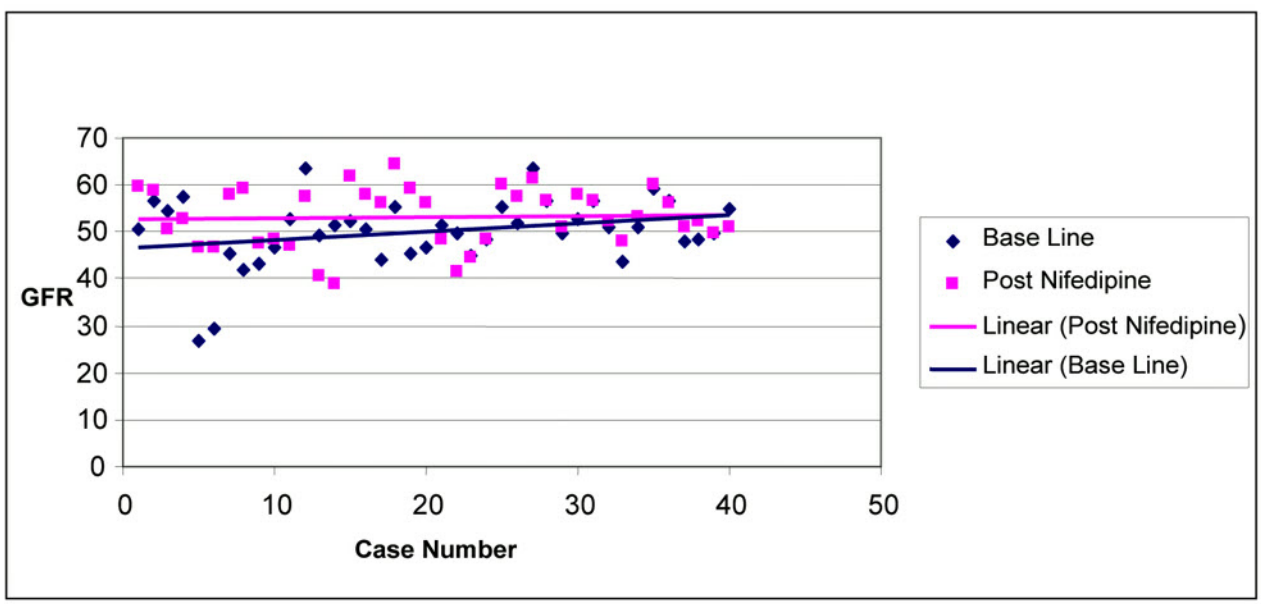

Figure 2 *GFR changes in normotensives*

nifedipine in both groups. GFR increased by 9.16% (p <0.05) in hypertensive group and 6.14% in normal group (p <0.05). Peak height /mCi increased by 6.55% (p <0.05) in hypertensive group and 5.8% (p <0.05) in normal group. Parenchymal uptake slope increased by 12.6% (p <0.05) in hypertensive group and 8.6% in normal group (p <0.05). T_{max} reduced by 10.6% (p <0.05) in hypertensive group and 11.95% in normal group (p <0.05). Statistically significant improvement in the renal excretory function parameters was observed only in hypertensive group. $T_{1/2max}$ decreased by 13.4% (p <0.05), Parenchymal retention index 20/3 and 30/3 improved by 9.6% (p <0.05) 21.6% (p <0.05) respectively in hypertensive group. However, no statistically significant change was observed in these parameters in the normal group. Target-to-background ratio improved by 10.4 (p <0.05) in hypertensive group and 11.5% in normal group (p <0.05).

Discussion

Calcium channel blockers are a relatively newer class of drugs and are widely used as anti hypertensive medication. The safety of calcium channel blockers and their ability to slow down the progress of renal damage in hypertension is well documented [5-8]. In this study, it was found that the calcium channel blocker also increases GFR and improves other renal parenchymal uptake and excretory function parameters.

The finding of 9% improvement in the GFR in hypertensive group was quite close to the findings of Reams *et al.* who determined GFR by three methods including creatinine clearance, ^{99m} Tc-DTPA clearance and inulin clearance. The authors reported a 13% increase in GFR after four weeks of Nifedipine monotherapy [8]. Tsunoda *et al* used a single oral dose of 20mg nifedipine on essential hypertension patients and measured GFR by creatinine clearance and reported a mild increase in GFR [9].

