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Does the inhibition of renin-angiotensin system decrease inter-dialytic weight gain in anuric hemodialysis patients?

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Abstract. – OBJECTIVE: Knowledge about the inhibition of centrally located angiotensin-I (AT-I) receptors by highly lipophilic AT-I receptor blockers and its' effect are limited with experimental studies. Thus, we aimed to investigate the effect of Telmisartan on Inter-dialytic weight gain (IDWG) % and echocardiographic measurements in anuric hemodialysis (HD) patients.

PATIENTS AND METHODS: A total of forty-one anuric HD patients with ≥ 6 months maintenance on HD were included in this prospective, randomized and self-controlled study. Four weeks prior the study, angiotensin converting enzyme blockers and AT-I receptor blocker drugs were stopped. Patients were assessed three times during the study protocol. These are baseline, three months later (without Telmisartan period) and three months after Telmisartan therapy.

RESULTS: IDWG % was significantly decreased in the period of with Telmisartan compared to period without Telmisartan (5.6 ± 1.0% vs 5.3 ± 1.0%, $p = 0.03$). After the administration of Telmisartan left ventricule end-diastolic diameter (LVEDD) ($p = 0.001$) and inferior vena cava diameter (IVCD) (19.1 ± 3.8 mm vs 17.3 ± 4.2 mm, $p = 0.001$) were significantly decreased compared to the period of without Telmisartan. Despite of significantly changes observed in IVCD and LVEDD measurements in a period without Telmisartan, there was no significantly difference in left ventricular mass index (LVMI) measurements in this period. However, LVMI was significantly regressed after the administration of Telmisartan (269.3 ± 82.7 g vs 256.3 ± 70.3 g, $p = 0.003$ respectively).

CONCLUSIONS: Treatment of anuric HD patients with Telmisartan at a dose of 40 mg a day reduces IDWG%, LVEDD and IVCD measurements. Further studies investigating the long-term effect of these beneficial effects on clinical outcomes are necessary.

Key Words:
Angiotensin II receptor antagonist, Hemodialysis, Inter-dialytic weight gain, Inferior vena cava diameter, Left ventricule mass index.

Introduction

Peripheral renin-angiotensin system (RAS) and its' effect on hemodynamic and cardiac functions have been firmly established in recent years[1,2]. In addition to peripheral RAS, the existence of a brain RAS with all components has been also identified. The brain RAS has been implicated in cardiovascular control, regulation of volume and dipsogenic responses[2,3]. In experimental models, it was shown that stimulation of the centrally located angiotensin-I (AT-I) receptors cause an elevated blood pressure[4], a release of vasopressin[5], a stimulation of drinking behaviour and an increase in salt[6] and water[7] intake. Therefore, the brain RAS represents a potentially important target system for the RAS inhibitors such as AT-I receptor antagonists to blockage these centrally related effects.

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Centrally related effects of RAS system could be important in hemodialysis (HD) patients, because of stimulation of drinking, increase in salt and water intake cause excessive inter-dialytic weight gain (IDWG) in these patients. IDWG is an important issue in HD patients and excessive IDWG is related to worse clinical outcome. Furthermore, increased IDWG is also associated with increased circulating intravascular volume and causes volume dependent hypertension in these patients[8-10].

In experimental study, it has been shown that AT-I receptor antagonist Telmisartan crosses the blood-brain barrier and interact with AT-I receptors in brain areas inside the blood brain barrier[11]. Furthermore, after peripheral administration, it also inhibits centrally mediated effects of AT-II. As a result of this effect, consumption of water is reduced in rats. Therefore, it is possible that IDWG might be decreased by inhibition of centrally mediated action of AT-II by Telmisartan in HD patients.

However, knowledge about the inhibition of centrally located AT-I receptors by highly lipophilic AT-I receptor blockers and its' effect are limited with experimental studies. Thus, we aimed to investigate the action of Telmisartan on IDWG% in anuric HD patients.

Patients and Methods

Study Design

This is a prospective, randomized and self-controlled study. A total of forty-one anuric HD patients with ≥ 6 months maintenance on HD were included to the study. Patients with uncontrolled diabetes mellitus (hemoglobin A1c ≥ 7% within three months before study and study duration), moderate to severe congestive heart failure (New York Heart Association class III-IV), atrial fibrillation, left ventricular dysfunction (shortening fraction 25%), limb amputation, decompansated chronic liver disease, severe malnutrition and malignancies were excluded.

Four weeks prior the study, angiotensin converting enzyme blockers and AT-I receptor blocker drugs were stopped (wash out period). If necessary, calcium channel blockers and alpha-1 receptor blocker drugs were used for the treatment of hypertension. Patients were assessed three times during the study protocol. These are baseline, three months later (without Telmisartan period) and three months after Telmisartan therapy (Figure 1). The study protocol was approved by the local Ethical Committee and written informed consent was obtained from all study participants.

