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A pilot study on the effect of telmisartan & ramipril on 24 h blood pressure profile & dipping pattern in type 1 diabetes patients with nephropathy

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***Background & objectives*: Angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) have been used to normalize the blood pressure and the dipping pattern in patients with type 1 diabetes mellitus (T1DM) and nephropathy. However, there are no data on the effect of the dual blockade on the dipping pattern in these subjects. We therefore, carried out this study to evaluate the effect of administrating an ACEI followed by ARB in the optimum doses in T1DM patients with nephropathy on 24 h blood pressure (BP) profile and nocturnal dipping pattern.**

***Methods*: An open label interventional pilot study was done during a one year period involving 30 consecutive patients who were treated with telmisartan 80 mg (0800-1000 h) for eight weeks followed by addition of ramipril 10 mg (1200-1400 h) for the next eight weeks. Ambulatory BP, dipping pattern and albumin excretion rate were studied after each phase. Twenty patients were hypertensive and 10 patients had macro- and 20 patients had microalbuminuria.**

***Results*: Telmisartan produced a fall in the clinic BP by 4/1.3 mm Hg ($P<0.05$ and $P<0.362$, respectively), 2/1.9 mm Hg in the mean 24 h BP, 1.4/1.1 mm Hg in the day BP and 3.7/3 mm Hg in the trough BP. Addition of ramipril to telmisartan produced a further reduction of 6.3/5.9 mm Hg in the clinic BP ($P<0.001$ for both), 4.3/4.2 mm Hg in the mean 24 h BP ($P<0.01$ and $P<0.0001$, respectively), 5.8/3.9 mm Hg in the day BP ($P<0.01$ for both), 4.2/2.5 mm Hg in the trough BP, with a reduction of clinic SBP and DBP of 10.3/7.2 mm Hg from the baseline. Telmisartan restored normal systolic dipping pattern in 33.3 per cent of the nondippers ($P<0.01$) but addition of ramipril was not complimentary. Hyperkalamia (>5.5 mmol/l) was observed only in 2 patients towards the end of the study.**

***Interpretation & conclusions*: The dual blockade with telmisartan and ramipril had complimentary effect on lowering of the BP, however, similar beneficial effect on the nocturnal dipping was not observed. Further studies with large number of subjects with longer duration of follow-up are required to validate these observations.**

Key words Albuminuria - ambulatory BP - hypertension - type 1 diabetes

Among the microvascular complications, nephropathy has the maximum impact on survival in patients with type 1 diabetes mellitus (T1DM) accounting for almost all the early mortality in the first twenty years with the disease[1]. In T1DM, the onset of hypertension is observed to coincide with the development of microalbuminuria. Currently the diagnosis and the treatment of hypertension is based on the blood pressure (BP) values recorded at the office and the therapies designed to lower these BP values have been found to have a positive impact on micro- and macrovascular end points in diabetes[1,2].

Current recommendations by the American Diabetes Association (ADA) support the use of angiotensin converting enzyme inhibitors (ACEIs) in T1DM with micro- or macroalbuminuria and consider angiotensin receptor blockers (ARBs) as an alternative, if ACEIs are not tolerated[3]. These recommendations are based on the proven efficacy of these drugs for renoprotection and reduction of urinary albumin[3]. The role of using both the drugs simultaneously in a dual blockade strategy in the patients with T1DM is not very clear.

Recent studies have demonstrated that the ambulatory blood pressure (ABP) monitoring is better correlated to end organ damage and cardiovascular morbidity from hypertension than the office blood pressure readings[4,5]. Impairment of nocturnal blood pressure regulation has been reported in adolescents and young adults with T1DM[5-7] and ambulatory BP abnormalities, especially a nocturnal increase in systolic blood pressure, has been shown to precede the onset of microalbuminuria[8]. Compared with the non-diabetic population, adult patients with T1DM demonstrate a deleterious blood pressure pattern even in the absence of diabetic kidney disease[9]. It is not clear whether the restoration of nocturnal dipping profile has any beneficial effect on survival, cardiovascular diseases or progression of renal failure. In light of the observational studies, it would seem logical to use the therapies that produce favourable changes in the nocturnal dipping.

