Valsartan Decreases Platelet Activity and Arterial Thrombotic Events in Elderly Patients with Hypertension

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Abstract

Background: Angiotensin type 1 receptor (AT1R) antagonists are extensively used for blood pressure control in elderly patients with hypertension. This study aimed to investigate the inhibitory effects of AT1R antagonist valsartan on platelet aggregation and the occurrence of cardio-cerebral thrombotic events in elderly patients with hypertension.

Methods: Two-hundred and ten patients with hypertension and aged > 60 years were randomized to valsartan (n = 140) or amlodipine (n = 70) on admission. The primary endpoint was platelet aggregation rate (PAR) induced by arachidonic acid at discharge, and the secondary endpoint was the rate of thrombotic events including brain infarction and myocardial infarction during follow-up. Human aortic endothelial cells (HAECs) were stimulated by angiotensin II (Ang II, 100 nmol/L) with or without pretreatment of valsartan (100 nmol/L), and relative expression of cyclooxygenase‑2 (COX‑2) and thromboxane B2 (TXB2) and both p38 mitogen-activated protein kinase (p38MAPK) and nuclear factor-kB (NF-kB) activities were assessed. Statistical analyses were performed by GraphPad Prism 5.0 software (GraphPad Software, Inc., California, USA).

Results: PAR was lower after treatment with valsartan (11.49 ± 0.69% vs. 18.71 ± 2.47%, P < 0.001), associated with more reduced plasma levels of COX-2 (76.94 ± 7.07 U/L vs. 116.4 ± 15.89 U/L, P < 0.001) and TXB2 (1667 ± 56.50 pg/ml vs. 2207 ± 180.20 pg/ml) (all P < 0.001). Plasma COX-2 and TXB2 levels correlated significantly with PAR in overall patients (r = 0.109, P < 0.001). During follow-up (median, 18 months), there was a significantly lower thrombotic event rate in patients treated with valsartan (14.3% vs. 32.8%, P = 0.002). Relative expression of COX-2 and secretion of TXB2 with concordant phosphorylation of p38MAPK and NF-kB were increased in HAECs when stimulated by Ang II (100 nmol/L) but were significantly decreased by valsartan pretreatment (100 nmol/L).

Conclusions: AT1R antagonist valsartan decreases platelet activity by attenuating COX-2/TXA2 expression through p38MAPK and NF-kB pathways and reduces the occurrence of cardio-cerebral thrombotic events in elderly patients with hypertension.

Key words: Angiotensin Type 1 Receptor Antagonist; Elderly; Hypertension; Platelet Activity; Thrombosis

INTRODUCTION

A large body of evidence has demonstrated that activation of renin-angiotensin system (RAS) plays a key role in the development and progression of hypertension and cardiovascular disease.[1] Angiotensin II (Ang II), the major effector of RAS,[2] exerts its biological effects mainly through specific receptors, namely angiotensin type 1 receptor (AT1R) and type 2 receptor.[3] Since AT1R antagonists have been shown to improve endothelial function and vascular remodeling in addition to their predominant vasodilatation effects,[4,5] these agents are extensively used for blood pressure control in elderly patients with hypertension.[6] Activation of platelets bears the brunt of complicate cascades of thrombogenesis. Among the physiological activators of platelet, thromboxane A2 (TXA2) is the primary one which is converted from arachidonic acid in the platelets and catalyzed by cyclooxygenase (COX).[7-9] TXA2 is regulated by two isoforms of COX. COX-1 is usually found in the physical condition, whereas COX-2 is induced by lipopolysaccharide and some cytokines.[10-12] Clinical studies have demonstrated a close relationship between plasma levels of TXA2 or COX-2 and platelet activities.[13] AT1R antagonists are known to exhibit potent anti-platelet properties which may differ from other anti-platelet agents.[14] However, the impact of these agents on arterial thrombotic events in elderly patients with hypertension remains largely unclear.

