EFFECTS OF DILTIAZEM ON RENAL FUNCTION

(Received 1 April, 1994)

S. Topcu, M.D.* / S. Sağır, M.D.** / F. Candan, M.D.*****
S. İçağasıoğlu, M.D.*** / C. Yıldırır, M.D.****

* *Associate Professor, Department of Internal Medicine, Faculty of Medicine, Cumhuriyet University, Sivas, Turkey.*
** *Associate Professor, Department of General Surgery, Faculty of Medicine, Cumhuriyet University, Sivas, Turkey.*
*** *Assistant Professor, Department of Internal Medicine, Faculty of Medicine, Cumhuriyet University, Sivas, Turkey.*
**** *Specialist, Social Security Hospital, Sivas, Turkey.*

SUMMARY

We planned to investigate the effect of diltiazem on urine volume, urine sodium (Na^+) and potassium (K^+) excretion and glomerular filtration rate (GFR). Twenty healthy men, aged between 23 and 36 (mean age: 29 ± 0.87) were examined. A double - blind placebo controlled study was completed by weekly intervals in 3 periods. In each period, first day no drug was given, the second day placebo, the third day diltiazem (30 mg or 60 mg) or placebo was given.

In the first 6 hour period following diltiazem 30 or 60 mg administration, increases in GFR ($p<0.05$), urine volume ($p<0.01$) and urine Na^+ excretion were significant ($p<0.001$), but increase in urine K^+ excretion was not significant ($p>0.05$). In the next 18 hour period, we observed that diltiazem did not affect the excretion of K^+ urine volume and GFR ($p> 0.05$), but increased the excretion of Na^+ ($p<0.05$).

Key Words : Diltiazem, GFR, Natriuretic, Diuretic effect.

INTRODUCTION

Calcium antagonists are widely used in the treatment of many disorders (1,2) and various opinions on their effects on renal functions (urine volume, urine Na^+ and K^+ excretion, GFR) have been reported in different studies (3-8). The majority of these studies involved nifedipine, verapamil and nitrendipine. It has been reported that calcium antagonists have natriuretic and diuretic effects with insignificant changes in GRF and urine K^+ excretion (4-8). Drugs preferred in the treatment of coronary artery disease (CAD) and hypertension must not cause Na^+ and fluid retention. However, we sometimes have to combine diuretics with most of the drugs used in these disorders, due to Na^+ and fluid retentive features of these drugs (9).

In this study, we aimed to investigate the effect of diltiazem on urine volume, urine Na^+ and K^+ excretion and GFR.

MATERIALS AND METHODS

Twenty healthy male volunteers aged between 23 and 36 (mean age: 29.65 ± 0.87) participated to our study . At first, all of them were examined by complete physical examinations. Their complete blood and urine analyses, hepatic function tests, serum urea, creatinine and electrolytes were studied.

All subjects were offered not to take any medications before the study. They were put on a standard diet (100 mEq / day Na^+ and 80 mEq / day K^+) for one week and had normal sleep patterns. A double - blind and placebo - controlled study was completed by week intervals in 3 periods. Each period lasted 3 consequent days and nothing was applied during the next four days. In the first day of each study period, nothing was done or given. On the second and third days of the first study period, placebo was given. In the second period; on the second day placebo and on the third day 30 mg diltiazem were given. In the third period; of the second day placebo and on the third day 60 mg diltiazem were given. All medications were given peroraly at 8.00 am., then urine samples were collected between 08.00 - 14.00 and 14.00 - 08.00 hours and urine volumes, Na^+, K^+ and creatinine values were measured. In each period second and third day at 11.00 am. and 11.00 pm. blood samples for creatinine measurement were obtained and GFR as ml / sec., was calculated for two hours for each period using the formula: Urine volume x urine creatinine / blood creatinine x minute. All biochemical measurements were done at our hospital in biochemistry laboratory by Technicon R-A 1000 autoanalyzer.

Statistical examination was done using the program "NCSS V (4,21)". The paired t-test was used for importance controlling the difference among the pairs.

RESULTS

Physical examinations and laboratory values studied in each period were normal. No individuals experienced any side effects related with the drugs.

Group administered placebo in the first week were compared at 6 hours and 18 hours. Their urine volume, GFR, urine K^+ and Na^+ values were not statistically significant ($p>0.05$).

