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Original Article

Hypouricemic Effects of Angiotensin Receptor Blockers in High Risk Hypertension Patients

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ABSTRACT

Background: Hyperuricemia is a currently recognized cardiovascular risk. The angiotensin II receptor blocker (ARB), losartan, is known to decreases serum uric acid (UA) levels. A recent experiment demonstrated strong interaction between irbesartan and UA transporters in-vitro, exceeding that of losartan. We also reported recently, improvement of lipid metabolism and oxidative stress in high risk hypertension patients with irbesartan. The purpose of this study was to evaluate the hypouricemic effect of irbesartan in a clinical setting.

Methods: Forty high risk hypertensive outpatients with coronary artery disease, cerebrovascular disease and/or diabetes complications who had received ARBs other than irbesartan or losartan were enrolled. After a 4 week control term, prescribed ARBs were exchanged to an equivalent dose of irbesartan. We assessed blood pressure and heart rate, and measured serum UA level, parameters of lipid and glucose metabolisms, cardiac and renal functions, and inflammatory and oxidative stress markers from blood samples taken at the following 2 points; at baseline just prior to starting irbesartan, and 12 weeks after irbesartan treatment.

Results: All 40 recruited patients were categorically followed-up (31 men and 9 women, mean age: 68 yr). During the 12 weeks of irbesartan treatment, there were no significant changes in systolic (124 ± 12 to 122 ± 12 mmHg) and diastolic blood pressures (72 ± 7 to 70 ± 6 mmHg). No significant changes in heart rate were observed either. Levels of total cholesterol, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglyceride, fasting blood glucose, glycohemoglobin (Hb) A1c, N-terminal pro-brain natriuretic peptide (NT-proBNP), estimated glomerular filtration rate (eGFR) and high sensitivity C-reactive protein (hsCRP), showed no significant change during the observation period. However, UA levels (5.9 ± 1.6 to 5.5 ± 1.6 mg/ml, P = 0.028) and the oxidative stress marker, derivative reactive oxygen metabolites

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(dROMs) (354±83 to 310±65 U.CARR, P<0.001), decreased significantly following the 12 week irbesartan treatment.

Conclusion: These results suggest irbesartan may exhibit beneficial effects on hyperuricemia and oxidative stress.

INTRODUCTION

Hyperuricemia is currently recognized as a risk of cardiovascular diseases, like hypertension,[1-4] coronary artery disease and heart failure,[5,6] and type 2 diabetes.[7] More recent data also point to serum uric acid (UA) as a risk marker for progression of chronic kidney disease.[8-10] The angiotensin II receptor blocker (ARB), losartan has been shown to increase urinary UA excretion and consequently decrease serum UA levles.[11] Other ARBs such as candesartan and valsartan, however, do not demonstate these effects of serum UA reduction.[12,13] A recent in-vitro experiment demonstrated strong interaction between irbesartan and UA transporters, exceeding that of losartan.[14] Additionally, a clinical report showed trends where irbesartan decreases serum UA level in hypertensive patients with hyperuricemia.[15] However, very few reports indicate the hypouricemic effect of irbesartan. We have on the other hand, recently reported how irbesartan improved lipid metabolism and oxidative stress in high risk hypertension patients.[16] The aim of the present study, therefore, was to elucidate whether irbesartan could lower serum UA levels in high risk hypertension patients in the real clinical setting.

METHOD

Study design

We recruited 40 outpatients with high risk hypertension complicated with coronary artery disease, cerebrovascular disease or diabetes into the present study, All patients were receiving ARBs, other than irbesartan or losartan, for over 3 months and maintained a stable blood pressure. We provided an additional 4-week control period to select patients with well controlled blood pressure, having a systolic blood pressure<135 and diastolic blood pressure<85 mmHg. After the control period, all patients were switched to irbesartan on a dose that corresponded their former ARB. We assessed blood pressure and heart rate, and performed blood sampling for measurement of serum UA level, parameters of lipid and glucose metabolisms, cardiac and renal functions and inflammatory and oxidative stress markers at the following 2 points, at baseline just prior to starting irbesartan and after 12 weeks of irbesartan treatment. During the 12 week irbesartan treatment, doses were not changed. At each blood tests were performed, fasting venous blood was taken from the antecubital vein and sampled blood was used first for routine blood tests. The remaining blood was immediately centrifuged at 1,500×g for 15 min at room temperature and used to measure specific biomarkers. Serum was frozen and stored at −80°C until analyzed. The study protocol was approved by the local medical ethics committee and informed consent was obtained from each patient.

