EFFECTS OF ACUTE ADMINISTRATION OF NIFEDIPINE ON GLOMERULAR FILTRATION RATE AND URINARY EXCRETION OF SODIUM AND URIC ACID IN PATIENTS WITH MILD-MODERATE ESSENTIAL HYPERTENSION

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Summary : A prospective study was conducted in 25 patients with essential hypertension to study the effects of sublingual administration of nifedipine on some renal functions. Glomerular filtration rate was estimated by radioisotope clearance techniques using Tc-99m diethylene triamine pentaacetic acid (DTPA). The change in urinary excretion of sodium and uric acid were also monitored.

A basal estimation of these parameters was followed by repeat studies after lowering the blood pressure to normotensive levels by sublingual administration of nifedipine.

It was observed that acute administration of nifedipine does not produce a significant change in the glomerular filtration rate, but causes marked and significant natriuresis and uricosuria.

INTRODUCTION

Calcium slow channel blockers (CCB), referred to by some as calcium entry blockers and calcium antagonists, have come to be widely used as antihypertensive drugs in the last 4-5 years. They act primarily by inhibiting the entry of calcium into cardiac and smooth muscle cells through calcium channels in the cell plasma membrane (7, 9, 15, 18). Their

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relative freedom from side effects greatly improves patients' compliance despite the need for two to three divided doses every day. They are useful in the management of hypertension when the patients have associated angina or supraventricular arrhythmias and are also effective in the management of hypertensive emergencies (9, 18). Although they may not replace β-adrenoceptor blockers, they do provide an alternative, when certain clinical considerations preclude their use.

Effects of β-blockers on renal function in patients with hypertension has been the subject of many studies (2, 5, 17) but relatively little is known about the renal effect of CCB (See 1, 3, 6, 10, 11, 12, 14, 16, 19). The present prospective study was carried out to elucidate the acute effects of nifedipine on renal function with particular reference to glomerular filtration rate (GFR) and sodium and uric acid excretion in patients suffering from mild-moderate essential hypertension.

MATERIAL AND METHODS

Twentyfive patients (13 males and 12 females; aged between 25 and 64 years, with a mean age of 47 years) with hypertension were chosen for this study. All patients were subjected to a set of laboratory investigations, which included routine and microscopic urine examination, estimation of blood urea, serum creatinine, serum sodium, serum potassium, blood sugar, serum uric acid and cholesterol, x-ray of the kidney, ureter and bladder (KUB) area, abdominal ultrasound, x-ray chest and a twelve lead electrocardiogram. VMA was also estimated in urine in two cases.

No patient suffering from diabetes mellitus, malignant hypertension, congestive heart failure, markedly impaired renal function, obstructive uropathy or any bladder disease, or having evidence suggestive of secondary hypertension was included in the study.

Patients having a systolic blood pressure above 160 mm Hg and/or diastolic pressure above 95, but not greater than 115 mm Hg were included. Blood pressure was always measured by a sphygmomanometer with the individual resting in supine position.

All patients were informed about the nature of the study and their informed consents were taken and were informed not to change their diet from the usually taken diet, especially so in terms of salt and meat products. All drugs including the antihypertensives were witheld for at least 72 hrs before the tests. Measurement of GFR and urinary excretion of sodium and uric acid were carried out twice; once without any medicine (base line) and then after

sublingual administration of nifedipine (13). On the day of measuring the basal GFR, patients were called in a fasting state (but with no restriction to water intake) in the morning.

Glomerular filtration rates were estimated using Tc-99m DTPA. The DTPA kits were obtained from the Bhaba Atomic Research Centre, Bombay. GFR was calculated by a ' single injection" method using a "single compartment" model (as described by Klopper *et al.*, 8; Fig. 1). Using this method GFR was calculated as follows :

$$GFR = \frac{Dose}{I} \times \lambda$$

Where, GFR = Clearance of Tc-99m DTPA.
DOSE = Total radioactive dose (Tc-99m DTPA) injected iv in cpm (counts per min)
λ = Slope of the exponential expressing the disappearance of activity from plasma.
and I = Intercept of that line at time "O" (Fig. 1)