Groups administered 30 mg and 60 mg diltiazem in the second and third week had significantly high urine volume, GFR and urine Na^+, compared with placebo group in the first 6 hours after drug intake ($p<0.05$). There was no difference between groups in urine K^+ levels ($p>0.05$) (Tables I and II). In the 60 mg diltiazem group, urine volume and urine Na^+ were significantly higher than the values of the group that received 30 mg diltiazem ($p<0.05$). But, there were not any difference in urine K^+ and GFR levels between the groups ($p>0.05$) (Table III).

When we compared 18 hour urine collection of 30 mg or 60 mg diltiazem groups in the first 6 hours with placebo, urine Na^+ levels were statistically high, ($p<0.05$) but urine volume, urine K^+ and GFR were not significantly different between the groups ($p>0.05$) (Tables I and II). Urine Na^+ levels were statistically high in group administered 60 mg of diltiazem when compared with 30 mg diltiazem group ($p<0.05$). Other parameters were found to be insignificant ($p>0.05$) (Table III).

Table I- Comparison of urine volume Na^+, K^+ and GFR values of placebo and diltiazem 30 mg groups (In the first 6 hours and the following 18 hours).

		(ml) Vi	(mMol/L) Na^+	(mMol/L) K^+	(ml/dk) GFR
In the first 6 hours.	n = 20 Placebo X ± Sx	228.00 ± 8.79	137.95 ± 3.37	53.86 ± 2.64	110.10 ± 1.91
	n = 20 Diltiazem 30 mg X ± Sx	862 ± 16.75	291 ± 5.62	53.91 ± 2.27	114.63 ± 1.60
	Results	t = 8.75 p < 0.01	t = 36.68 p < 0.001	t = 0.02 p > 0.05	t = 2.19 p < 0.05
In the following 18 hours.	n = 20 Placebo X ± Sx	270.00 ± 25.60	137.85 ± 4.85	49.80 ± 2.52	110.19 ± 1.84
	n = 20 Diltiazem 30 mg X ± Sx	841.50 ± 39.69	147.25 ± 3.94	46.90 ± 2.62	109.70 ± 1.59
	Results	t = 1.62 p > 0.05	t = 3.18 p < 0.05	t = 1.34 p > 0.05	t = 0.30 p > 0.05

Table II- Comparison of urine volume Na^+, K^+ and GFR values of placebo and diltiazem 60 mg groups (In the first 6 hours and the following 18 hours).

		Vi (ml)	Na^+ (mMol/L)	K^+ (mMol/L)	GFR (ml/dk)
In the first 6 hours.	n = 20 Placebo X ± Sx	209.00 ± 6.51	142.15 ± 3.75	53.00 ± 3.22	109.37 ± 1.74
	n = 20 Diltiazem 60 mg X ± Sx	454.50 ± 32.30	303.20 ± 4.23	52.68 ± 2.66	113.04 ± 1.87
	Results	t = 8.94 p < 0.01	t = 49.04 p < 0.001	t = 0.15 p > 0.05	t = 2.15 p < 0.05
In the following 18 hours.	n = 20 Placebo X ± Sx	766.00 ± 29.95	137.05 ± 3.59	49.45 ± 2.79	112.36 ± 1.79
	n = 20 Diltiazem 60 mg X ± Sx	809.00 ± 28.50	152.15 ± 4.11	47.55 ± 2.91	110.73 ± 1.61
	Results	t = 1.44 p > 0.05	t = 4.82 p < 0.05	t = 0.94 p > 0.05	t = 1.01 p < 0.05

Table III- Comparison of urine volume Na^+, K^+ and GFR values of diltiazem 30 mg and diltiazem 60 mg groups (In the first 6 hours and the following 18 hours).

		Vi (ml)	Na^+ (mMol/L)	K^+ (mMol/L)	GFR (ml/dk)
In the first 6 hours.	Diltiazem 30 mg X ± Sx	362.50 ± 16.74	291.90 ± 5.62	53.91 ± 2.27	114.63 ± 1.60
	Diltiazem 60 mg X ± Sx	454.50 ± 32.30	303.20 ± 4.23	52.68 ± 2.66	113.04 ± 1.87
	Results	t = 3.94 p < 0.05	t = 2.22 p < 0.05	t = 0.36 p > 0.05	t = 0.96 p > 0.05
In the following 18 hours.	Diltiazem 30 mg X ± Sx	841.50 ± 39.69	147.25 ± 3.94	46.90 ± 2.62	109.70 ± 1.59
	Diltiazem 60 mg X ± Sx	809.00 ± 28.50	152.15 ± 4.11	47.55 ± 2.91	110.73 ± 1.61
	Results	t = 1.03 p > 0.05	t = 1.05 p < 0.05	t = 0.21 p > 0.05	t = 0.52 p > 0.05

DISCUSSION

Calcium antagonists show their effects by selectively inhibiting the influx of calcium - ions into the myocardial and smooth muscle cells and thereby blocking the muscular contraction and decreasing the peripheral vascular resistance. So, they are freqently used in the treatment of CAD and hypertension (1,2).