A few studies have shown that the use of ACEIs restores the dipping profile[10,11] and similar data are available for ARBs as well[12]. In the present study we administered telmisartan, an ARB followed by dual blockade with the addition of ramipril, an ACEI at the optimal doses in patients with T1DM and nephropathy to evaluate their effect on the 24 h BP profile and on the nocturnal dipping pattern.

Material & Methods

Screening and recruitment: This study was an open label interventional pilot study to look for nocturnal dipping after dual blockade with telmisartan and ramipril in patients with T1DM with nephropathy. The patients were enrolled from Endocrinology Clinic of Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, between January 2007 and January 2008. Ethical approval for the study protocol was obtained from the institutional review board (Clinicaltrials.gov- reg.noNCT007386603). The inclusion criteria were: age ≥14 yr; type 1 diabetes [DM diagnosed by ADA criteria[3] with history of diabetic ketoacidosis (DKA)], HbA1c <7.5 per cent and albuminuria defined by albumin excretion rate (AER) ≥20 μg/min in two, timed overnight urine samples. The exclusion criteria were: patients with serum creatinine of more than 3 mg/dl at baseline, hyperkalemia >5.5 mmol/l, active urinary sediment or urinary tract infection (UTI), uncontrolled hypertension or congestive cardiac failure and suspected or proven non-diabetic renal disease.

Run in period before screening for albuminuria: Fifty eight eligible patients were consecutively recruited during the run in period. Seven patients were lost during this period as they did not return after the first visit. After the run in period of six weeks, a total of 51 patients were screened for the presence of microalbuminuria. Eighteen patients had no microalbuminuria and of the remaining 33 patients, two were excluded for other reasons. Thirty one patients were recruited into the study after obtaining a written informed consent while one patient was withdrawn because of DKA after completing four weeks of the study. Thirty patients eventually completed the study and were finally evaluated.

Clinical protocol: All patients recruited into the study underwent a detailed physical examination including assessment for the other diabetic complications. At baseline and at each visit, blood pressure was measured with an appropriate sized cuff in right arm with the patient seated and after 15 min of rest. Three readings were taken 5 min apart and the mean of these readings was taken as the clinic BP. The study consisted of two phases: in the first phase, telmisartan was started at a dose of 40 mg per day and after 2 wk uptitrated to 80 mg per day, administered between 0800 and 1000 h. Telmisartan was continued for 6 more weeks. Ramipril was added at a dose of 5 mg per day and after 2 wk uptitrated to 10 mg per day taken between 1200 and

1400 h, and was continued for 6 more weeks. At the end of the first phase and the second phase that is at the 8th and the 16th wk, respectively albuminuria estimation and 24 h ABP measurement were done. At each office visit the patients were enquired regarding the specific adverse effects of the drugs. Patients were withdrawn from the study if they developed any severe adverse effect including fall in estimated glomerular filtration rate (GFR) by ≥ 50 per cent or serum potassium>5.5 mmol/l.

Ambulatory blood pressure (ABP) measurement: ABP was measured using Spacelabs device (90207 Spacelabs Inc, USA). A uniform protocol of inflation once in every 30 min was used. The cuff was applied to the non-dominant arm. The recordings were started in all the patients between 0700 and 1000 h. For the purpose of ambulatory BP monitoring, daytime was defined as between 0600 and 2200 h and night time was defined as between 2200 to 0600 h. Using software provided by the manufacturer average of all the recordings of systolic, diastolic pressure and mean arterial pressures for each time period and the entire 24 h period were obtained. A value of 0.9 or lower for the ratio of mean night time systolic pressure to day time systolic pressures was defined as a normal drop in blood pressure during sleep (dipping pattern). Trough BP was defined as mean of BP recordings between 0200-0800 h, the last 6 h of the dosing interval of telmisartan.