Measurements

Serum UA level was determined by the uricase peroxidase method. For determination of lipid and glucose metabolism parameters, the levels of serum total cholesterol, triglyceride, high-density lipoprotein (HDL)-cholesterol, fasting blood glucose and glycohemoglobin (Hb) A1c were measured. Total cholesterol and triglyceride levels were determined using enzymatic methods. HDL-cholesterol was measured using the precipitation method. Fasting blood glucose was assayed using the glucose oxidase method. HbA1c was measured by high-performance liquid chromatography and expressed as a value of the National Glycohemoglobin Standardization Program. Low-density lipoprotein (LDL)-cholesterol was calculated using the Friedewald formula: (LDL-cholesterol = total cholesterol − HDL-cholesterol − triglyceride/5). Patients with triglyceride levels over 400 mg/dl were excluded as subjects in the LDL-cholesterol was calculated. NT-proBNP determinations were performed using a Roche Diagnostic NT-proBNP

Table 1 Baseline characteristics in 40 patients.

Age; yrs	68 ± 24
Males; *n* (%)	31 (78)
Ischemic heart disease; *n* (%)	32 (80)
Cerebrovascular disease; *n* (%)	2 (5)
Diabetes; *n* (%)	18 (45)
Baseline ARBs	
Candesartan; *n* (%)	10 (25)
Valsartan; *n* (%)	12 (30)
Olmesartan; *n* (%)	6 (15)
Telmisartan; *n* (%)	12 (30)
Combined drugs	
Ca blockers; *n* (%)	22 (55)
β-blockers; *n* (%)	5 (13)
α-blockers; *n* (%)	6 (15)
Thiazide; *n* (%)	4 (10)
Anti-diabetic drugs; *n* (%)	14 (35)
Statins; *n* (%)	35 (88)

ARBs = angiotensin receptor blockers.

electrochemiluminescent immunoassay kit on a Elecsys 2010 analyser (Roche Diagnostics, Mannheim, Germany) according to manufacturer's recommendations.[17] Serum creatinine level was measured using the enzymatical method, and the estimated glomerular filtration rate (eGFR) was calculated as a formula of the Japanese Society of Nephrology CKD Practice Guide: eGFR (ml/min/1.73 m^2) = 194 × (serum creatinine level [mg/dl])$^{-1.094}$ × (age [yr])$^{-0.287}$. The product of this equation was multiplied by a correction factor of 0.739 for women.[18] High sensitivity C-reactive protein (hsCRP) level was measured by particle-enhanced technology on a Behring BN II nephelometer (Dade Behring Inc., Newark, DE), using monoclonal anti-CRP antibodies and a calibrator that was traceable to WHO Reference Material.[19]

Oxidative stress is defined as an imbalance between the production of reactive oxygen metabolites (ROMs), (i.e., metabolites of reactive oxygen specimen [ROS]), and the removal of ROS by a variety of endogenous and exogenous antioxidants. In this study, we assessed oxidative stress using a simple method for the evaluation of ROMs, the dROMs test, which we introduced previously.[16] The dROM test is a photometric method based on the radical reaction of Fenton. The test measures the amount of hydroperoxides, which are strictly correlated with the amount of ROMs and free radicals.[20-22]

Data analysis

Values are expressed as the mean ± SD. Changes in values were assessed by paired t-test. A P value <0.05 was considered to be statistically significant.

RESULTS

All of 40 patients recruited have completely been followed up (31 men and 9 women, mean age: 68 yrs). In these 40 patients, previously prescribed ARBs were candesartan in 10 (25%), valsartan in 12 (30%), olmesartan in 6 (15%) and telmisartan in 12 patients (30%). Combined antihypertensive drugs were calcium channel blockers (CCBs) in 22 (55%), β-blockers in 5 (13%), α-blockers in 6 (15%) and thiazide diuretics in 4 (10%). Antidiabetic drugs and statins were prescribed in 14 (35%) and 35 patients (88%), respectively (Table 1). None of these drugs were discontinued during the study period. The dose of irbesartan was 50 mg/day in 6 (15%), 100 mg/day in 18 (45%) and 200 mg/day in 16 patients (40%).

The data in the measured parameters at baseline before and after irbesartan treatment are shown in Table 2. There were no significant changes in systolic (124 ± 12 to 122 ± 12 mmHg) and diastolic blood pressure (72 ± 7 to 70 ± 6 mmHg) during the 12 weeks of irbesartan treatment. Heart rate also did not change significantly. The levels of total cholesterol, LDL-cholesterol, HDL-cholesterol, triglyceride, fasting blood glucose, HbA1c, NT-proBNP, eGFR and hsCRP, did not change significantly during the observation period. However, the levels of serum UA (5.9 ± 1.6 to 5.5 ± 1.6 mg/ml, P = 0.028) and dROMs (354 ± 83 vs 310 ± 65 U.CARR, $P<0.001$) decreased significantly after the 12 weeks treatment (Table 2, Fig. 1).