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In this randomized trial, we assessed the effect of valsartan—an AT1, R antagonist on platelet aggregation rate (PAR) and the occurrence of cardio-cerebral thrombotic events including brain and myocardial infarction in hypertensive patients aged >60 years. To further elucidate the potential mechanisms of its anti-platelet property, relative expression of COX-2 and TXB, p38 mitogen-activated protein kinase (p38MAPK) and nuclear factor-kB (NF-kB) activities in human aortic endothelial cells (HAECs) stimulated by Ang II with or without pretreatment of valsartan were also determined.

**Methods**

**Study population**

Two hundred and thirty-six consecutive elderly (>60 years in age) patients with hypertension who were admitted to the Department of Geriatrics, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine between April 2011 and August 2013 were screened. Hypertension was diagnosed as systolic blood pressure ≥140 mmHg and/or diastolic pressure ≥90 mmHg before recruitment. For the purpose of research, patients with acute or chronic infection, hepatic or at least moderate renal insufficiency (estimated glomerular filtration rate [eGFR] <60 ml·min⁻¹·1.73 m⁻²) (n = 17), trauma or surgery within 2 months (n = 2), and other blood diseases (e.g. hemophilia, and leukemia, aplastic anemia) (n = 5) were excluded. We also excluded patients with resistant hypertension (n = 2). The remaining 210 eligible elderly hypertensive patients (191 men and 19 women, mean age 79.2 ± 1.0 years) were randomized to valsartan (Beijing Novartis Pharma Ltd., China) (AT1R group; n = 140) or amlodipine (Beijing Novartis Pharma Ltd.) (non-AT1R group; n = 70) in a 2:1 ratio [Figure 1] by random group design. For each group, the initial dose of valsartan (80 mg, once daily) or amlodipine (5 mg, once daily) was titrated to achieve target blood pressure (<140/90 mmHg for patients under 80 years and <150/90 mmHg for those older than 80 years). A small dose of diuretics like hydrochlorothiazide (Shanghai Xinyi Pharma Ltd., China) (12.5–25 mg, once daily) may be added if maximum daily dose of valsartan (160 mg) or amlodipine (10 mg) was insufficient for optimal blood pressure control. Other medications including β-blockers, anti-platelet agents, and statins were prescribed at the discretion of the physicians.

The study protocol was approved by the Ethics Review Committees of Shanghai Jiao Tong University and Ruijin Hospital, and informed consent was given by each subject.

**Biochemical investigation**

Platelets aggregation in platelet-rich plasma was tested at discharge among the patients. Light transmission aggregometry through Chrono-Log platelet aggregometer (Chrono-Log Corp., USA) induced by 0.5 μmol/L arachidonic acid described previously.[15] Plasma levels of COX-2 (My Biosource, USA) and TXA2 (Enzo Life Sciences, USA) were determined by ELISA. TXA2 were represented by its metabolite TXB2, because it is unstable in common condition.

**Follow-up**

All patients were followed-up in a special outpatient clinic or by telephone conversation with patients or their relatives every 3 months after discharge. The occurrence of arterial thrombotic events, including brain and myocardial infarctions were recorded. Brain infarction was defined by neurologic examination, head magnetic resonance imaging and/or computed tomography. Myocardial infarction was defined by the presence of typical chest pain, electrocardiographic ST-segment elevation with or without Q waves, and serum cardiac enzyme elevations at least twice the upper limit of the normal range. In order to guarantee rigorous data quality, all thrombotic events were reviewed by two experienced interventional cardiologists.

**Cell culture**

Human aortic endothelial cells were cultured in Dulbecco’s Modified Eagle’s Medium (Life Technologies Corporation, USA) supplemented with 10% v/v fetal bovine serum (Life Technologies Corporation) and 1% penicillin-streptomycin (Life Technologies Corporation), and incubated at 37°C in humidified atmosphere containing 5% CO2. Valsartan (Melonepharina, China), SB203580 (Beyotime, China), JSH-23 (Beyotime) and NS-398 (Sigma, USA) were preadded into the medium 30 min before Ang II treatment.

