Short-Term Administration of an Angiotensin II Receptor Blocker in Patients with Long-Term Hemodialysis Patients Improves Insulin Resistance

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Background: *Insulin resistance is commonly observed in uremic patients. Angiotensin II receptor blockers (ARB) are reported to act as insulin sensitizers in the animal model of hypertension and hypertensive patients. The authors investigated the effects of valsartan on insulin resistance and glucose metabolism in patients with long-term hemodialysis in the prospective, randomized controlled study.*

Material and Method: *Thirty-three hemodialysis patients were randomized into two treatment groups, valsartan 80 to 320 mg/day (n = 18) or non-renin-angiotensin-aldosterone-system blocking antihypertensive agents (control, n = 15), treated for 12 weeks. Insulin resistance determined by homeostasis model assessment (HOMA-IR), fasting plasma glucose (FPG), fasting plasma insulin, and blood pressure monitoring were measured during the study.*

Results: *At baseline, metabolic profiles did not significantly differ between the treatment and the control groups. After 12 weeks of treatment, the valsartan group significantly improved HOMA-IR from 2.6±0.9 to 2.3±0.7 (p = 0.041) and significantly decreased FPG from 90.1±15.1 to 84.8±13.2 mg/dL (p = 0.008). In contrast, the control group was not associated with any significant changes in HOMA-IR, FPG, and fasting insulin levels. At the end of 12-week treatment, HOMA-IR, FPG, and fasting insulin levels were not significantly different between the two groups.*

Conclusion: *These results indicate that the antihypertensive action of valsartan improves glucose metabolism by improving the peripheral insulin sensitivity in subjects with long-term dialysis.*

Keywords: *Insulin resistance, Glucose metabolism, Hemodialysis, Angiotensin II Receptor Blockers*

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Advanced-stage chronic kidney disease (CKD) can show abnormal glucose tolerance, suggesting that the uremic state alters glucose homeostasis[1]. Insulin resistance occurs commonly in end-stage renal disease (ESRD) and insulin resistance is an independent predictor of cardiovascular morbidity and mortality in a cohort of patients on dialysis[2,3]. Impaired insulin sensitivity in patients with ESRD after long-term dialysis was still higher than that of patients without dialysis[4]. Insulin resistance is thought to be one of the risk factors in dialysis patients that may contribute to the development of cardiovascular disease[5,6]. Improving insulin resistance in hemodialysis patients might therefore reduce the high morbidity and mortality rates from cardiovascular events[7].

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The agents most often used for hypertension include angiotensin receptor blockers (ARB) and angiotensin converting enzyme (ACE) inhibitors, which are both considered to improve glucose metabolism[8]. In addition, several clinical trials showed that ACE inhibitors and ARB suppressed the new onset of type 2 diabetes[9,10]. Angiotensin II is a potent vasoconstrictor and can contribute to the pathogenesis of hypertension and possibly the development of insulin resistance[11]. Angiotensin II receptor activation impaired insulin signaling in skeletal muscle with a consequent reduction in glucose uptake. Therefore, treatment with inhibition of the cellular actions of angiotensin II might increase insulin sensitivity in the setting of increased renin-angiotensin-aldosterone system (RAAS) activation and abnormal glucose metabolism especially hemodialysis patients. However, limited studies of ARBs on insulin resistance had been conducted among patients with dialysis[12,13]. The authors therefore tested the effect of a short-term 12-week ARB treatment on insulin

sensitivity and glucose disposal markers in subjects with hemodialysis.

Material and Method

Study population

This was a 12-week randomized controlled study conducted in patients undergoing maintenance hemodialysis three times weekly at the dialysis unit, Phramongkutklao Hospital, Bangkok, Thailand. The present study was approved by the Institutional Review Boards of the Phramongkutklao Hospital and College of Medicine. Treatment protocol patients were randomized by a method of block randomization by a research pharmacist. A computer generated randomization procedure in blocks of four was used. Inclusion criteria into the study were age 18 years or older, treatment with hemodialysis for at least three months, and a single pool Kt/Vurea of 1.2 or greater per dialysis treatment. No treatment was given with anti-glycemic agents or RAAS inhibitors within three months before starting the study. Exclusion criteria included diabetes mellitus, active malignancy, severe heart, lung or liver diseases, stroke, chronic infection (e.g., tuberculosis) within one year of starting the study, and any immunological or inflammatory disorders. Signed informed consents were obtained from all subjects after a thorough discussion of the protocol, its rationale, and potential risks.