DISCUSSION

The major finding of our study is the reduced levels of serum UA and dROMs followed a 12 week irbesartan treatment, substituted for ARBs other than losartan. These results suggest irbesartan is more effective at reducing serum UA levels and oxidative stress, versus

Table 2 Post irbesartan treatment parameter changes.

	Baseline	12 weeks after irbesartan treatment	P value
Systolic BP; mmHg	124 ± 12	122 ± 14	0.618
Diastolic BP; mmHg	72 ± 7	70 ± 6	0.793
Heart rate; /min	72 ± 11	73 ± 12	0.928
UA; mg/ml	5.9 ± 1.6	5.5 ± 1.6	0.028
Total cholesterol; mg/dl	149 ± 17	152 ± 17	0.535
LDL-cholesterol; mg/dl	71 ± 20	72 ± 21	0.642
HDL-cholesterol; mg/dl	46 ± 12	49 ± 13	0.379
Triglyceride; mg/dl	158 ± 80	149 ± 79	0.261
Fasting blood glucose; mg/dl	107 ± 24	108 ± 29	0.325
HbA1c; %	6.0 ± 0.8	6.0 ± 0.8	0.521
NT-proBNP; pg/ml	244 ± 259	225 ± 236	0.386
eGFR; ml/min	68 ± 15	68 ± 14	0.653
hsCRP; mg/ml	0.12 ± 0.14	0.09 ± 0.13	0.292
dROMs; U.CARR	354 ± 83	310 ± 65	<0.001

BP = blood pressure, UA = uric acid, LDL = low density lipoprotein, HDL = high density lipoprotein, HbA1c = glycohemoglobin A1c, NT-proBNP = N terminal pro-brain natriuretic peptide, eGFR = estimated glomerular filtration rate, hsCRP = high sensitivity C-reactive protein, dROMs = derivative of reactive oxygen metabolites.

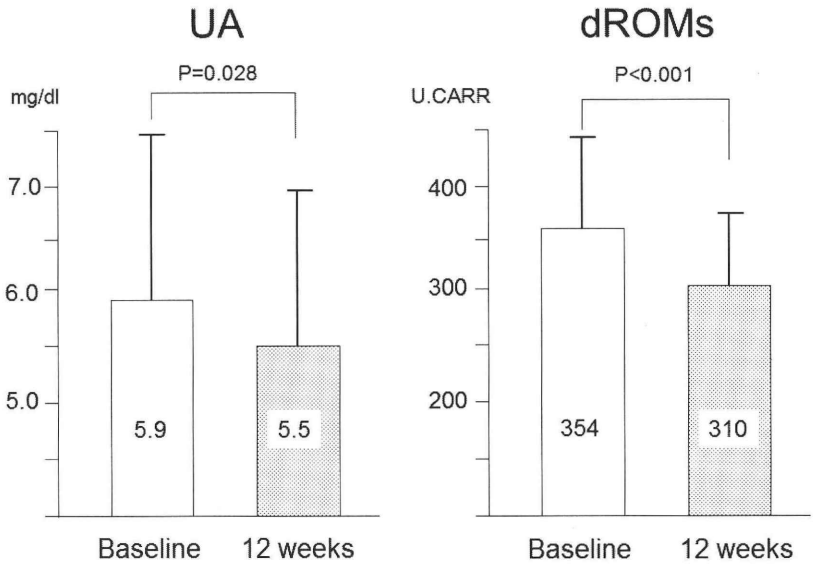

Fig. 1 Changes in the levels of serum UA and dROMs after irbesartan treatment.
Serum UA and dROMs decreased significantly at 12 weeks after irbesartan treatment.

other ARBs, except for losartan.

Several reports have previously shown the hypouricemic effects of losartan, a mechanism which largely appears to be mediated through reductions in human urate transporter 1 (URAT1) levels and decreased net reabsorption of urate, or UA, in the proximal tubule.[23-25] The proximal tubule has been identified the primary location for UA secretion and reabsorption. A central role in proximal tubule UA reabsorption has been ascribed to URAT1. URAT1 is located in the lumen side cell mem-

brane of the proximal tubular cells and reabsorbs UA in exchange for intracellular anorganic anions. Losartan increases UA excretion by inhibition of URAT1-mediated renal tubular UA reabsorption. Early studies in healthy population demonstrated that peak uricosuric effects of losartan were already observed 2 to 4 hours after administration. The time course of this effect suggests that it is losartan itself rather than its active metabolite that blocks URAT1 and causes the reduction in serum UA.[26] Recently Nakamura et al.[14] demonstrated irbesartan also had similar or stronger hypouricemic effects via the inhibition of URAT1-mediated renal tubular UA reabsorption, compared to losartan. Therefore, results of our present study seem to support their report.

