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A Comparative Safety and Efficacy Study of Olmesrtan, a Newer Angiotensin-II Type-1 Receptor Blocker in Early Stage Type–2 Diabetes with Hypertension

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A B S T R A C T

Patients with type-2 diabetes are at high risk for developing cardiovascular diseases, which are also the most common cause of death in these patients. Angiotensin II type-1 receptor blockers (ARB) are widely used for the treatment of hypertension. Among the several ARBs available in the clinical setting, olmesartan is thought to have a significantly stronger blood pressure lowering effect than losartan or valsartan with their respective starting doses. In addition, recent data demonstrated that olmesartan more adequately achieved ambulatory blood pressure monitoring (ABPM) goals during the early morning surge period than did candesartan. Considering the importance of strict blood pressure control, olmesartan offers certain advantages in clinical use. With regard to its metabolic effect, telmisartan has the unique property of selective peroxisome proliferation–activated receptor (PPARγ) modulating activity, at least in-*vitro*. Thus, telmisartan might have clinical effects similar to those of PPARγ agonists, such as improving insulin resistance and increasing serum adiponectin levels. In fact, a recent study demonstrated that replacement of valsartan with telmisartan reduced serum highly sensitive C-reactive protein (hs-CRP) and increased serum adiponectin. Another study revealed that telmisartan has superior effects on metabolic parameters compared to losartan in hypertensive patients with metabolic syndrome. In addition, telmisartan blood pressure lowering effect is reported to last longer than valsartan's. To gain insight into the respective properties of ARB for type-2 diabetic patients with hypertension, an open-label crossover trial was conducted to compare the efficacy of the starting doses of olmesartan and telmisartan on blood pressure, and metabolic parameters. A clinical study has shown that a doses in patients with type-2 diabetes, olmesartan seems to have more potent blood pressure lowering than telmisartan, but similar effects on metabolic parameters. Our results suggest that olmesartan can be considered an ideal agent to prevent future onset of cardiovascular disease in type-2 diabetic patients with hypertension.

Keywords: cardiovascular, diseases, Angiotensin II, olmesartan, telmisartan, hypertension.

A R T I C L E I N F O

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1. Introduction

Hypertension is a common disorder in adults around the globe and is among the most common attributable causes of mortality [1]. The goal of antihypertensive therapy is to maintain blood pressures of < 140/90 mmHg for most people [2-7]. Recent hypertension guidelines recommend that diuretics, calcium channel blockers (CCBs), angiotensin receptor blockers (ARBs) and ACE inhibitors are all appropriate initial antihypertensive therapies for most people. In the USA, it is suggested that African-Americans with hypertension should be started on diuretics or calcium channels blockers due to evidence-based clinical efficacy results. In addition, the ACE inhibitors or ARBs are advocated for people with stage I–II hypertension and type 1 or 2 diabetes [3]. The ARBs have been in clinical use since 1995 and are known to be effective antihypertensive agent with excellent tolerability profiles. The ARBs have additive BP lowering effects when combined with thiazide diuretics and dihydropyridine calcium channel blockers without increasing adverse event rates. Furthermore, the ARBs have proven mortality and morbidity effects in heart failure and chronic renal disease, particularly when associated with type-2 diabetes. Concerns were raised surrounding the association of ARBs with the development of solid cancers and coronary artery disease. These issues have largely been dismissed by both clinicians and Food and Drug Administration (FDA) regulators [8-10]. Herein, we will review the pharmacology and pharmacokinetics of the ARBs. We will also present pertinent research trials comparing the antihypertensive effects and cardiovascular benefits of ARBs including the safety and tolerability issues encountered.

2. Material and methods

Study design and medication

A 16 week open-label crossover design was used in patients with type 2 diabetes mellitus and hypertension. Patients will be treated with valsartan 80 mg/day during run in period and with either olmesartan medoxomil 20 mg/day or telmisartan 40 mg/day during treatment periods.

Subjects Inclusion and Exclusion Criteria

All patients with type-2 diabetes mellitus were asked to participate in the study. Patients with type-2 diabetes mellitus and hypertension who were being treated with valsartan 80 mg once daily for at least 8 weeks. Patients with HbA1c exceeding 7.0% and/or patients treated with insulin or more than a minimal dose of sulfonylurea agents were excluded from the study. In addition, patients with diabetic microangiopathy, severe renal or hepatic disease, overt cardiovascular disease, or malignancy were excluded.