**Real-time polymerase chain reaction**

Total RNA prepared with RNAprep Pure Cell/Bacteria Kit (Tiangen biotech, China) was reverse transcribed to cDNA using SuperScript™ Preamplification system (TaKaRa Biotech, China). Prime used in the reaction were as follows: COX-2: 5’-CCCACCCCATGTGCAAACCGA-3’ (forward), 5’-CCGGGTACAATCGCACCCTTACT-3’ (reverse); GAPDH: 5’-ATGGGGAAGGTGAAGGTCG-3’ (forward), 5’-GGGTCAT-TGATGGCAACAATA-3’ (reverse). Real time-polymerase chain reaction (7900 HT by Applied Biosystems, USA) was performed using SYBR Green.
Master Mix (Roche, Switzerland) with the following conditions: 94°C for 5 min, followed by 40 cycles at 94°C for 30 s and 60°C for 30 s. The relative gene expression between treatment and control was calculated using the 2^−ΔΔCt method with GAPDH as the reference gene.

**Western blotting assay**
Protein was extracted with RIPA lysis buffer (Beyotime, China), separated with 10% SDS-PAGE gel, and transferred onto nitrocellulose membrane. After blocking with 5% nonfat milk in TBST (tris-buffered saline, Tween 20), the membrane was probed with diluted primary antibodies at 4°C overnight. The membrane was washed 10 min for three times by TBST and then incubated with horseradish peroxidase-conjugated secondary antibody for 2 h at room temperature, washed three times again, and exposed by enhanced chemiluminescence. All antibodies were purchased from Cell Signaling Technology (USA).

**Statistical analysis**
The primary endpoint was PAR induced by arachidonic acid at discharge, and the secondary endpoint was the rate of thrombotic events including brain infarction and myocardial infarction during follow-up. All statistical analyses were performed by GraphPad Prism 5.0 software (GraphPad Software, Inc., California, USA). Student’s t-test or one-way analysis of variance (ANOVA) was used for comparison of quantitative data between different groups. Chi-square test was used for comparing qualitative data. Data are expressed as mean ± standard deviation (SD) or frequency. A two-sided \( P < 0.05 \) was considered to be statistically significant.

**Results**

**Baseline characteristics**
Both AT_R and non-AT_R groups were well-matched with respect to age, sex, risk factors for coronary artery disease, blood pressure control, hepatic and renal function, and nonantihypertensive medications including \( \beta \)-blockers, anti-platelet agents, and statins [Table 1].

**Platelets activity and plasma levels of cyclooxygenase-2 and thromboxane B2**
Arachidonic acid-induced PAR and plasma levels of COX-2 and TXB\(_2\) were significantly lower in the AT_R group than in the non-AT_R group (for all such comparisons, \( P < 0.001 \)) [Table 2]. PAR correlated significantly with COX-2 (\( r = 0.109, P < 0.001 \)) and TXB\(_2\) (\( r = 0.070, P < 0.001 \)), and COX-2 was closely related to TXB\(_2\) (\( r = 0.251, P < 0.001 \)).

**Thrombotic events**
During follow-up (median 18 months), 9 patients in the AT_R group and 11 in the non-AT_R group developed brain infarction (\( P = 0.031 \)), and 11 patients in the AT_R group and 12 in the non-AT_R group experienced myocardial infarction (\( P = 0.042 \)). This resulted in a significantly lower overall arterial thrombotic event rate in the AT_R group compared with that in the non-AT_R group (\( P = 0.002 \)) [Table 3].

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**Table 1: Baseline characteristics of elderly hypertensive patients**