Patient Characteristics and Dialysis

Patients' clinical and demographic characteristics were recorded at the initiation of the study. Kt/V, eritropoietin, statin and antihypertensive drugs usage were recorded. An average of three blood pressure measurements, before HD session in the same week, was considered as blood pressure value.

Conventional bicarbonate HD was performed, with an ultrafiltration-controlled delivery system, with Baxter TINA HD machine (Largo, FL, USA) and standard heparin was used as anticoagulant agent. The biocompatible membranes, low flux polysulfone (F5, F6 Fresenius, Bad Homburg, Germany) were used. Dialysate sodium was 138 meq/dL in all patients during study duration. Dialysis dose (Kt/V) was determined on mid-week HD day before dialysis session.

Assessment of Weight and IDWG

The body weight was determined using an Electronic Chair Scale (CAS dl 200, 2004, Korea). IDWG% was calculated as the patients' weight at the beginning (pre-weight) minus the weight after (post-weight) each dialysis session divided by dry weight. Assessment of dry weight and ultrafiltration rate was performed as described before[12]. The participant was offered two options: to finish meal before starting dialysis or

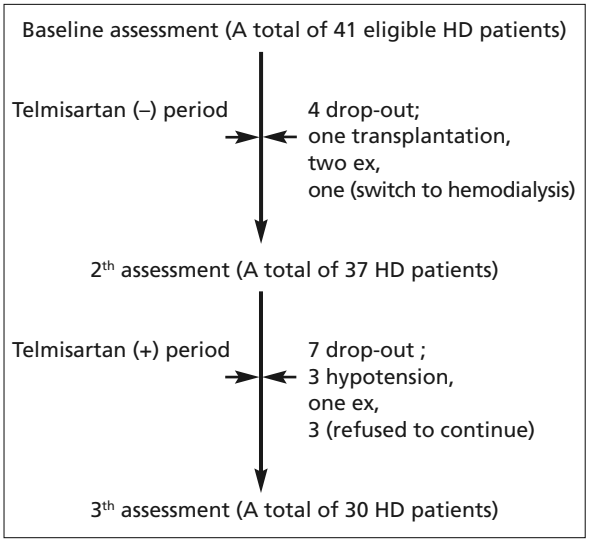

Figure 1. Study design.

to eat meal within 1 h after starting dialysis. After choosing an option, the participant stayed with it throughout the study period, and the meal eaten after starting dialysis was weighted to guide the setting of ultrafiltration rate.

Echocardiographic and IDWG% Measurements

In all subjects, transthoracic M-mode and two-dimensional echocardiographic examinations were performed using a Vingmed System V echocardiographic system (General Electric Vingmed Ultrasound, Horten, Norge), using 2.5-3.5 MHz transducers. All measurements were done by a trained single sonographer (YT) who was blinded to data of the patients and study design. It has been reported that the inferior vena cava diameter (IVCD) measured by echocardiographic method is a reliable parameter to determine the body fluid status of regular HD patients[13]. In present study IVCD was measured at the level just under the diaphragm in the hepatic segment by two dimensional guided pulse-wave doppler echocardiography. Measurement of IVCD was repeated three times in quitet expiration and the average of three measurements was recorded. Simultaneously, echocardiographic measurements were performed. Left ventricule end-diastolic diameter (LVEDD) and left ventricule mass index were recorded.

LV mass was calculated using the following equation:

$$\text{LV mass} = 0.8 \times [1.04 \times (\text{LVEDD} + \text{LVPWT} + \text{IVST})^3 - (\text{LVEDD})^3]$$

where LVEDD indicates LV end-diastolic diameter, LVPWT LV posterior wall thickness, and IVST interventricular septum thickness. All measurements were done on mid-week HD day before dialysis session.

Baseline LVEDD and IVCD measurements performed. After baseline assessment, IDWG% of the patients was recorded for three consecutive months in Telmisartan free period. At the end of this period, all above measurements were repeated and recorded. Then, 40 mg a day Telmisartan was added ongoing treatment of the all patients for three consecutive months. At the end of this period (Telmisartan period) all measurements were also repeated. A total of 2280 patients × dialysis sessions IDWG% were recorded and IDWG% of the patients in the periods with and without Telmisartan were compared. The primary end-point of the study is the comparison of the change in the IDWG% between two periods and secondary end-points are to assess the changes in LVEDD and IVCD.

Statistical Analysis

All results were presented as means ± SD. Student's *t* paired test was used to compare IDWG% between two periods. LVEDD and IVCD levels Values of $p < 0.05$ were considered statistically significant.