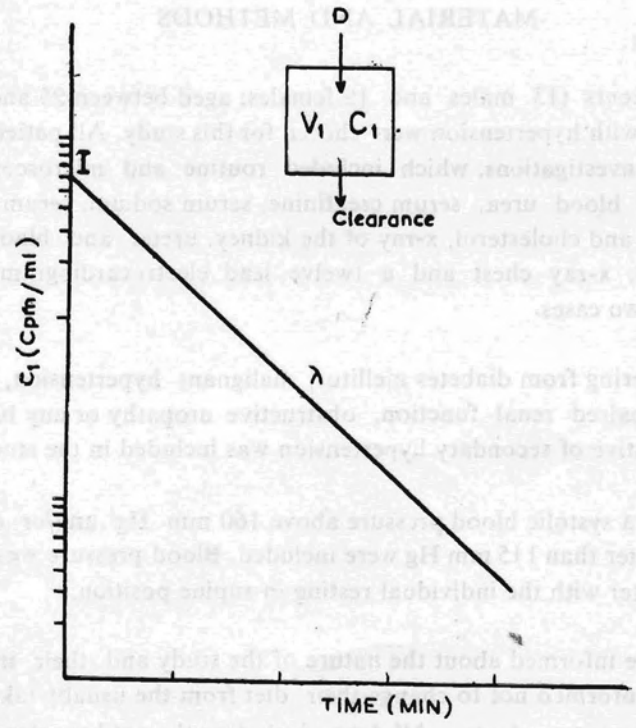

Fig. 1 : A typical single compartment model. The dose is injected into a single compartment (V_1) and the curve obtained as a single component on a semilog graph paper (the concentration axis is in $\log_{10}$). The clearance is calculated from slope (λ) of the exponential curve expressing the disappearance of activity from plasma.

Note that Dose/I, is equal to the apparent volume of dilution of the tracer. This simple technique establishes GFR as the product of volume of dilution and the disappearance (clearance) constant (λ) of the fitted exponential. λ was determined from the formula, $\lambda = 0.693/T\frac{1}{2}$ and $T\frac{1}{2}$ from the plasma clearance curve which was routinely obtained from the *cpm/ml* of the blood samples collected at 1 hr, 2 hr, 2 5 hr, 3 hr, 3.5 hr, and 4 hr after the iv injection of the tracer.

Before doing the clearance test, the patients were asked to empty the urinary bladder. Subsequently all the urine samples till the end of the test (approximately 4 to 4.5 hr) were collected and urinary sodium and uric acid levels of the pooled urine were estimated.

GFR following sublingual nifedipine : Immediately after the base line study, the patients were asked to continue their normal diet and antihypertensive drugs. They were asked to report again after seven days, after witholding the antihypertensive drugs for 72 hr. They reported fasting in the morning. There was no restriction to water intake. Their base line blood pressure levels were recorded. Sublingual nifedipine was then administered to each patient, 10 *mg* to start with, and the blood pressure was then measured every 5 min till it was normalised (160/90 mm Hg). GFR was determined at this stage as before. The urine samples were also similarly collected during the test and urinary sodium and uric acid excretions were estimated from the pooled urine.

Blood pressure readings were taken every fifteen min during the clearance test. If the blood pressure at any time rose above 160/90 mm Hg, it was quickly normalised by an additional 5 *mg* of sublingual nifedipine.

Data analysis was done using paired 't' test.

RESULTS

It was possible to bring down blood pressure to normotensive levels in all patients within 15-30 min of sublingual administration of nifedipine and once it was brought down to normal in most patients it remained at that level for the next 4-5 hr. Only in two out of 25 patients a second dose was needed during the study. In few patients reflex tachycardia was observed, but was not severe enough to abandon the study. No significant change was observed in glomerular filtration rate following nifedipine as compared to the base values ($P > 0.05$). However, marked and significant natriuresis ($P < 0.001$) and uricosuria ($P < 0.005$) was observed as a result of nifedipine intervention. Table I provides the quantitative details of these results.

TABLE I : Effect of acute administration of nifedipine on GFR and on sodium and uric acid excretion in mild-moderate hypertensive patients. Values are means (±SEM) from 25 patients. Parentheses indicate the range of values encountered.