Intervention

Subjects who met the entrance criteria were enrolled in this randomized control trial study and were randomly assigned to one of two interventional groups: a treatment group that received valsartan 80 to 320 mg orally daily for control predialytic blood pressure less than 140/90 mmHg and a control group that received other non-RAAS antihypertensive medications. Both treatments were given for 12 weeks. A complete medical history and physical examination were performed on all subjects. Adherence was monitored by pill counting during each visit.

Laboratory investigation

Complete blood counts and comprehensive serum chemistries were measured at baseline and during treatment at weeks 4, 8, and 12. All subjects were fasted for at least 12 hours overnight before all blood drawing. Blood samples were collected mid-week after two-day interdialytic interval before dialysis treatment. Fasting plasma glucose level was measured by the glucose oxidase method[14]. Fasting plasma insulin levels was analyzed by electrochemiluminescence immunoassay (Roche Elecsys 2010, USA)[15]. The serum obtained at baseline and at the 12-week interval was measured in each subject for glucose and insulin concentrations in the same assay to eliminate the effects of inter-assay variation. Insulin resistance was quantified using the validated model of homeostasis model assessment insulin resistance (HOMA-IR), and these indices correlated well with insulin sensitivity as determined by the hyperinsulinemic euglycemic clamp[16]. HOMA-IR was calculated using the following formula: HOMA-IR = [fasting plasma insulin (μU/mL) x fasting plasma glucose (mmol/L)] ÷22.5.

Statistical analysis

Data are given as means ± SD for continuous variables or as a percentage in categorical variables. Normal data distribution was confirmed by the Kolmogorov-Smirnov test. Data were analyzed using the Student's t test and Fisher's exact test for comparisons at baseline and after treatment with ARB. Within group, changes were evaluated using paired t-tests. All statistical analyses were performed using SPSS version 16.0 for Windows.

Results

Characteristics of subjects with ESRD

Thirty-three subjects were enrolled and randomized into the two treatment arms. Causes of kidney failure in these subjects were chronic glomerulonephritis (n = 11), nephropathy of unknown origin (n = 9), hypertensive nephropathy (n = 9), chronic tubulointerstitial nephritis (n = 2), and polycystic kidney disease (n = 2). Baseline characteristics are shown in Table 1. No significant difference was found in age, gender, time on dialysis, body weight, blood pressure, primary renal disease, and co-morbid diseases. The medications prescribed before the present study to all patients in both groups did not differ significantly, except alpha-blocker usage appeared to be significantly greater in the valsartan group (44.4% vs. 6.7%, p = 0.021). The baseline laboratory data of the treatment and control groups including glucose metabolism profiles were not different as shown in Table 2. During study in the treatment group, the average dose of valsartan was 136 mg/day and only one patient received valsartan 320 mg/day.

Table 1. Baseline characteristics of the study population

Variables	Valsartan (n = 18)	Control (n = 15)	*p*-value
Male (n, %)	9 (50.0%)	11 (73.3%)	0.284
Age	52.94±14.63	57.07±10.03	0.363
Time on dialysis (months)	6.67±5.53	6.40±4.87	0.885
Body weight	57.59±10.15	60.80±12.65	0.425
Systolic blood pressure (mmHg)	149.44±17.98	143.33±16.33	0.319
Diastolic blood pressure (mmHg)	80.83±8.79	81.33±8.34	0.869
Co-morbid diseases (n, %)			
Hypertension	17 (94.4%)	12 (80.0%)	0.308
Dyslipidemia	10 (55.6%)	5 (33.3%)	0.296
Cerebrovascular disease	-	1 (6.7%)	0.455
Cardiovascular disease	1 (5.6%)	2 (13.3%)	0.579
Gout	3 (16.7%)	4 (26.7%)	0.674
Previous medications (n, %)			
Diuretic	3 (16.7%)	4 (26.7%)	0.674
ACEI/ARB	4 (22.2%)	-	0.108
Calcium channel blocker	17 (94.4%)	13 (86.7%)	0.579
Beta-blocker	11 (61.1%)	4 (26.7%)	0.080
Alpha-blocker	8 (44.4%)	1 (6.7%)	0.021*
Vasodilator	4 (22.2%)	3 (20.0%)	1.000
Statin	11 (61.1%)	6 (40.0%)	0.303
Fibrate	1 (5.6%)	-	1.000