Adjustment of other antihypertensive medications: Throughout the study period, a goal BP of <130/80 mm Hg was targeted. At baseline evaluation, 11 patients were on antihypertensives, seven of whom were on amlodipine only. Three patients were on two antihypertensives and one patient required three. After the first 8 wk, all the 7 patients requiring one antihypertensive were switched to telmisartan alone. The remaining four patients who were on two or more antihypertensives continued to require two additional antihypertensives throughout the study as their target BP was not achieved on withdrawal of these drugs. Serum creatinine and potassium were estimated at each visit.

Statistical analysis: Statistical analysis was carried out using SPSS version 10 (Chicago, USA). Comparison of variables for significance was done by Wilcoxon's signed rank test (for data with skewed distributions) and paired samples t-test (for data approximating normal distributions). Normality of distribution was assessed using skewness. Differences in proportion on repeated evaluations were compared using the McNemar's test, differences in proportions between groups were compared using the chi square test. Effect of telmisartan and ramipril on blood pressure and proteinuria was not adjusted for other antihypertensives as only four patients required other antihypertensives medications for the control of blood pressure.

Results

Baseline characteristics of study population: Thirty patients (10 females) completed the study. The mean (SD) age of the patients and the duration of diabetes were 26.1 ± 9.69 yr and 12.4 ± 8.1 yr, respectively. The mean body mass index was 19.73 ± 2.28 kg/m^2 and the HbA_1C at baseline was 6.4 ± 0.6 per cent. The mean clinic SBP and DBP were 123.6 ± 9.2 and 75.9 ± 7.4 mm Hg, respectively. Twenty patients were hypertensive and ten were normotensive by the ADA criteria. Twenty five (83.3%) out of 30 patients demonstrated loss of dipping for systolic blood pressure (nocturnal/daytime SBP >0.9).

The mean estimated GFR, serum creatinine and potassium were 123.7 ± 41.41 ml/min, 0.82 ± 0.36 mg/dl and 4.38 ± 0.45 mmol/l, respectively. Two patients had a GFR less than 60 ml/min. Ten patients had macroalbuminuria and 20 patients had microalbuminuria (AER 20-199 μg/min). Of the 30 patients, 23 (76%) had never received ACEIs/ARBs prior to the study and only seven had received either ACEIs or ARBs earlier.

Eighteen patients (60%) had neuropathy, 16 (53.3%) were found to have retinopathy. Among the subjects with macroalbuminuria, 70 per cent had proliferative diabetic retinopathy. None had macrovascular complications.

Antihypertensive effect of the study drugs: Telmisartan produced a modest reduction of clinic BP by 4/1.3 mm Hg (SBP/DBP) from the baseline. Only the reduction in SBP was statistically significant (P<0.05). There was a reduction of 1.4/1.1 mm Hg for the day time BP, 2.7/3mm Hg in the night BP (*P*<0.05 for both) and 2/1.9 mm Hg for the mean 24 h BP. The addition of ramipril to telmisartan produced a 6.3/5.9 mm Hg fall in the clinic BP (P<0.001 for both). There was a reduction of 5.8/3.9 mm Hg in the daytime BP (P<0.01 for both), 2.9/2.9 mm Hg in the night time BP (P=0.115 & P<0.05, respectively) and 4.3/4.2 mm Hg in the mean 24 h BP (P<0.01 and P<0.001, respectively) (Table).