Theoretically, uricosuric effects of irbesartan and losartan could lead to increases in urinary UA concentration, potentially leading to supersaturation of UA and in extreme cases, precipitate UA nephropathy. However, risk of developing UA crystals with these ARBs is reduced due to the drugs' urinary alkalinizing effects. Treatment with these ARBs raises urinary pH, attributed to blockade of angiotensin II–induced stimulation of bicarbonate reabsorption. This increase in urinary pH offsets the formation of uric acid crystals and reduces the risk of acute uric acid nephropathy.[27] These findings support the postulate that uric acid–lowering therapy slows progression of chronic kidney disease. The effect of losartan on serum UA reduction explained its 20% renoprotective effect.[27] The renoprotective effects of irbesartan in hypertensive patients with diabetic nephropathy have been established in large clinical trials.[28, 29] From our results, we can envision that renoprotective effects of irbesartan may also be attributed in part by reduction of serum UA.

We previously observed antioxidative effects of irbesartan, demonstrated by lowering of dROMs, in our own I-Mets (irbesartan's metabolic, anti-inflammatory and anti-oxidative properties) study.[16] Lowering of dROMs by irbesartan treatment was also shown in the present study, in addition to serum UA reduction. UA is the final product of the purine metabolism in humans. The final two reactions of its production catalyzing the conversion of hypoxanthine to xanthine and the latter to UA are catalysed by an enzyme, xanthine oxidoreductase, which may attain two inter-convertible forms, namely xanthine dehydrogenase and xanthine oxidase. The latter uses molecular oxygen as an electron acceptor and generates superoxide anions and other reactive oxygen products.[30] The role of UA in conditions associated with oxidative stress is not entirely clear. Evidence mainly based on epidemiological studies suggests increased serum UA levels are a risk factor for cardiovascular disease where oxidative stress plays an important pathophysiological role. Also, allopurinol, a xanthine oxidoreductase inhibitor that lowers serum UA levels exerts its protective effects in situations associated with oxidative stress.[30] Recently, there is increasing experimental and clinical evidence showing UA plays an important role in vivo as an antioxidant. One of several suggestions on the role of UA in vivo indicates that unlike the deleterious influence of hyperuricemia on development of gout and lifestyle-related disease, UA may be considered a powerful antioxidant.[31, 32] Hence, researchers have suggested that hyperuricemia might be a compensatory response to counteract excessive oxidative stress.[31] In fact, intensive exercise-induced oxidative stress was reduced by venous infusion of UA.[33] Since obesity is associated with increased oxidative stress,[34] hyperuricemia related to obesity may represent a response to this increased oxidative stress. Tsukimori et al.[35] reported that increased serum UA leves correlated closely with plasma hydrogen peroxide levels and plasma protein carbonyl levels, thus, serving as an indicator of underlying oxidative stress.

Our previous I-Mets study described above,[16] demonstrated irbesartan treatment improved lipid metabolism and suppressed inflammation, in addition to its anti-oxidative effect. We observed in the I-Mets study, increase in HDL-cholesterol level and reduction of triglyceride and hs-CRP levels, associated with a decrease in dROMs level. In the present study, however, no significant changes in the levels of HDL-cholesterol, triglyceride, and hs-CRP were observed. This could be attributed to the smaller sample size of this study versus the I-Mets study. The present study essentially showed, however, trends similar to the I-Mets study. A long-term observation with a larger sample size would show significant changes in these parameters, as lipid

metabolism, inflammation and oxidative stress are possibly related to one another.

In the present study, fasting blood glucose, HbA1c, NT-proBNP and eGFR did not change significantly. However, several reports have demonstrated that reduction of serum UA and oxidative stress attribute to the improvement of glucose metabolism, heart failure and renal function. If patients are stratified according to baseline levels, irbesartan treatment would show effectiveness for glucose metabolism, heart failure and renal function.

As for cardiovascular endpoints, a subanalysis from the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study showed that superior effects of losartan could partly be explained by its effect on serum UA.[36] However, treatment of coronary artery disease or heart failure guidelines do not describe clearly recommendations on serum UA controls.[37] It is because UA works diversely corresponding to various situations in cardiovascular diseases.[38] Serum UA levels at baseline and gender at least influence the effects of UA lowering therapy,[38] therefore, when evaluating effects, it may be very important to stratify patients using several parameters. Prospective randomized, controlled trials for hard endpoints are needed to confirm that the UA lowering approach improves long-term outcomes of cardiovascular diseases. In addition, it is expected that basic research will elucidate in vivo interactions of the roles of UA, oxidative stress and inflammation.

CONCLUSION

Irbesartan may exhibit beneficial effects on hyperuricemia in addition to those of oxidative stress in the high risk hypertensive patients.

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