ACEI/ARB = angiotensin converting enzyme inhibitor/angiotensin receptor blockers

Table 2. Baseline laboratory data of the study population

Variables	Valsartan (n = 18)	Control (n = 15)	*p*-value
BUN (mg/dL)	54.0±15.8	67.1±21.2	0.052
Creatinine (mg/dL)	10.1±2.2	11.7±3.5	0.117
spKt/V	1.88±0.27	1.82±0.22	0.464
URR (%)	75.41±17.23	71.36±19.13	0.482
Sodium (mEq/L)	139.5±2.1	137.1±3.2	0.013
Potassium (mEq/L)	4.9±0.7	4.5±0.5	0.083
Bicarbonate (mEq/L)	24.9±3.9	24.1±2.3	0.452
Calcium (mg/dL)	9.5±0.5	8.2±1.0	0.455
Phosphorus (mg/dL)	4.9±1.4	5.1±1.4	0.729
Cholesterol (mg/dL)	163.5±32.0	169.1±43.0	0.673
Triglycerides (mg/dL)	96.9±40.9	106.5±37.4	0.491
HDL (mg/dL)	49.1±12.7	52.3±15.6	0.516
LDL (mg/dL)	95.1±24.6	94.3±29.1	0.939
Albumin (g/dL)	4.2±0.3	4.5±0.6	0.511
Hematocrit (%)	33.4±3.7	36.0±5.2	0.106
Intact-PTH (ng/L)	423.1±348.6	359.2±254.7	0.559
FPG (mg/dL)	90.1±15.1	92.8±7.9	0.598
Fasting plasma insulin (μU/mL)	11.5±4.3	9.6±3.0	0.211
HOMA-IR	2.6±0.9	2.3±0.8	0.447

BUN = blood urea nitrogen; spKt/V = single pool Kt/V; URR = urea reduction ratio; LDL = low-density lipoprotein; HDL = high-density lipoprotein; PTH = parathyroid hormone; FPG = fasting plasma glucose; HOMA-IR = homeostasis model assessment-insulin resistance

* Indicates significant difference ($p<0.05$)

Table 3. Changes in blood pressure and biochemical outcomes after 12 weeks

Variables	Valsartan				Control				Δ between group	*p*-value
	Baseline	Week 12	Δ change	*p*-value	Baseline	Week 12	Δ change	*p*-value		
SBP (mmHg)	149.4±18.0	135.6±14.6	-13.9±10.4	<0.001[c]	143.3±16.3	139.3±21.9	-4.0±9.1	0.111	-9.9 (-16.9, -2.9)	0.007[a]
DBP (mmHg)	80.8±8.8	76.1±8.5	-4.7±7.4	0.015[b]	81.3±8.3	80.7±10.3	-0.7±7.0	0.719	-4.1 (-9.2, 1.1)	0.118
BUN (mg/dL)	54.0±15.8	58.4±15.4	5.2±14.5	0.260	67.1±21.2	65.0±17.2	-2.1±20.4	0.692	7.3 (-7.5, 22.2)	0.318
Creatinine (mg/dL)	10.1±2.2	10.1±2.4	0.3±1.6	0.544	11.7±3.5	11.5±3.6	-0.2±1.7	0.734	0.5 (-0.9, 1.8)	0.495
Sodium (mEq/L)	139.5±2.1	140.0±3.6	0.9±4.3	0.498	137.0±3.2	137.7±2.6	0.7±3.5	0.435	0.2 (-2.9, 3.3)	0.902
Potassium (mEq/L)	4.9±0.7	4.5±0.5	-0.2±0.5	0.232	4.5±0.5	4.7±0.7	0.1±0.6	0.367	-0.3 (-0.8, 0.1)	0.138
Bicarbonate (mEq/L)	24.9±3.9	24.5±4.1	-0.9±3.9	0.469	24.0±2.3	24.4±1.8	0.4±2.3	0.470	-1.3 (-4.1, 1.5)	0.331
Calcium (mg/dL)	9.5±0.5	9.0±1.3	-0.3±0.8	0.198	8.2±1.0	8.7±0.6	0.5±1.1	0.124	-0.8 (-1.6, 0.1)	0.057
Phosphorus (mg/dL)	4.9±1.4	4.5±1.7	-0.5±1.4	0.276	5.1±1.4	4.9±1.7	-0.2±1.4	0.652	-0.3 (-1.5, 0.8)	0.544
Hematocrit (%)	33.4±3.7	30.4±2.9	-3.6±4.5	0.024[b]	36.0±5.2	35.3±4.4	-0.7±2.9	0.391	-2.9 (-6.2, 0.4)	0.077