Method:

A total of 20 subjects in each group were recruited for this study. The study protocol was approved by the hospital ethics committee, and informed consent was obtained from each subject. The study was carried out in accordance with the guiding principles of GCP. An open-label crossover design was used. After completion of a run-in period consisting of once-daily administration of valsartan 80 mg, blood pressure during a 24-h interval was monitored with ABPM, and fasting blood samples were collected. The participants were then randomized into one of two treatment groups who received either 20 mg olmesartan medoxomil or 40 mg telmisartan once daily in the morning instead of valsartan. After 8 weeks of olmesartan /telmisartan treatment, blood pressure was again monitored with Ambulatory blood pressure monitoring (ABPM) and fasting blood samples were collected. Then, the subjects on olmesartan were switched to telmisartan and those on telmisartan were switched to olmesartan. This treatment was given for 8 weeks, after which another ABPM was performed with fasting blood sampling. All subjects were advised to consume their usual diet during the study period. Each patient was reviewed for general health and compliance with medication, which was assessed by tablet counts and checking of blood pressure, body weight, diet, and exercise status at each visit. During this study period the medication was not altered except for ARBs. The clinical characteristics of the study patients are listed in Table 1.

Table 1: Baseline Characteristics of Study Subjects

Age (years)	**62.8± 5.8**
Gender (male/female)	15/5
Body weight(kg)	65.0 ±12.4
Body mass index (kg/m^2)	24.6 ±0.9
Waist (male/female) (cm)	86.8 ±2.2/ 85.1 ±6.5
Mean duration of diabetes (years)	9.1± 10.5
Current smokers (n)	10
Presence of metabolic syndrome(n) medication	14
Other antihypertensive medication	8
Calcium antagonist (n)	4
Diuretic (n)	
Hypoglycemic treatment	7
Sulfonylurea(n)	2
Glinide(n)	4
α-Glucosidase (n)	1
Thiazolinedione (n)	
Statin (n)	2
Aspirin (n)	4

n=20, Data are mean ± SD or number of subject

Biochemical Measurements

Blood samples were obtained between 8:00 and 10:00 after overnight fasting. Serum lipids (total cholesterol, HDL

cholesterol, low-density lipoprotein [LDL] cholesterol, and triglycerides), glucose, and HbA1c were measured with standard techniques.

Ambulatory blood pressure monitoring (ABPM)

Ambulatory blood pressure monitors were used for 24-h ABPM. On the day of ABPM, study medication was administered as close to 8:00 as possible and about 24 h after the previous medication. After the ABPM device was attached, blood pressure was recorded every 60 min. The device was removed after a minimum of 24 h of recording. The daytime (7:00–22:00) and night time (0:00–6:00) ABPM were also defined as previously reported.

Statistical Analysis

Two-way analysis of variance (ANOVA) was used to compare demographic and laboratory parameters between the olmesartan and telmisartan-treatment groups. To approximate normal distribution, natural log-transformed values for IL-6 and IL-18 were used in the analysis, and were reported as the geometric means and 95% confidence intervals (CI) for those means. ANOVA was used to analyze the ABPM data of the olmesartan and telmisartan-treated groups. All statistical tests were two-sided with a 5% significance level. Data are presented as mean ± SD.

3. Results and Discussion

All enrolled patients (*n* =20) completed the trial. The demographic characteristics and mean baseline data are shown in Table 21. The subjects were relatively obese (body mass index [BMI] 25.6 ± 1.1 kg/m, and their rate of metabolic syndrome was 65%. Their blood glucose, blood pressure, and lipid data were well controlled. Table 2 shows the mean blood pressure analyzed by 24-h ABPM. Figure 1-3 shows the graphical representation of the results of Blood pressure.