| Variables                                | AT_R group (n = 140) | Non-AT_R group (n = 70) | \( P \) |
|-------------------------------------------|----------------------|-------------------------|--------|
| Gender (male/female)                      | 128/12               | 63/7                    | 0.734  |
| Age (years)                               | 78.59 ± 0.82         | 79.83 ± 1.17            | 0.964  |
| Diabetes mellitus (n, %)                  | 49 (35.0)            | 26 (37.1)               | 0.760  |
| Coronary artery disease (n, %)            | 50 (35.7)            | 26 (37.1)               | 0.839  |
| Transient ischemic attack (n, %)          | 38 (27.1)            | 22 (31.4)               | 0.420  |
| Systolic blood pressure (mmHg)            | 130.70 ± 1.33        | 127.50 ± 1.94           | 0.617  |
| Diastolic blood pressure (mmHg)           | 74.45 ± 0.55         | 73.23 ± 1.12            | 0.345  |
| White blood cell (×10^6/L)                | 5.97 ± 0.15          | 6.13 ± 0.21             | 0.616  |
| Platelets (×10^9/L)                       | 196.40 ± 3.53        | 203.60 ± 6.85           | 0.606  |
| Alkaline phosphatase (IU/L)               | 22.68 ± 0.92         | 23.53 ± 2.02            | 0.927  |
| Aspartate aminotransferase (IU/L)         | 23.57 ± 0.73         | 24.86 ± 1.61            | 0.525  |
| Uric acid (µmol/L)                        | 56.83 ± 1.74         | 56.28 ± 1.85            | 0.608  |
| Creatinine (µmol/L)                       | 88.53 ± 1.95         | 87.78 ± 3.61            | 0.198  |
| Uric acid (µmol/L)                        | 384.60 ± 23.41       | 346.10 ± 10.65          | 0.189  |
| Glucose (mmol/L)                          | 4.13 ± 0.09          | 4.18 ± 0.13             | 0.740  |
| Cholesterol (mmol/L)                      | 1.31 ± 0.03          | 1.20 ± 0.04             | 0.260  |
| Low-density lipoprotein (mmol/L)          | 2.37 ± 0.07          | 2.52 ± 0.11             | 0.159  |
| Fasting blood-glucose (mmol/L)            | 5.18 ± 0.09          | 5.37 ± 0.17             | 0.122  |
| \( \beta \)-blockers (%)                 | 16 (11.4)            | 9 (12.9)                | 0.763  |
| Anti-platelet (n, %)                      | 130 (92.9)           | 67 (95.7)               | 0.418  |
| Statins (n, %)                            | 56 (40.0)            | 30 (42.9)               | 0.691  |

Data are shown as mean ± SD or frequency (%). AT_R: Angiotensin type 1 receptor; SD: Standard deviation.

**Table 2: Platelet aggregation rate and plasma level of COX-2 and TXB\(_2\)**

| Variables                                   | AT_R group (n = 140) | Non-AT_R group (n = 70) | \( P \) |
|---------------------------------------------|----------------------|-------------------------|--------|
| Platelet aggregation rate (%)               | 11.49 ± 0.69         | 18.71 ± 2.47            | <0.001 |
| COX-2 (U/L)                                 | 75.94 ± 7.07         | 116.4 ± 15.89           | <0.001 |
| TXB\(_2\) (pg/ml)                           | 1667 ± 56.50         | 2207 ± 180.20           | <0.001 |

Data are shown as mean ± SD. SD: Standard deviation; AT_R: Angiotensin type 1 receptor; COX-2: Cyclooxygenase-2; TXB\(_2\): Thromboxane B\(_2\).

**Angiotsensin II up-regulated expression of cyclooxygenase-2 via phosphorylation of p38 mitogen-activated protein kinase and nuclear factor-kb in human aortic endothelial cells**
The expression of COX-2 mRNA in HCACEs was dose-and time-dependently increased after stimulation with Ang II, with maximum expression (4 times higher than control, \( P < 0.001 \)) 1 h after stimulation with Ang II (100 nmol/L) [Figure 2a and 2b]. At protein level, the peak expression of COX-2 occurred 2 hours after Ang II stimulation (100 nmol/L) [Figure 2c]. Ang II also increased the phosphorylation of p38MAPK (p-p38MAPK) and NF-kB (p-NF-kB) [Figure 2d]; when pretreating HAECS
with p38MAPK inhibitor SB203580 (25 μmol/L) and NF-kB inhibitor JSH-23 (25 μmol/L), the expression of COX-2 was significantly decreased at both mRNA and protein levels [Figure 2e and f].

Cyclooxygenase-2 inhibitor suppressed angiotensin II-induced secretion of thromboxane B2 in human aortic endothelial cells

Ang II (100 nmol/L) led to a rapid increased secretion of TXB2 in HAECS with peak secretion of 122.09 pg/ml at 3 h after its stimulation (4.47 times compared with 0 h, \(P < 0.001\)) [Figure 3a] and this effect could be suppressed by COX-2 specific inhibitor NS-398 (\(P < 0.001\)) [Figure 3b].