SBP = Systolic blood pressure; DBP = diastolic blood pressure
Values were all obtained immediately before the onset of a hemodialysis treatment
Data are mean ± SD; compared with control group: [a] $p<0.05$. Week 12 value compared with baseline; [b] $p<0.05$; [c] $p<0.01$

Blood pressure and biochemical measurements

Blood chemistries and blood pressure over period of the study were shown in Table 3. In comparison to baseline values, the valsartan-treated group underwent a decrease in systolic blood pressure (149.4±18.0 vs. 135.6±14.6 mmHg, $p<0.001$) and diastolic blood pressure (80.8±8.8 vs. 76.1±8.5 mmHg, $p<0.015$), whereas no change in the control group. Moreover, the change in systolic blood pressure in the valsartan-treated group was significantly greater than the change during this time period in the control group (-13.9±10.4 vs. -4.0±9.1 mmHg, $p<0.007$). Levels of hematocrit also decreased from baseline in the valsartan-treated group (33.4±3.7 vs. 30.4±2.9%, $p<0.024$), whereas no change in the control group ($p = 0.391$). No change was observed in other biochemical profiles in either group of patients.

Glucose metabolism and insulin resistance index

Fasting plasma glucose (90.1±15.1 vs. 84.8±13.2 mg/dL, $p<0.008$) and insulin resistance index as determined by HOMA-IR (2.6±0.9 vs. 2.1±0.7, $p = 0.041$) decreased from baseline in the valsartan-treated group, whereas no change in the control group. However, these changes were not significantly different between the two groups ($p>0.05$) (Fig. 1). In addition, no difference was found between the two groups regarding to fasting plasma insulin levels at baseline and at the end of the study.

Safety profile

During the 12-week study period, no serious adverse events such as cardiac arrhythmia, myocardial ischemia, stroke, and hyperkalemia were reported in both groups. One subject developed hypotension during dialysis after taking valsartan 160 mg for four weeks. This event improved within one week after decreased dosage of valsartan.

Discussion

The results indicated that treatment with valsartan for 12 weeks significantly augmented improvement of fasting plasma glucose and insulin resistance in hemodialysis patients who were at high risk for abnormal glucose metabolism. However, these outcomes were not significantly different with the control group. The present study provided the evidence of insulin sensitivity modulation after treatment with ARBs in ESRD with long-term hemodialysis patients.

Patients with uremia on dialysis present a high prevalence of insulin resistance[11]. Our study supported

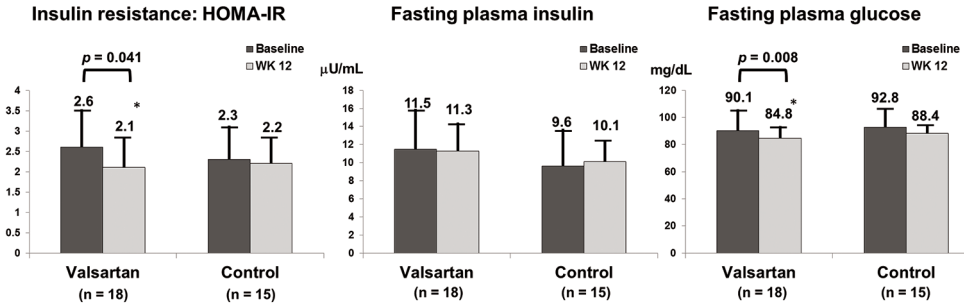

Fig. 1 Changes of insulin resistance index (HOMA-IR), fasting plasma glucose and fasting plasma insulin are shown for the groups receiving valsartan (filled bars), and control (open bars).
* Significant difference from baseline, $p<0.05$.