Majority of antihypertensive drugs cause reflex tachycardia, retention of water and salt (1,3). For twenty years calcium antagonists have been used in the treatment of hypertension, and they are now accepted as the first line therapy with their success in the treatment, with no metabolic side effects and they can be used in both young and old hypertensive people (9-11).

Reports related with the effect of calcium antagonists on renal function have been inconsistent (4-6, 12-15). In the studies of Kinoshita et al. (16,17), it is reported that diltiazem given peroral 30 and 60mg/day causes increase in urine Na^+ excretion in patients with CAD and chronic renal failure (CRF). Also, further studies involving diltiazem given intravenously (IV) 0,5 mg / kg / bw within 10 minutes to 2 hours, show increase in urine Na^+ excretion in patients with hypertension or CRF (18, 19). There are also reports in literature related with long term diltiazem treatment (by 480 mg/d up to 24 weeks) stating that it has no influence on serum and urine electrolytes and urine volume (20-22). However, Carter et al. (7), report an increase in both urine volume and Na+ excretion with the dose of 150 mg / kg / bw IV in their study.

Natriuretic and diuretic potential of diltiazem is thought to be because of its effects on neurohumoral factors (prostaglandins, renin - angiotensin - aldosterone system and natriuretic factor) (7,8,10,23,24).

In our study after 30 mg and 60 mg diltiazem administration in the first 6 hours, increase in urine volume and Na^+ excretion were higher than those received placebo. When 30 and 60 mg diltiazem groups were compared, increase in urine Na^+ excretion and urine volume were significantly higher in the diltiazem 60 mg group ($p < 0.05$). Some studies are in accordance (7, 16-19) with our study, and some are not (20-22).

Groups which received placebo - drugs showed a significant increase in GFR within the first 6 hours following diltiazem intake. However this increase was within the limit values. In 18 hour urine collection following 6 hour after drug intake, GFR values did not change significantly compared with all study periods.

Single dose of diltiazem (30 mg or 90 mg) showed no influence on GFR and renal blood flow (RBF) in patients with CAD and congestive heart failure with or without hypertension (16,17,23). In 1987 Reams et al. (19), reported that I.V. diltiazem (0,2 - 0,5 mg / kg / bw) decreased blood pressure but had no significant effect on GFR or RBF. Similar results were reported in Sunderrajan et al's study involving administration of long term and high dose diltiazem therapy (22).

Increase in GFR and RBF following diltiazem therapy, may be due to its blocking effects on vasoconstrictive angiotensin II and norepinephrine (21-26).

In conclusion, our study suggests that single dose peroral diltiazem has natriuretic and diuretic effects with no significance in GFR and K^+ excretion. However, further studies with longer periods in wide populations must be done in order to confirm these results.