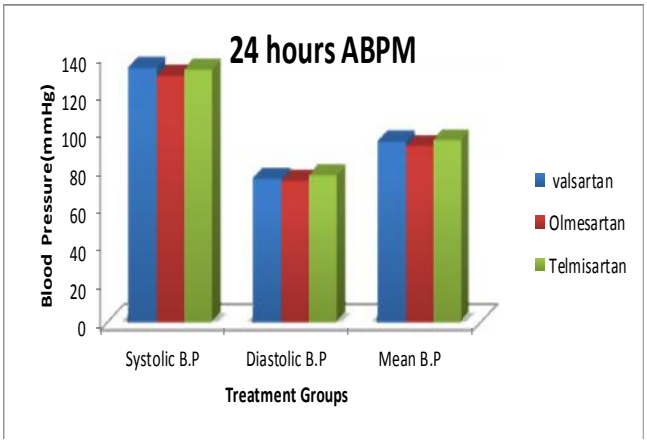

Figure 1: Showing 24 hours ABPM in different Treatment Groups

The recommended target blood pressure level (<130/80 mmHg) was achieved in 8, 9, and 7 cases during valsartan, olmesartan, and telmisartan treatment, respectively. Olmesartan reduced systolic, diastolic, and mean blood pressure by 3.3, 2.7, and 3.1 mmHg more than did telmisartan, respectively; these were statistically significant differences. Similarly, olmesartan significantly reduced diastolic and mean blood pressure during the daytime by 3.2 and 3.1 mmHg, and reduced systolic, diastolic, and mean blood pressure during the nighttime by 5.4, 3.3, and 4.0 mmHg, respectively, more than telmisartan did; these differences between treatments were statistically significant. Table 3 shows the Biochemical Measurements at Baseline, Olmesartan Treatment and Telmisartan Treatment. Figure 4-7 shows the graphical representation of results of biochemical parameters.

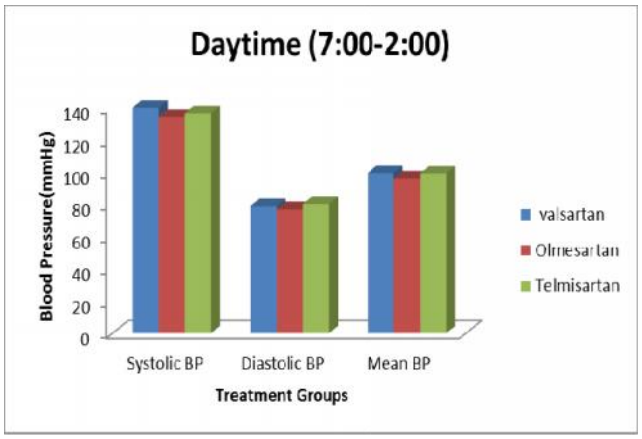

Figure 2: Showing Day Time ABPM In different Treatment Groups

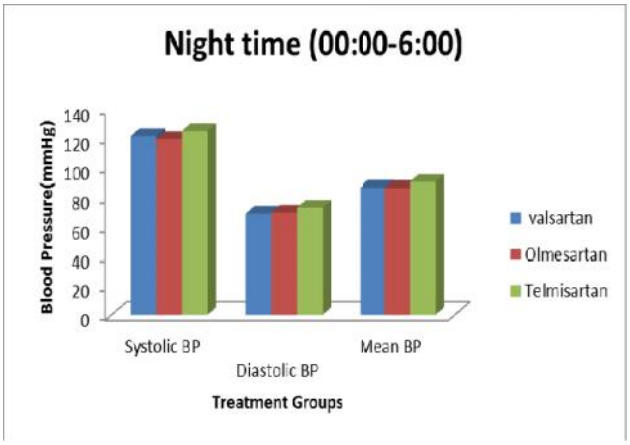

Figure 3: Showing Night Time ABPM In different Treatment Groups

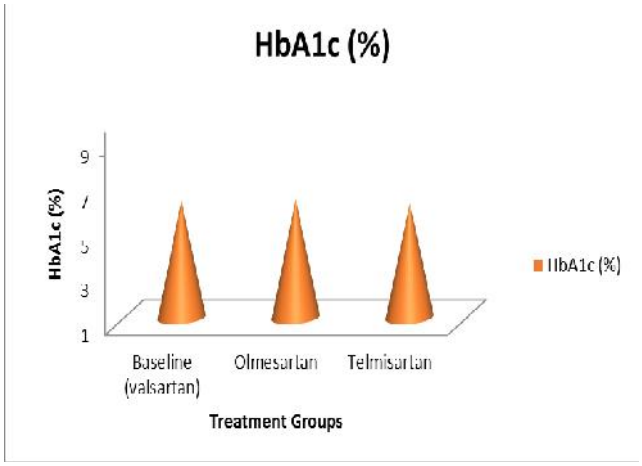

Figure 4: Showing HbA1c (%) in different treatment groups

Table 2: Blood Pressure (mmHg) Recorded by 24-h ABPM during Each Treatment

Variables	Baseline (valsartan)	Olmesartan	Telmisartan	*P* value
24h				
Systolic BP	133.6 ±12.1	129.4 ±15.8	132.7 ±18.3	0.0305
Diastolic BP	75.5 ±6.3	74.6 ±7.4	77.3 ±8.7	0.0087
Mean BP	94.9± 7.7	92.7 9.9	95.8 ±11.6	0.0058
Daytime (7:00-2:00)				
Systolic BP	139.7 ±14.0	134.1 ±17.5	136.3 ±16.7	0.2097
Diastolic BP	78.8 ±6.4	76.9 ±8.5	80.1 ±9.3	0.0215
Mean BP	99.1 ±8.5	95.7 ±11.2	98.8 ±11.4	0,0241
Night time (00:00-6:00)				
Systolic BP	121.4 ±17.9	119.5 ±20.3	124.9 ±21.6	0.0281
Diastolic BP	68.9 ±12.0	69.6 ±9.6	72.9 ±10.0	0.0321
Mean BP	86.4 ±13.5	86.2 ±12.7	90.2 ±13.4	0.0212