that valsartan administration decreased blood pressure and inhibited RAAS in patients undergoing maintenance hemodialysis, resulting in a reduction of HOMA-IR and fasting plasma glucose. The positive effect of valsartan on insulin sensitivity in the present study was consistent with the previous studies, which showed that inhibition of angiotensin II action could improve insulin sensitivity and inhibit the sodium-retaining action associated with hyperinsulinaemia in essential hypertension[17-19]. Limited information regarding the effect of angiotensin type 1-subtype inhibition on insulin resistance in patients with advanced CKD on dialysis had been reported. One study demonstrated that the administration of the ARB improved insulin resistance and inflammation markers in patients with CKD stage 3-4[20] and ESRD patients undergoing hemodialysis[12]. However, one study did not show the effect of losartan on insulin sensitivity in ESRD patients[21]. The discrepancy with the results from these studies might be less precise due to the small number of patients and nonrandomized study design.

Although the evidence of the linkage between ARB and insulin resistance was mounting, the mechanism how ARB modulates insulin resistance remains unclear. ARB might restore activation of the glucose transporter via PI3-kinase and reveal enhancement in skeletal-muscle glucose transport, and the long-term effect of angiotensin II receptor antagonism might increase in GLUT-4 protein expression and glucose uptake on type I skeletal-muscle[22]. Another possible mechanism was likely mediated through blocking the effects of angiotensin II in adipocytes. ARB induces adipogenesis and PPAR-gamma target gene expression in human adipocytes and increases adiponectin, which contributes to improved insulin sensitivity via angiotensin type 1 receptors[23]. This was hypothesized to be the mechanism of ARB in reducing insulin resistance and blood glucose. However, even in the case of animal experiments, few reports were available concerning how long ARB affect glucose metabolism. Among clinical trials as well, only a few trials were conducted, over short time periods and with small numbers of cases especially ESRD. Our findings support the notion that ARB can improve blood pressure and glucose metabolism by blocking the inhibitory effect of angiotensin II on insulin signal transmission in ESRD subjects with high insulin resistance index.

Regarding the side effects of the treatment, we could not find serious cardiovascular events in valsartan-treated group. However, hypotension during dialysis was transient and identified as mild symptoms in one subject. Besides, they had no change in serum potassium after treatment. Our results demonstrated minimal serious side effects with oral doses of 80 to 320 mg valsartan daily used within three months. Therefore, the treatment regimen could be well tolerated in hemodialysis patients.

Several limitations were associated with the present study. First, the long-term outcomes of ARB treatment on dialysis patients were not demonstrated in the present study, making these agents undesirable for long-term metabolic effects. Second, no difference of HOMA-IR and fasting plasma glucose levels were found at the end of the study between the treatment group and the control. This failure seems in conflict with the reported reduction in risk for diabetes attributed to ARB therapy. This lack of effect of valsartan on insulin resistance might be a consequence of the ESRD patient's characteristics, short time, duration of treatment, or dosage. It is not known at present. Thus, it might not confirm the additional benefits of

ARB treatment in the dialysis population. In addition, a significant decrease in systolic blood pressure was observed in the valsartan treated-group.

Conclusion

The present study demonstrated the improvement of insulin sensitivity and plasma glucose after a short course of valsartan therapy in hemodialysis patients. Thus, ARBs could be useful for treating patients on hemodialysis not only for their antihypertensive capacity but also for their insulin sensitivity actions. These effects may provide a rationale for early pharmacological intervention aimed at ameliorating abnormal glucose metabolism and cardiovascular risk in dialysis subjects with metabolic disease.

What is already known on this topic?