The calculation of the trough BP and the assessment of the change in dipping status in patients not requiring

Table. Effect of telmisartan and ramipril on blood pressure and albumin excretion rate

	Baseline	8th week telmisartan	16th week telmisartan and ramipril	Fall in BP (*P* value)		
				0-8 wk	8-16 wk	0-16 wk
Clinic SBP (mmHg)	123.63±9.2	119.63±10.83	113.3±9.41	-4 (<0.05)	-6.3 (<0.001)	-10.3 (<0.001)
Clinic DBP (mmHg)	75.87±7.39	74.5±8.15	68.57±6.79	-1.3 (0.362)	-5.9 (<0.001)	-7.2 (<0.01)
24h SBP (mmHg)	120.83±8.9	118.87±9.62	114.6±10.33	-2.0 (0.053)	-4.3 (<0.01)	-9 (<0.001)
24h DBP (mmHg)	77.10±7.46	75.2±8.46	70.97±7.65	-1.9 (0.085)	-4.2 (<0.0001)	-6.1 (<0.001)
Day SBP (mmHg)	123.43±9.62	122.03±9.9	116.23±12.31	-1.4 (0.213)	-5.8 (<0.01)	-7.2 (<0.01)
Day DBP (mmHg)	79.6±7.54	78.5±7.9	74.67±7.59	-1.1 (0.406)	-3.9 (<0.01)	-5 (<0.01)
Night SBP (mmHg)	115.72±8.92	113.03±10.39	110.10±10.91	-2.7 (<0.05)	-2.9 (<0.115)	-5.6 (<0.001)
Night DBP (mmHg)	71.97±8.79	68.97±10.29	66.03±9.88	-3 (<0.05)	-2.9 (<0.05)	-5.9 (<0.001)
Trough SBP 0200-0800 h (mmHg) {n=26}	115±9.1	111.3±9.5	107.1±9.9	-3.7 (<0.05)	-4.2 (0.091)	-7.9 (<0.01)
Trough DBP 0200-0800 h (mmHg) {n=26}	72.5±9.7	69.5±10	67.02±9.02	-3 (0.064)	-2.5 (0.058)	-5.5 (0.023)
Albumin excretion rate+ (µg/min) mean ± SEM	441.37±137.83	269.85±82.38	167.59±44.9	-171.52 (38.8%, <0.01)	-102.26 (33.04%, <0.05)	-273.78 (62.02%, <0.001)

SBP, systoblic blood pressure; DBP, diastolic blood pressure; Values are mean ± SD; +Fall in AER (% reduction, *P* value) with each treatment period

any additional antihypertensives at the end of 8th and 16th wk (n=26). The baseline and 8th wk mean trough BP were 115 ± 9.1/72.5 ± 9.7 and 111.3 ± 9.5/69.5 ± 10 mm Hg, respectively. The fall in the mean trough SBP was 3.7mm Hg (P<0.05) and the mean trough DBP was 3 mm Hg. For the same patients the corresponding 0200-0800 h BP values after the addition of ramipril were 107.1 ± 9.9/67.0 ± 9.0, a reduction of 4.2/2.5 mm Hg when compared to 8th wk values but this reduction was not significant.

Change in dipping profile with the study medications: Out of 26 evaluated patients, 24 (92.3%) were non-dipper at baseline. Restoration of nocturnal dipping was observed in 8 of the 24 patients (33.3%) at the 8th wk after telmisartan, while only 3 of the 24 (12.5%) could sustain it at the end of 16th wk after dual blockade. There was a reversal of the dipping pattern to a non-dipping pattern in 5 of the 8 dippers between the 8th and the 16th wk of evaluation (62%) (P<0.05). The dipping pattern was not influenced by the presence or the absence of hypertension, or the stage of albuminuria.

Only two patients had a serum potassium>5.5 mmol/l towards the end of the study and were managed with potassium binding resin. Two patients experienced transient postural giddiness on the initiation of telmisartan which disappeared on continued therapy. There were no episodes of acute renal dysfunction.

Discussion

Our study showed that the dual blockade with telmisartan and ramipril produced a significant decrease in the clinic and the 24 h ambulatory BP. The therapy with telmisartan resulted in a significant reduction in the trough BP and the nocturnal BP after a morning dose demonstrating a significant round the clock BP lowering effect. It also restored a normal dipping pattern in one third of the patients, however, the addition of ramipril was not complimentary possibly due to inappropriate chronotherapy.