REFERENCES

1. Kayaalp O. Rasyonel Tedavi Yönünden Tıbbi Farmakoloji. Vol 2, 5th ed. Ankara: Faryal Mat-San ve Ltd. Şti, 1991: 1109-1115.
2. Prager G, Varchmin G, Hönig E. Nitrendipine in coronary heart disease. J Cardiovasc Pharmacol 1987; 9 (supp 4) : 208-215.
3. Mohinder P. Saluretic and diuretic effects of antihypertensive nitrendipine monotherapy in man. Angiology 1988;39(1):106-112.
4. Leonetti G, Sala C, Bianchini C, Terzoli L, Zanchetti A. Antihypertensive and renal effects of orally administered verapamil. Eur J Clin Pharmacol 1980;18:375-382.
5. Leonetti G, Cupsidi C, Terzoli L, Zanchetti A. Comporison of cardiovascular renal and humoral effects of acute administration of two calcium channel blockers in normotensive and hypertensive subjects. J Cardiovasc Pharmacol 1982; 4: 319,324.
6. Yokoyama S, Kaburagi T. Clinical effects of intravenous nifedipine on renal function. J Cardiovasc Pharmacol 1983;5:67-71.
7. Carter AJ, Gardiner DG, Burges RA. Natriuretic activity of amlodipine, diltiazem, and nitrendipine in saline-loaded anesthetized dogs. J Cardiovasc Pharmacol 1988;12(suppl 7) : 34-38.
8. Krussel LR, Christensen CK, Lederballe Pederson O. Acute natriuretic effect of nifedipine in hypertensive patients and normal controls - a proximal tubular effect? Eur J Clin Pharmacol 1987;32:121-126.
9. The joint national committee on detection evaluation and treatment of high blood pressure. The 1988 report of the joint national committee on detection evaluation and treatment of high blood pressure Arch Intern Med 1988;148:1023-1032.
10. Distler A. Review of current therapeutic principles in hypertension. J Cardiovasc Pharmacol 1987; 10 (suppl I): 134-138.
11. Ram CV. Southwestern Internal Medicine Conference. Calcium antagonists in the treatment of hypertension. Am J Med Sci 1985;290 (3) : 118-133.
12. Loutzenhiser R, Epstein M. Calcium antagonists and the kidney. Am J Hypertens 1989; 2:154-161.
13. Wight JP, Brown CB, El Nahas AM. Short-term effects of calcium antagonists on renal haemodynamics in patients with chronic renal failure. Nephron 1991;58:62-67.
14. Sunderrajan S, Reams G, Bauer JH. Renal effects of diltiazem in primary hypertension. Hypertension 1986;8:238-242.
15. Vanschaik BAM, Van Nistelrooy DEJ, Geyskes GG: Antihypertensive and renal effects of nicardipine. Br J Clin Pharmacol 1984; 18:57-63.
16. Kinoshita M, Kusukawa R, Shimono Y, Motomura M, Tomonaga G, Hoshino T. Effects of diltiazem hydrochloride on renal hemodynamics and urinary electrolyte excretion. Jpn Circ J 1978;42:553-560.
17. Kinoshita M, Kusukawa R, Shimono Y, Motomura M, Tomonaga G, Hoshino T. The effect of diltiazem hydrochloride upon sodium diuresis and renal function in chronic congestive heart failure. Arzneimittel-Forsch 1979;29:676-681.
18. Funyu T, Nigawara K, Ohno K, Hamada W, Yagihashi Y. Effects of benzothiazepine derivative (CRD-401) on blood pressure, excretion of electrolytes and plasma renin activity. Clin Therap 1981; 3:456-466.
19. Reams GP, Lau A, Messian C, Villarreal D, Bauer JH. Efficacy, electrocardiographic and renal effects of intravenous diltiazem for essential hypertension. Am J Cardiol 1987;60:781-841.
20. Inouye IK, Massie BM, Benowitz N, Simpson P, Loge D. Anti-hypertensive therapy with diltiazem and comparison with hydrochlorothiazide. Am J Cardiol 1984;53:1588-1592.
21. Trimarco B, Beluca N, Ricciardeli B, et al. Diltiazem in the treatment of mild or moderate essential hypertension. Comparison with metoprolol in a crossover double-blind trial. J Clin Pharmacol 1984;24:216-227.
22. Sunderrajan S, Reams G, Bauer JH. Long-term renal effects of diltiazem in essential hypertension. Am Heart J 1987;114:383-388.
23. Kulick DL, McIntosh N, Campese VM, et al. Central and renal hemodynamic effects and hormonal response to diltiazem in severe congestive heart failure. Am J Cardiol 1987;59:1138-1143.
24. Garnic JD, Blackshear JL, Harrington DP, Hollenberg NK. Calcium channel blockade and renal blood supply. Enchanced vascular responses to diltiazem in normotensive off spring of hypertensive patients .Circulation 1983;68 (p7.11) : 45-55.
25. Blackhear JL, Garnic JD, Williams GH, Harrington DP, Hollenber NK. Exaggerated renal vasodilator response to calcium entry blockade in first degree relatives of essential hypertensive subjects. Hypertension 1987;9:384-389.
26. Loutzenhiser R, Horton J, Epstein M. Effects of diltiazem and manganese renal hemodynamics. Studies in the isolated perfused rat kidney. Nephron 1985;39:382-388.