The agents most often used for hypertension include angiotensin receptor blockers (ARB) and angiotensin converting enzyme (ACE) inhibitors, which are both considered to improve glucose metabolism. Angiotensin II receptor activation impaired insulin signalling in skeletal muscle with a consequent reduction in glucose uptake. Treatment with inhibition of the cellular actions of angiotensin II can increase insulin sensitivity in the setting of increased RAAS activation and abnormal glucose metabolism in patients with hypertension.

What this study adds?

The present study demonstrated the improvement of insulin sensitivity and plasma glucose after a short course of ARBs therapy in hemodialysis patients. These effects may provide a rationale for early pharmacological intervention aimed at ameliorating abnormal glucose metabolism in dialysis subjects with metabolic disorders.

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Potential conflicts of interest

None.

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การใช้ยา angiotensin II receptor blocker รักษาภาวะดื้อต่ออินซูลินในผู้ป่วยโรคไตเรื้อรังที่ฟอกเลือดด้วยเครื่องไตเทียม

บัญชา สถิระพจน์, กุลชน ลีละสิริ, อุปถัมภ์ ศุภสินธุ์, พรรณบุปผา ชูวิเชียร

ภูมิหลัง: ภาวะดื้ออินซูลินพบได้บ่อยในผู้ป่วยไตเรื้อรังระยะสุดท้าย ยายับยั้งตัวรับแอนจิโอเทนซินมีรายงานว่าสามารถลดภาวะดื้ออินซูลินได้ทั้งในสัตว์ทดลองและผู้ป่วยโรคความดันโลหิตสูง คณะผู้นิพนธ์ศึกษาแบบทดลองสุ่มถึงผลของยา valsartan ต่อภาวะดื้ออินซูลินและเมตะบอลิซึมของกลูโคสในผู้ป่วยไตเรื้อรังที่ฟอกเลือดด้วยเครื่องไตเทียม

วัสดุและวิธีการ: ผู้ป่วย 33 ราย ถูกสุ่มทดลองเป็น 2 กลุ่ม โดยกลุ่มหนึ่ง 18 ราย ได้ยา valsartan ขนาด 80-320 มิลลิกรัม/วัน และอีกกลุ่มหนึ่ง 15 ราย ได้ยาลดความดันโลหิตที่ไม่ใช่กลุ่มยายับยั้งตัวรับแอนจิโอเทนซินเป็นระยะเวลา 12 สัปดาห์ มีการติดตามความดันโลหิตระหว่างการศึกษา ระดับอินซูลินในเลือด และทำการวัดภาวะดื้ออินซูลินก่อนให้ยาและเมื่อได้ยาครบ โดยใช้ homeostasis model assessment (HOMA-IR) เป็นตัวประเมินภาวะดื้อต่ออินซูลิน

ผลการศึกษา: พบว่า ผู้ป่วยทั้ง 2 กลุ่ม มีผลทางเมตะบอลิซึมไม่แตกต่างกันก่อนเข้าการศึกษา หลังจากที่ได้ยาครบ 12 สัปดาห์ พบว่ากลุ่มที่ได้ยา valsartan มีค่า HOMA-IR ลดลงจาก 2.6±0.9 เป็น 2.33±0.65 ($p = 0.041$) ระดับน้ำตาลในเลือดจาก 90.1±15.1 เป็น 84.8±13.2 มิลลิกรัม/เดซิลิตร ขณะที่ระดับอินซูลินในเลือดไม่แตกต่างกัน ส่วนกลุ่มควบคุมที่ไม่ได้ยา valsartan นั้น ทั้งก่อนและหลังการรักษาไม่มีความแตกต่างกันของ HOMA-IR ระดับน้ำตาลในเลือดและระดับอินซูลินหลังการรักษา ณ 12 สัปดาห์ ค่า HOMA-IR ระดับน้ำตาลในเลือดและระดับอินซูลินไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติในผู้ป่วยทั้ง 2 กลุ่ม

สรุป: จากผลการศึกษานี้บ่งชี้ว่า ยาลดความดันโลหิต valsartan มีผลทำให้กลูโคสเมตะบอลิซึมดีขึ้น โดยลดภาวะดื้อต่ออินซูลินได้ในกลุ่มผู้ป่วยไตเรื้อรังที่ฟอกเลือดด้วยเครื่องไตเทียม