	Base line value	*After nifedipine*	*Change*
GFR[(a)] *(ml/min)*	89.54±5.4 (38.3 to 145.5)	92.99±5.33* (53.6 to 168.3)	3.47±3.01 (−38.8 to 39.9)
Uric acid excretion[(b)] *(mg/lit)*	201.28±17.76 (71 to 460)	282.84±18.10** (100 to 500)	81.56±8.75 (15 to 170)
Sodium excretion[(b)] *(mEq/lit)*	77.12±4.29 (52 to 132)	195.48±9.17*** (102 to 252)	118.36.9.73 (22 to 200)

* Not significant

** Values differ significantly from the base line study, $P<0.005$ (paired 't' test)

*** Values differ significantly from the base line study, $P<0.001$ (paired 't' test)

a as determined by Klopper *et al.* (8) using Tc-99m DTPA

b based on 4.5 to 5 hr urine collection

See text for nifedipine administration

DISCUSSION

As in the present study, in 9 out of 12 other studies, which were conducted with acute administration (10 oral and 2 iv) of calcium channel blockers, there was no change in GFR (see 12). Nevertheless, significantly enough in 3 studies there was a marked rise in GFR in hypertensive subjects. Besides, in certain experimental studies, the CCBs have been shown to increase the GFR and renal blood flow (RBF) in the isolated kidney and the isolated renal vessel preparations in which the vascular tone was increased. This effect was shown to be through the selective attenuation of vasoconstriction of preglomerular or afferent vessels. Similar increased vascular tone is seen in hypertensive subjects and seems to be the hall mark of essential hypertension (see 12).

While some studies like the one by Yokoyama and Karubagi (19) have found that in conscious humans too, CCB may raise GFR, other studies (see above) do not indicate it so. This can be explained by the complex interactions that take place between the CCB and intrarenal mechanisms for the control of GFR. The possible interactions are outlined below.

The CCB may lower the afferent arteriolar tone as well as the efferent arteriolar tone, but the former more so. This would cause an overall increase in GFR. However, there are

counteracting mechanisms. The sodium reabsorption from proximal tubules is decreased and this through the tubuloglomerular feed-back mechanism raises the afferent arteriolar tone resulting in a fall in GFR and this is followed by a rise in ultrafiltration co-efficient (kf). This produces a fall in GFR either directly or by changing the tone in pre and post glomerular vessels. CCBs lower the agonist induced products of PGI 2 and PGE 2, thus causing a rise in the efferent and afferent vessel tones. The ultimate result is a differential change in GFR, which modifies the changes produced in the same by a direct action of the CCB on these vessels (12). There are some putative pathways through which the CCB may cause a rise in GFR. They may raise the ultrafiltration co-efficient either by decreasing mesangial cell contraction or through podocyte alteration. The effect of CCB on GFR is thus dependent on various neural and humoral influences.

In addition to effects of CCB reported here and similar results by others, Bakris and Burnett (1) demonstrated that the administration of CCB (Diltiazem) attenuates the magnitude and duration of radiocontrast mediated renal vasoconstriction and thus abolishes the resultant fall in GFR. Such observations suggest future potentially important therapeutic approaches for the use of calcium antagonists in a number of clinical settings, including prevention of radiocontrast induced renal insufficiency (12).

Natriuresis induced by nifedipine has also been reported earlier by various authors (4, 11, 12). The effect is in contrast to many other antihypertensives (4). High salt intake is a known determinant of the blood pressure levels and CCB may have thus a favourable place, particularly since the natriuretic effect has been shown to be present even with chronic administration of CCB (16). This however needs further corroboration. The natriuretic effect of CCB is probably a direct tubular effect and is not dependent on changes in GFR as appears from the present study.

As with sublingual administration, the uricosuric effect has also been shown following intravenous administration of nifedipine in patients with essential hypertension (10) and may be attributed to a tubular effect of the drug, because it is not accompanied by a rise in GFR. If chronic administration also shows similar changes, nifedipine may become a very useful drug for hypertensive subjects with hyperuricemia with renal involvement. Uric acid excretion has been postulated to reflect the severity of renal vascular disease and one may speculate that nifedipine may also have prognostic implications for renal disease.

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