P values by ANOVA for differences between data of the Olmesartan and Telmisartan groups

Table 3: Biochemical Measurements at Baseline, Olmesartan Treatment and Telmisartan Treatment

Parameter	Baseline (valsartan)	Olmesartan	Telmisartan	*P* value
HbA1c (%)	6.2 ±0.5	6.3 ±0.5	6.1± 0.3	n.s.
Fasting blood sugar (mmol/L)	7.5 ±2.2	7.6 ±2.6	7.5 ±1.8	n.s.
Insulin (µU/mL)	7.3 ±5.3	10.4 ±1.6	9.0 ±6.8	n.s.
Total cholesterol (mmol/L)	5.2± 0.6	5.2 ±0.8	5.2 ±1.0	n.s.
HDL cholesterol (mmol/L)	1.4 ±0.4	1.4 ±0.3	1.4 ±0.4	n.s.
LDL cholesterol (mmol/L)	3.0 ±0.3	3.0 ±0.7	3.1 ±0.6	n.s.
Triglyceride (mmol/L)	14.7 ±6.6	21.0 ±25.1	17.8 ±18.1	n.s.

P values by ANOVA for differences between data of the olmesartan groups. N.s.-not significant

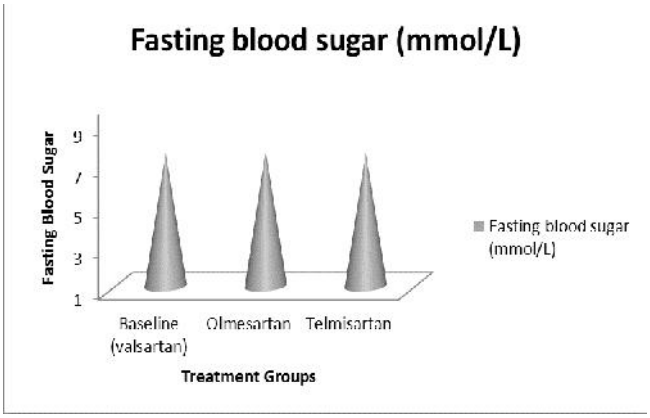

Figure 5: Showing Fasting Blood Sugar (mmol/l) in different treatment groups

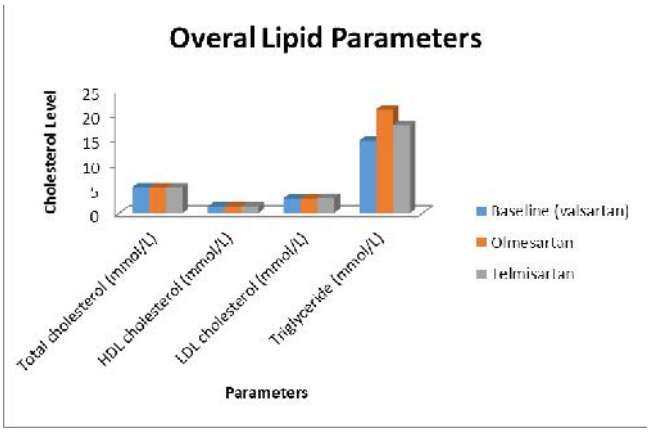

Figure 7: Showing Overall LPP (mmol/l) in different treatment groups

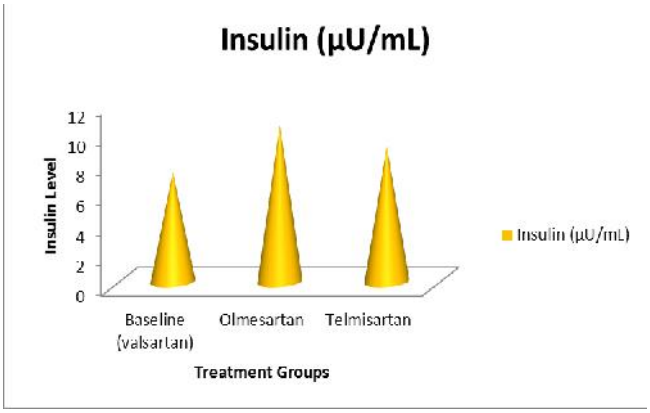

Figure 6: Showing Insulin Level (µU/l) in different treatment groups

The metabolic markers, including HbA1c, and serum adiponectin, were comparable between the two treatments. In total cholesterol level, HDL, LDL level there is no change in different treatment groups. Our data demonstrated that olmesartan at 20 mg/day had more potent blood pressure lowering than telmisartan at 40 mg/day. Although recent data demonstrated that telmisartan has unique PPAR γ modulating activity the metabolic parameters during each treatment were comparable. Blood pressure on a particular day, olmesartan was significantly more effective than telmisartan at reducing systolic, diastolic, and mean blood pressure. Recently, several large trials showed that strict blood pressure control could reduce the onset of cardiovascular disease in patients with type-2

diabetes. For example, a 4 mmHg fall in diastolic blood pressure in the Hypertension Optimal Treatment (HOT) study was equated with a 51% decrease in the onset of cardiovascular disease. Similarly, a 1.92 mmHg decrease in systolic blood pressure in the Heart Out-comes Prevention Evaluation (HOPE) study was equated with a 25% reduction in cardiovascular mortality in type-2 diabetic patients.

Therefore, the fall in arterial pressure recorded in our study was more than a subtle change. In addition, olmesartan therapy reduced mean systolic and diastolic blood pressure to below130/80 mmHg. After adjustment for classic risk factors, the increases in 24-h daytime (8:00–20:00) and night time (0:00–6:00) ambulatory blood pressure were associated with cardiovascular events. While olmesartan and telmisartan are regarded as ARBs with a longer duration of action, olmesartan significantly reduced both daytime and night time mean blood pressure levels compared with telmisartan. These results suggest that the superiority of olmesartan's blood pressure lowering effect might depend on its strength rather than on the duration of its pharmacological action. In addition to their beneficial effects on lowering blood pressure, ARBs have anti-atherogenic effects by blocking angiotensin II, which promotes oxidative stress, inflammation, vasoconstriction, and thrombosis, as well as anti-diabetic effects by regulating insulin sensitivity.

