



Brief report

Effect of valsartan, an angiotensin II receptor blocker, on markers of oxidation and glycation in Japanese type 2 diabetic subjects: Blood pressure-independent effect of valsartan

Yoshifumi Saisho, Naoko Komiya, Hiroshi Hirose *

Department of Internal Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

Received 8 February 2006; received in revised form 3 April 2006; accepted 12 April 2006

Abstract

Aims: Although it has been reported that angiotensin II receptor blocker inhibited the formation and accumulation of advanced glycation endproducts (AGEs) in vitro and in vivo, whether it can do so clinically is unknown. We therefore examined the effect of valsartan on markers of oxidation and glycation.

Methods: We started 40 mg/day valsartan treatment in 15 type 2 diabetic subjects with hypertension, and metabolic parameters, lipid peroxide, paraoxonase activity, platelet-activating factor acetylhydrolase activity, AGEs and urine 8-isoprostane were measured at baseline and after 3 and 6 months of treatment.

Results: Even after valsartan treatment, the blood pressure level of the patients did not change during the study. However, AGEs and urine 8-isoprostane levels had decreased at 6 months ($p < 0.05$ and < 0.01) as well as urine microalbumin level ($p < 0.01$), although other oxidative stress markers were unchanged.

Conclusion: In this study, low-dose valsartan treatment decreased serum AGEs level, whereas blood pressure level was unchanged. The effect of valsartan on AGEs might be a blood pressure-independent effect in type 2 diabetic subjects.

© 2006 Elsevier Ireland Ltd. All rights reserved.

Keywords: Angiotensin II receptor blocker; Advanced glycation endproducts; Oxidative stress marker; Type 2 diabetes

1. Introduction

Although it is thought that valsartan, an angiotensin II receptor blocker (ARB), has renoprotective effects independently of blood pressure [1], the mechanisms of such effects remain unclear. Advanced glycation endproducts (AGEs) are increased in diabetes and associated with diabetic microangiopathy [2]. Although ARB inhibited the formation and accumulation of AGEs in vitro [3] and in vivo [4–6], whether it can do so

clinically is unknown. We therefore examined the effect of valsartan on markers of oxidation and glycation in type 2 diabetic subjects.

2. Research design and methods

Fifteen type 2 diabetic outpatients with hypertension participated in this study. Informed consent was obtained from each patient. The patients included 13 men and 2 women. The mean age was 63 ± 8 (S.D.) years and the mean duration of diabetes was 8 ± 4 years. Mean BMI was 24.7 ± 4.0 kg/m². Five were being treated with a calcium channel blocker at baseline, but none with an angiotensin converting enzyme inhibitor (ACE-I) or ARB. All patients were treated with oral hypoglycemic agents, but none with insulin.

* Corresponding author. Tel.: +81 3 3353 1211x62383; fax: +81 3 5269 3219.

E-mail address: hhirose@hc.cc.keio.ac.jp (H. Hirose).

Treatment with 40 mg/day of valsartan in the morning was started, and metabolic parameters, lipid peroxide, paraoxonase activity, platelet-activating factor acetylhydrolase activity (PAF-AH), AGEs and urine 8-isoprostane were checked at baseline and 3 and 6 months after initiation of treatment. The blood samples were collected in the morning after an overnight fast. Serum lipid peroxide was measured as thiobarbituric acid reactive substances (TBARS). Serum paraoxonase activity was measured by colorimetric assay, as previously described [7]. Plasma PAF-AH was measured by colorimetric assay (PAF acetylhydrolase assay kit, Cayman, Ann Arbor, MI). Serum AGEs was measured by ELISA as previously described, and intra- and inter-assay CV values of this ELISA system were 4.8–10.2% and 3.5–6.2%, respectively [8]. Urine-8-isoprostane was measured by ELISA (8-isoprostane EIA kit, Cayman). Creatinine clearance (Ccr) was calculated by the Cockcroft-Gault equation.

3. Results

The change in each parameter before to after the treatment is shown in Table 1. Even after valsartan treatment, the blood pressure level of the patients did not change during the study. Body weight and HbA1c level increased during the study, though not significantly. The other medications taken by the patients were not changed during the study. Lipid peroxide, paraoxonase activity and PAF-AH levels were also unchanged after valsartan

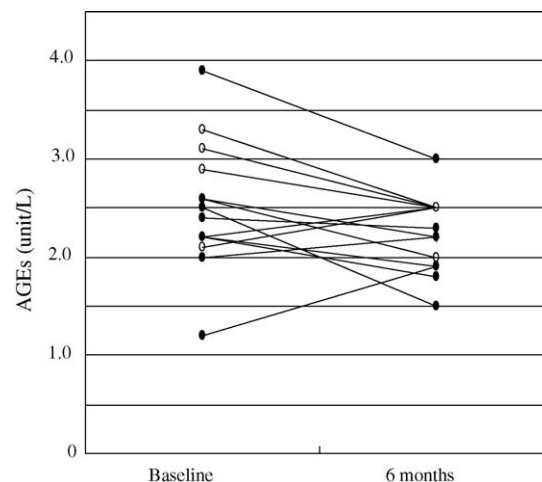


Fig. 1. Serum AGEs level before and after low-dose valsartan treatment in each patient with (closed circles, $n = 8$) or without (open circles, $n = 7$) nephropathy.