Telmisartan is a potent antihypertensive drug with a long duration of action and it reduced BP by 7.4/5 mm Hg in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET trial)[13,14]. In our study the BP lowering with telmisartan was modest 2/1.9 mm Hg for the mean 24 h BP. We presume that previous antihypertensive therapy in the 11 of the 30 patients (36%) coupled with a normal baseline BP reduced the magnitude of observed BP reduction with telmisartan alone in our study. However, there was a significant reduction of the nocturnal BP and the trough BP supporting the round the clock action of telmisartan[13-15].

Various studies have shown variable efficacy of the dual blockade[13,14,16-20]. Systolic and diastolic blood

pressures were reduced by 5.2 (2.1-8.4) mm Hg and 5.3 (2.2-8.4) mm Hg, respectively[20]. In our study there was an impressive reduction of 10.3 and 7.2 mm Hg of systolic and diastolic clinic blood pressure respectively from the baseline. This finding corroborates the finding of Candesartan and Lisinopril Microalbuminuria study (CALM)[21]. The combination was more effective at reducing blood pressure and urine albumin- creatinine-ratio (ACR) in hypertensive patients with type 2 diabetes than either drug alone.

The dipping of nocturnal systolic and diastolic BP is a physiological phenomenon. In patients with T1DM nocturnal dipping is lost even before the onset of microalbuminuria and hypertension[8]. In our study more than three fourth of the patients had a loss of the nocturnal dipping pattern and all of them had confirmed microalbuminuria or clinical nephropathy. This observation is similar to that of Lurbe *et al*[8] who observed that 80 per cent of T1DM patients with proteinuria had a loss of nocturnal dipping. Restoration of dipping pattern with the use of ACEIs or ARBs have been reported erlier[10-12]. Telmisartan therapy alone restored a dipping profile in addition to modest antihypertensive efficacy which is similar to olmesartan[12], probably due to its 24 h duration of action. Addition of ramipril produced a reversal of effects on dipping probably because of its time of administration during the day between 1200-1400 h which led to a disproportionately higher reduction in day rather than night BP. A study including 115 patients found better effects of 5 mg ramipril on nocturnal dipping profile when it was administered at the night rather than in the morning[22]. It can be suggested that therapy with ramipril in the night and telmisartan in the day should have had beneficial effects on the dipping pattern. Whether such chronotherapy has other benefits in addition to just BP lowering in terms of renal and cardiovascular outcomes is a topic of interest.

The exact mechanism of the normal dipping profile and the reasons for its derangement have been elusive. The proposed mechanisms include autonomic dysfunctions and pressure natriuresis hypothesis. Normally during sleep, there is a decrease in heart rate and stroke volume but in autonomic dysfunction state this physiological alteration is attenuated and accompanied with increase in heart rate and stroke volume, hence increased cardiac output resulting in loss of nocturnal dipping pattern. Patients with diabetes have more extracellular sodium as sodium is absorbed along with glucose by sodium-glucose co-transporter and may be responsible for the non-dipping BP profile in these patients. This is well illustrated in sodium sensitive hypersensitive subjects, as the non-dipping BP pattern can be converted to the dipping BP profile with sodium restricted diet or with the use of diuretics[23]. It is well established that the non dipping profile predisposes to cardiovascular events[23,24] and accelerates progression of chronic kidney disease[25], but it is not clear if restoration of the dipping profile leads to the reduction in cardiovascular risk[23].

In conclusion, dual blockade with telmisartan and ramipril had complimentary effects on lowering of BP, however, a similar beneficial effect on the nocturnal dipping was not observed possibly due to inappropriate chronotherapy. Further studies on larger number of subjects with a longer duration of follow up are required to substantiate these observations.

***Conflict of interest*:** The authors state that they have no conflict of interest.

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