Recent studies suggest that telmisartan, but not other ARBs, could act as a partial PPARγ agonist. Since PPARγ plays an important role in the regulation of insulin sensitivity, at least in part by increasing serum adiponectin level, telmisartan might have a preferable effect on patients with diabetes. In a 3-month study comparing telmisartan 80 mg and losartan 50 mg in hypertensive patients with metabolic syndrome, only telmisartan improved blood glucose level and insulin sensitivity. Here, we compared the effects of olmesartan and telmisartan on various metabolic parameters. However, our results showed no differences in metabolic parameters, including serum adiponectin level, between telmisartan and olmesartan. It is not clear why telmisartan did not change metabolic parameters in our study. We used a starting dose of telmisartan (40 mg/day) for 8 weeks. It is possible that a higher dose and/or longer administration may be required to observe the unique metabolic effect of telmisartan.

4. References

[1] Data from the National Health and Nutrition Examination Survey (NHANES). National Center for Health Statistics. Health, United States, 2013: With Special Feature on Prescription Drugs. Hyattsville, MD: **2014**. Downloaded from http://www.cdc.gov/nchs/data/hus/hus13.pdf#064.

[2] Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. JAMA. **2003**; 289:2560–2572.

[3] James PA, Oparil S, Carter BL, et al. Evidence-based guideline for the management of high blood pressure in adults: Report from the Panel Members Appointed to the Eighth Joint National Committee (JNC 8) JAMA. **2014**; 311:507–520.

[4] White WB, et al. Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension. J Clin Hypertens (Greenwich) **2014**; 16:14–26.

[5] Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension. Eur Heart J. **2013**; 34:2159–2219.

[6] Dasgupta K, Quinn RR, Zarnke KB, et al. The 2014 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. Can J Cardiol. **2014**; 30:485–501.

[7] American Diabetes Association. Standards of medical care in diabetes-2013. Diabetes Care. **2013**; 36(suppl 1):s11–s66.

[8] Sipahi I, Debanne SM, Rowland DY, Simon DI, Fang JC. Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials. Lancet Oncol. **2010**;11:627–36.

[9] Bangalore S, Kumar S, Kjeldsen SE, et al. Antihypertensive drugs and risk of cancer: network meta-analyses and trial sequential analyses of 324,168 participants from randomised trials. Lancet Oncol. **2011**;12:65–82.

[10] Pasternak B, Svanström H, Callréus T, Melbye M, Hviid A. Use of angiotensin receptor blockers and the risk of cancer. Circulation. 201, 123: 1729–36.