Table 1
Changes in parameters before to after low-dose valsartan treatment

	Baseline	3 months	6 months
Body weight (kg)	66.7 \pm 12.1	67.5 \pm 12.3	69.1 \pm 11.1
Systolic blood pressure (mmHg)	149 \pm 19	145 \pm 22	148 \pm 20
Diastolic blood pressure (mmHg)	85 \pm 13	86 \pm 13	85 \pm 11
HbA1c (%)	6.8 \pm 0.7	7.0 \pm 1.1	7.1 \pm 1.1
Lipid peroxide (μ mol/L)	3.0 \pm 0.8	2.7 \pm 0.6	3.0 \pm 0.8
Paraoxonase activity (unit/L)	245 \pm 74	238 \pm 92	232 \pm 76
PAF-AH (μ mol/L/min)	19.3 \pm 5.1	19.5 \pm 4.7	18.1 \pm 6.1
AGEs (unit/L)	2.5 \pm 0.6	2.4 \pm 0.5	2.2 \pm 0.4*
Urine 8-isoprostane (pg/mL)	383 \pm 249	269 \pm 196	204 \pm 136 ⁺
Creatinine (Cr) (mg/dL)	0.9 \pm 0.1	–	0.9 \pm 0.2
Calculated Ccr (mL/min)	84.4 \pm 28.4	–	86.3 \pm 30.0
Urine microalbumin (mg/gCr)	177 \pm 274	–	127 \pm 232 ⁺

Values are the mean \pm S.D.

* $p < 0.05$ vs. baseline (Wilcoxon signed-rank test).

⁺ $p < 0.01$ vs. baseline (Wilcoxon signed-rank test).

treatment. In contrast, the AGEs level gradually decreased, and at 6 months this decrease was significant ($p < 0.05$). The change in AGEs level in each patient is shown in Fig. 1. Urine 8-isoprostane level was significantly decreased at 6 months ($p < 0.01$). Serum creatinine level and calculated Ccr did not change during the study. Urine microalbumin level significantly decreased after 6 months of valsartan treatment ($p < 0.01$). There was no significant correlation of the change in AGEs level with the change in urine microalbumin level or the change in calculated Ccr ($r = 0.335$, $p > 0.3$ and $r = -0.264$, $p > 0.3$, respectively).

4. Discussion

This study showed that low-dose valsartan therapy decreased serum AGEs and urine 8-isoprostane levels as well as urine microalbumin excretion in type 2 diabetic patients, although it did not affect blood pressure. Although the lack of change in blood pressure was unexpected, these findings suggest a kind of blood pressure-independent effect of valsartan therapy.

AGEs result from glycation and oxidation in the Maillard reaction, both in vitro and in vivo, and are increased in diabetic subjects [2,8]. The association of the AGEs with diabetic microangiopathy has been reported and intervention to reduce AGEs is considered an important strategy in treating diabetic nephropathy [9]. Miyata et al. reported that ARB and ACE-I decreased AGEs formation in vitro via radical scavenging and transition metal chelation [3], and it

has been shown that some ARBs reduced renal AGEs accumulation and proteinuria in diabetic rodents in vivo [4–6], as well as that of ACE-I [10]. Although Sebekova et al. reported that treatment with ramipril, an ACE-I, for 2 months significantly decreased fluorescent AGEs level in 12 subjects with nondiabetic nephropathy [11], the effects of ACE-I and ARB on AGEs in diabetic subjects remain unclear. Recently, Odetti et al. reported effects of valsartan on AGEs and oxidative stress markers in type 2 diabetic subjects [12]. They found that 6-month valsartan treatment significantly decreased plasma and urine pentosidine, one of the components of AGEs, while other oxidative stress markers did not change significantly [12]. In our study, valsartan significantly decreased urine 8-isoprostane level as well as AGEs, although other markers did not change during the study. This discrepancy in findings may have been due to differences in glycemic control of the patients. Although the mechanisms of the effect of valsartan on AGEs in vivo are still unclear, the anti-oxidative effect of valsartan might be one of them. Also, when the AGE levels were higher before treatment, they tended to decrease more after 6 months of valsartan treatment in this study. The reason of this phenomenon was not clear. In our study, although the change in AGEs level was not associated with the change in urine microalbumin level or calculated Ccr, a significant positive correlation between renal pentosidine content and proteinuria has been reported in a rat model [4,5]. Further longitudinal studies are needed to clarify whether the lowering of serum AGEs level affects the clinical outcome of diabetic microangiopathy.