Renal parenchymal uptake function parameters calculated from renogram curves all showed improvement in both normotensive and hypertensive groups. Improvements in these parameters were more marked in hypertensive group than in normotensive group except for T_{max} which showed slightly more reduction in normotensive than hypertensive group. Our findings of improvement in the GFR and renal parenchymal uptake function parameters can be explained on the basis of the reported ability of calcium channel blockers to improve the renal perfusion by blocking the L-type calcium channels [10, 11]. Renal perfusion is dependent on the systemic blood pressure. However, the actual blood flow to the kidneys and the glomerular perfusion is further dependent on intrarenal vascular resistance. Intrarenal vascular resistance is affected by intrinsic intrarenal control mechanisms responsible for autoregulation. Some extrinsic factors are also involved in autoregulation including, renal nerve activity and hormones that can affect vascular contractility, as well as to a lesser extent, the actual composition and viscosity of the blood perfusing the kidney. This intrarenal vascular resistance controlled by the intrinsic autoregulatory mechanisms of the kidneys ensures a stable renal blood flow and glomerular filtration over a wide range of changes in the systemic blood pressure. Although these autoregulatory mechanisms are primarily local but systemic inputs also affect renal blood flow [12].

The ability of calcium channel blockers to improve the renal blood flow by causing vasodilatation and reducing the resistance of the glomerular arterioles is reported in a few studies carried out in human and animal subjects [13, 14]. Loutzenhiser and Epstein reported that calcium channel antagonists had variable effects on the renal vascular bed, i.e. either no change or an increase in the blood flow, but GFR is raised [15]. Yokoyama and Kaburagi determined renal blood flow by intravenous injection of paraaminohippurate and reported 44.2% and 2.2% increase in the renal blood flow in hypertensive and normotensives human subjects respectively after use of I/V nifedipine [16]. These findings are also supported by the findings of *in vitro*

studies done to explain the observations that at a whole organism level the autoregulatory ability of the kidney is reduced by calcium channel blockers [17-18].

Renal excretory function parameters like $T_{1/2max}$ and parenchymal retention indexes 20/3 ratio and 30/3 ratio, also showed statistically significant improvement in the hypertensive group after nifedipine trial. Improvement in these parameters was also noticed in the normotensive group; however, these changes were not statistically significant. The finding of an improvement in the renal excretory function in the hypertensive group may be due to diuretic and natriuretic effects of calcium channel blockers [9, 19, 20]. These findings are in agreement with the findings of Leonetti *et al* who reported a 1.59-fold increase in the renal excretory function with nifedipine [21]. Yokoyama and Kaburagi also reported 0.83-fold rise in the excretory function of the kidneys 45 minutes after I/V nifedipine [16]. The mechanisms underlying this action of the calcium channel blockers are not clear but two possibilities exist: firstly, that the compounds have a direct tubular action and secondly, that the excretory response is an indirect consequence of changes in intrarenal haemodynamics [22].

Target-to-background ratios were also compared in both groups to investigate possible change in this parameter after the nifedipine trial. Results show a statistically significant improvement of 11.4% (p <0.05) and 10.5% (p <0.05), respectively in normotensive and hypertensive groups after the trial of nifedipine. The reason for the improvement in the target-to-background ratio can also be defined in the light of above discussion that nifedipine improves the renal perfusion and also causes diuresis resulting in improved first-pass extraction and early background clearance.

Clinical Implications

The one obvious and immediate implication is the effect on the test itself, i.e. by enhancing blood clearance, calcium channel blockers might mask information about basal renal function. Another implication might be the use of the investigation as a test of assessing renal reserve especially in hypertensive individuals who are candidates for transplant donation. Individual kidney GFR can be calculated, which is a definite advantage over total GFR calculated by other methods.

Conclusions

Short-term use of nifedipine even in a small dose has significant impact on the different quantitative parameters derived from renal scintigraphic renogram curves. It improved all the quantitative renal uptake and excretory functional parameters in hypertensive subjects. In the normal group, parameters related to uptake function demonstrate significant improvement, and the excretory function parameters showed no significant change. Significant changes observed in different renal parameters after nifedipine trial despite having no statistically significant drop in mean arterial pressure favours the idea that the renal effects of calcium channel blockers are independent of their systemic effects.

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