Results

Patient Characteristics

A total of 41 anuric HD patients, between the ages of 27-73 years were enrolled in this study. However, thirty of them completed the study protocol. Eleven patients dropped out (Figure 1). The causes of dropped out are as follows; three patients died due to cardiovascular disease, three patients refused to continue study protocol, three patients did not tolerate Telmisartan therapy due to hypotension, one patient underwent renal transplantation and one patient switched to HD. Dropped out patients were also excluded from statistical analysis.

There were twenty-two male and eight female patients. The mean age was 53.9 ± 14.4 years and the mean dialysis duration was 54.8 ± 32.1 months. The primary renal disease was hypertensive nephrosclerosis in thirteen patients, diabetic nephropathy in six patients, chronic glomerulonephritis in six patients, chronic pyelonephritis in three patients and polycystic renal disease in two patients (Table I).

IDWG% and Echocardiographic Measurements

IDWG% was decreased in 22 of 30 patients by the administration of 40 mg/day Telmisartan in present study. However, it increased in 8 of 30 patients. IDWG% was significantly decreased in the period of with Telmisartan compared to period without Telmisartan (5.6 ± 1.0% vs 5.3 ± 1.0%, $p = 0.03$, respectively).

Baseline LVEDD was 50.9 ± 6.9 mm and in a period without Telmisartan it increased to 52.2 ± 7.1 mm. However, after the administration of Telmisartan LVEDD was significantly decreased compared to the period of without Telmisartan ($p = 0.001$). Similarly, compared to baseline value

Table I. Demographic properties, clinical and laboratory findings of the patients.

Male/Female	22/8
Age (years)	53.9 ± 14.4
Dialysis duration (month)	54.8 ± 32.1
Smoker (n)	3
Drug usage	
Antihypertensive	5
Statin	4
Eritropoietin	16
Primary renal disease (n)	
Hypertension	13
Diabetes Mellitus	6
Glomerulonephritis	6
Pyelonephritis	3
Cystic renal disease	2
Hemoglobin A1c (%) in diabetics *	5.4 ± 1.2

*Result of Hemoglobin A1c measurements during study period.

IVCD was increased in a period without Telmisartan (17.9 ± 4.2 vs 19.1 ± 3.8 mm, $p = 0.001$ respectively). After the administration of Telmisartan IVCD was also significantly decreased compared to the period without Telmisartan (19.1 ± 3.8 vs 17.3 ± 4.2 mm, $p = 0.001$ respectively). Despite of significantly changes observed in IVCD and LVEDD measurements in a period without Telmisartan, there was no significantly difference in LVMI measurements in this period (271.1 ± 83.6 vs 269.3 ± 82.7 g, $p > 0.05$ respectively). However, LVMI was significantly regressed after the administration of Telmisartan (269.3 ± 82.7 vs 256.3 ± 70.3 g, $p = 0.003$ respectively) (Table II).

Discussion

The main finding of this study is that the administration of Telmisartan at a dose of 40 mg/day significantly decreased IDWG% in anuric HD patients. Moreover, LVEDD and IVCD were decreased and LVMI was regressed after administration of Telmisartan in anuric HD patients.

Although, the inhibition of the centrally mediated pressor and drinking response to AT-II was shown in experimental studies there is no clinical studies investigating these effects of peripherally administration of lipophilic AT-I receptor on IDWG% in anuric HD patients. Thus, this is the first study investigate this relationship. We would like underline that the number of the patients is limited and the duration of the study is short. Moreover, we do not know whether the effect of Telmisartan on IDWG% and echocardiographic measurements are dose and time dependent manners.

IDWG is an important issue in HD patients because higher IDWG gain may contribute to hypertension in these patients[8-10]. Furthermore, it was shown that higher rate of IDWG% is associated with o modestly increased mortality risk[14] and lower survival[15]. Thus, restriction of water intake is important and essential in the management of HD patients particularly with chronic volume overload patients. The main step of the treatment in these patients is advice on the restriction of sodium and fluid intake. However, the compliance rate is still lower and one third of patients receiving dialysis may have chronic fluid overload[16]. There are alternatives to restrict ID-

Table II. Measurements during study protocole.