**Table 3: Comparison of thrombotic event rate during follow-up (\(n(\%)\))**

| Variables              | AT1R group (\(n = 140\)) | Non-AT1R group (\(n = 70\)) | P    |
|------------------------|----------------------------|-----------------------------|------|
| Brain infarction       | 9 (6.43)                   | 11 (15.71)                  | 0.031|
| Myocardial infarction  | 11 (7.86)                  | 12 (17.14)                  | 0.042|
| Overall thrombotic     | 20 (14.3)                  | 23 (32.8)                   | 0.002|
| events \(\times\) 1000 |                           |                            |      |

AT1R: Angiotensin type 1 receptor.

**Valsartan decreased phosphorylation of p38 mitogen-activated protein kinase and nuclear factor-kB, as well as expression of cyclooxygenase-2 induced by angiotensin II in human aortic endothelial cells**

After pretreatment with valsartan (100 nmol/L), HAECS were stimulated with Ang II (100 nmol/L) for 10 min to detect the p-p38MAPK and p-NF-kB, 1 h to detect COX-2 mRNA and 3 h to detect COX-2 protein. Valsartan (100 nmol/L) significantly inhibited Ang II-induced COX-2 mRNA and protein expression (\(P < 0.001\)) [Figure 4a and 4b], with parallel decrease in p-p38MAPK and p-NF-kB [Figure 4c].

**DISCUSSION**

This randomized trial demonstrates that AT1R antagonist valsartan reduces cardio-cerebral thrombotic events in
we found that Ang II up-regulates the expression of COX-2 in human endothelial cells, which subsequently catalyzes arachidonic acid into prostaglandin and leads to an increased level of TXA₂. These observations suggest that AT₉ R antagonists may retard the process of thrombus formation by inhibiting platelet aggregation.

Our in vitro study indicates that the effect of Ang II on the expression of COX-2 was at least partially through the modulation of p38MAPK and NF-kB pathways. The activity of transcription factor NF-kB is a hallmark of cellular inflammation response and has already been demonstrated in the expression of VCAM-1 regulated by ROS induced by Ang II. However, the role of classic G protein, receptor tyrosine kinases (EGFR, platelet-derived growth factor and insulin receptor), NADPH oxidases and serine/threonine kinases such as PKC and MAPKs (JNK and p42/44MAPK) in the action of Ang II need further studies.

We recognized several limitations in the present study. First, the number of patients in this study had insufficient power to detect the difference in terms of clinical outcome, thus further prospective studies with larger sample size are needed to confirm the beneficial effects of AT₁ R antagonists in the antithrombotic treatment of elderly hypertensive patients. Second, we could not completely eliminate the effect of other factors on the platelets activity, such as coronary artery disease and diabetes, which are common co-morbidities in these patients.

References

1. Marchesi C, Paradis P, Schiffrin EL. Role of the renin-angiotensin system in vascular inflammation. Trends Pharmacol Sci 2008;29:367-74.
2. Tocci G, Castello L, Volpe M. A review of angiotensin receptor blocker-based therapies at all levels of cardiovascular risk. Eur Cardiol Rev 2011;7:254-56.
3. Pellegrin M, Mazzolai L. Angiotensin ii as an inducer of atherosclerosis: Evidence from mouse studies. J Clin Exp Cardiol 2013;5:1.".
4. Schiffrin EL, Park JB, Intengan HD, Touyz RM. Correction of arterial structure and endothelial dysfunction in human essential hypertension by the angiotensin receptor antagonist losartan. Circulation 2000;101:1653-9.
5. Duprez DA. Role of the renin-angiotensin-aldosterone system in vascular remodeling and inflammation: A clinical review. J Hypertens 2006;24:983-91.
6. Balkrishnan R, Phatak H, Gleim G, Karve S. Assessment of the use of angiotensin receptor blockers in major European markets among paediatric population for treating essential hypertension. J Hum Hypertens 2009;23:420-5.
7. Jacob S, Laury-Kleintop L, Lanza-Jacoby S. The select cyclooxygenase-2 inhibitor celecoxib reduced the extent of atherosclerosis in apo E-/- mice. J Surg Res 2008;146:135-42.
8. Cipollone F, Fazia ML. COX-2 and atherosclerosis. J Cardiovasc Pharmacol 2006;47 Suppl 1:S26-36.
9. Davi G, Patrono C. Platelet activation and atherothrombosis. N Engl J Med 2007;357:2482-94.
10. Li YB, Han JY, Jiang W, Wang J. Selenium inhibits high glucose-induced cyclooxygenase-2 and P-selectin expression in vascular endothelial cells. Mol Biol Rep 2011;38:2301-6.
11. Briones AM, Salaices M, Vila E. Ageing alters the production of
nitric oxide and prostanoids after IL-1 beta exposure in mesenteric resistance arteries. Mech Ageing Dev 2005;126:710-21.