In our study, low-dose valsartan treatment did not decrease mean blood pressure. JNC-7 [13] and JSH 2004 [14] both recommended that the target blood pressure in the patients with diabetes should be below 130/80 mmHg. In our study, one of the reasons low-dose valsartan treatment could not decrease mean blood pressure might have been the increase in body weight during treatment, though in diabetic subjects, low-dose valsartan treatment might have been insufficient to achieve the target blood pressure. Now, in accordance with the guidelines, we are increasing the dose of valsartan and/or adding other types of anti-hypertensive drugs.

In conclusion, in this study, low-dose valsartan treatment decreased serum AGEs level in type 2 diabetic subjects, whereas blood pressure level was unchanged. The effect of valsartan on AGEs might be a blood pressure-independent effect in type 2 diabetic subjects.

References

- [1] G. Viberti, N.M. Wheeldon, for the MicroAlbuminuria Reduction with Valsartan (MARVAL) Study Investigators, Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus. A blood pressure-independent effect, *Circulation* 106 (2002) 672–678.
- [2] M. Brownlee, Advanced protein glycosylation in diabetes and aging, *Annu. Rev. Med.* 46 (1995) 223–234.
- [3] T. Miyata, C. van Ypersele de Strihou, Y. Ueda, K. Ichimori, R. Inagi, H. Onogi, et al., Angiotensin II receptor antagonists and angiotensin-converting enzyme inhibitors lower in vitro the formation of advanced glycation end products: Biochemical mechanisms, *J. Am. Soc. Nephrol.* 13 (2002) 2478–2487.
- [4] M. Nangaku, T. Miyata, T. Sada, M. Mizuno, R. Inagi, Y. Ueda, et al., Anti-hypertensive agents inhibit in vivo the formation of advanced glycation end products and improve renal damage in a type 2 diabetic nephropathy rat model, *J. Am. Soc. Nephrol.* 14 (2003) 1212–1222.
- [5] Y. Izuhara, M. Nangaku, R. Inagi, N. Tominaga, T. Aizawa, K. Kurokawa, et al., Renoprotective properties of angiotensin receptor blockers beyond blood pressure lowering, *J. Am. Soc. Nephrol.* 16 (2005) 3631–3641.
- [6] Q. Fan, J. Liao, M. Kobayashi, M. Yamashita, L. Gu, T. Gohda, et al., Candesartan reduced advanced glycation end-products accumulation and diminished nitro-oxidative stress in type 2 diabetic KK/Ta mice, *Nephrol. Dial. Transplant.* 19 (2004) 3012–3020.
- [7] H.W. Eckerson, J. Romson, C. Wyte, B.N. La Du, The human serum paraoxonase polymorphism: identification of phenotypes by their response to salts, *Am. J. Hum. Genet.* 35 (1983) 214–227.
- [8] Y. Ono, S. Aoki, K. Ohnishi, T. Yasuda, K. Kawano, Y. Tsukada, Increased serum levels of advanced glycation end-products and diabetic complication, *Diab. Res. Clin. Pract.* 41 (1998) 131–137.
- [9] G. Jerums, S. Panagiotopoulos, J. Forbes, T. Osicka, M. Cooper, Evolving concepts in advanced glycation, diabetic nephropathy, and diabetic vascular disease, *Arch. Biochem. Biophys.* 419 (2003) 55–62.
- [10] J.M. Forbes, M.E. Cooper, V. Thallas, W.C. Burns, M.C. Thomas, G.C. Brammar, et al., Reduction of the accumulation of advanced glycation end products by ACE inhibition in experimental diabetic nephropathy, *Diabetes* 51 (2002) 3274–3282.
- [11] K. Sebekova, K. Gazdikova, D. Syrova, P. Blazicek, R. Schinzel, A. Heidland, et al., Effects of ramipril in nondiabetic nephropathy: improved parameters of oxidative stress and potential modulation of advanced glycation end products, *J. Hum. Hypertens.* 17 (2003) 265–270.
- [12] P. Odetti, A. Poggi, F. Monacelli, S. Rossi, A. Durante, M. Cirnigliaro, et al., Effects on glycation of valsartan therapy in vivo, *Ann. N.Y. Acad. Sci.* 1043 (2005) 942.
- [13] A.V. Chobanian, G.L. Bakris, H.R. Black, W.C. Cushman, L.A. Green, J.L. Izzo Jr., et al., The National High Blood Pressure Education Program Coordination Committee. The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure, *JAMA* 289 (2003) 2560–2572.
- [14] T. Saruta, The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2004), *Nippon Rinsho* 63 (2005) 945–951 (in Japanese).