12. Caughey GE, Cleland LG, Penglis PS, Gamble JR, James MJ. Roles of cyclooxygenase (COX)-1 and COX-2 in prostanoid production by human endothelial cells: Selective up-regulation of prostacyclin synthesis by COX-2. J Immunol 2001;167:2831-8.

13. Vane JR, Bakhle YS, Botting RM. Cyclooxygenases 1 and 2. Annu Rev Pharmacol Toxicol 1998;38:97-120.

14. Chrysant SG, Chrysant GS. The pleiotropic effects of angiotensin receptor blockers. J Clin Hypertens (Greenwich) 2006;8:261-8.

15. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206-52.

16. Gasparyan AY, Ayvazyan L, Mikhailidis DP, Kitas GD. Mean platelet volume: A link between thrombosis and inflammation? Curr Pharm Des 2011;17:47-58.

17. Xu ZH, Jiao JR, Yang R, Luo BY, Wang XF, Wu F. Aspirin resistance: Clinical significance and genetic polymorphism. J Int Med Res 2012;40:282-92.

18. Wing LM, Reid CM, Ryan P, Beilin LJ, Brown MA, Jennings GL, et al. A comparison of outcomes with angiotensin-converting – enzyme inhibitors and diuretics for hypertension in the elderly. N Engl J Med 2003;348:583-92.

19. Wang T, Yin KS, Liu KY, Lu GJ, Li YH, Chen JD. Effect of valsartan on the expression of angiotensin II receptors in the lung of chronic antigen exposure rats. Chin Med J 2008;121:2312-9.

20. Touyz RM, Schiffrin EL. Effects of angiotensin II and endothelin-1 on platelet aggregation and cytosolic pH and free Ca2+ concentrations in essential hypertension. Hypertension 1993;22:853-62.

21. Senchenkova EY, Russell J, Almeida-Paula LD, Harding JW, Granger DN. Angiotensin II-mediated microvascular thrombosis. Hypertension 2010;56:1089-95.

22. Beltrán AE, Briones AM, García-Redondo AB, Rodríguez C, Miguel M, Alvarez Y, et al. p38 MAPK contributes to angiotensin II-induced COX-2 expression in aortic fibroblasts from normotensive and hypertensive rats. J Hypertens 2009;27:142-54.

23. Xu YM, Sharma D, Li GP, Zhao YN. Effect of angiotensin II type 1 receptor antagonist, losartan on inflammatory factor in atherosclerotic rabbits. Res Cardiovasc Med 2013;1:128-31.

24. Wu KK. Differential cyclooxygenase-2 transcriptional control in proliferating versus quiescent fibroblasts. Prostaglandins Other Lipid Mediat 2007;83:175-81.

25. Mehta PK, Griendling KK. Angiotensin II cell signaling: Physiological and pathological effects in the cardiovascular system. Am J Physiol Cell Physiol 2007;292:C82-97.

26. Shang J, Yang YY, Guo XL, Liu HG. Ang II type 1 receptor expression in rat aorta exposed to chronic intermittent hypoxia: Effects of p38MAPK and ERK1/2 signaling. Chin Med J 2013;126:3264-9.

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