Parameters	Baseline	Telmisartan (–) period	Telmisartan (+) period	p*
Systolic BP (mmHg)	135.4 ± 10.0	135.4 ± 7.3	131.9 ± 13.7	0.22
Diastolic BP (mmHg)	84.0 ± 6.1	83.8 ± 6.0	83.4 ± 5.5	0.74
BUN (mg/dL)	70.2 ± 14.5	81.8 ± 27.9	79.7 ± 26.9	0.61
Creatinine (mg/dL)	9.4 ± 2.7	9.0 ± 2.8	8.7 ± 2.6	0.44
Kt/V	1.22±0.2	1.26 ± 0.1	1.23 ± 0.1	0.28
Sodium (meq/L)	139.6 ± 2.8	138.2 ± 3.7	134.2 ± 23.3	0.37
Potassium (meq/L)	5.2 ± 1.4	5.3 ± 1.0	5.6 ± 1.1	0.23
Albumin (g/dL)	3.87± 0.33	3.4 ± 0.4	3.4 ± 0.3	0.57
Hemoglobin (g/dL)	10.6 ±1.8	10.8 ± 1.6	10.7 ± 1.7	0.66
IDWG%	–	5.6 ± 1.0	5.3 ±1.0	0.03
LVEDD (mm)	50.9 ± 6.9	52.2 ± 7.1	50.4 ± 6.4	0.001
IVCDD (mm)	17.9 ± 4.2	19.1 ± 3.8	17.3 ± 4.2	0.001
LVMI (g)	271.1 ± 83.6	269.3 ± 82.7	256.3 ± 70.3	0.003

*Comparison of Telmisartan (+) and (–) periods. Student's paired test was used to compare both periods.

WG in HD patients such as reduction of dialysate sodium with advice to reduce dietary sodium intake. It was shown that reduction of dialysate sodium results in marked improvement in IDWG[17] and regression of left ventricule hypertrophy[18]. In present study, we did not change the dialysate sodium. Therefore, reduction in IDWG% in present patients with Telmisartan is seen not to be related with dialysate sodium.

AT-II is involved in the maintenance and regulation of salt and volume homeostasis and in the cardiovascular control by peripherally as well as centrally mediated effects. It has also a wide spectrum of physiological effects via interaction with angiotensin receptor subtypes. However, dispogenic activity is being mediated only by AT-I receptors[19]. Brain tissue, with the exception of the circumventricular organs, is separated from the circulation by the blood–brain barrier. AT-I receptors are wide spread in brain and stimulation of AT-I receptors in circumventricular organs causes drinking and pressor responses. In addition to circumventricular organs, AT-I receptors are also located inside the blood brain barrier and activation of these AT-I receptors also causes drinking and pressor responses[20].

In experimental, studies the centrally related inhibitor effects of AT-I receptor blockers are contradictory[21,22]. It appears that AT-I receptor antagonists, such as losartan[22,23] and irbesartan[24], have only a limited access to brain AT-I receptors located inside the blood–brain barrier. These AT-I receptor antagonists were not very effective at blocking central AT-II actions, unless high doses were used. It was shown that AT-I receptor blockers are quite different in terms of inhibiting the vasopressin release and water intake in response to centrally injected AT-II. It could be related with lipophilicity. Highly lipophilic, nonpeptide AT-I receptor blocker Telmisartan could inhibit centrally related effect of angiotensin II by dose and time dependent[11]. Furthermore, the higher potency of Telmisartan to inhibit the Ang II-induced effects compared with losartan or irbesartan might be associated lipophilic properties. In present study, we also found that IDWG% of the patients significantly decreased by the administration of Telmisartan. However increase in IDWG% was not prominent. This could be associated with low dose and short time of Telmisartan therapy.

There are many previous reports indicating the usefulness of echocardiographic measurements in estimating volume status[13]. Natori et al[25] reported the correlation between IVCD and central venous pressure and also LVEDD has also been reported to be a reliable tool for dry weight estimation in HD patients[26]. In this study, we found that IVCD and LVEDD decreased by the administration of Telmisartan. However, we do not know the clinical importance of these effects on patients' survival. Indeed these positive effects might be associated with lower intra vascular volume.

Left ventricular hypertrophy is the most common cardiac abnormality and an independent predictor of mortality in end-stage renal disease patients[27]. The pathogenesis of left ventricular hypertrophy in HD patients is multifactorial and includes hemodynamic overload and such neurohormonal activations as the RAS. Therefore, various therapeutic options can be considered for the treatment of left ventricular hypertrophy including RAS blockers, optimal blood pressure and volume status control, etc[28-31]. Furthermore, it has been documented that regression of left ventricular hypertrophy in HD patients is possible[32]. It has been shown that decreasing hemodynamic overload by means of ultrafiltration and reduction in salt intake causes a regression of left ventricular hypertrophy in hypertensive HD patients without antihypertensive drugs[18]. In addition, the beneficial and independently of its antihypertensive effect of AT-I receptor antagonist valsartan on left ventricular mass index has been reported in continuous peritoneal ambulatory dialysis patients[33]. In this study, we also found that left ventricular mass decreases after the administration of Telmisartan in a short time period. However, we do not know whether this beneficial effect is related with hemodynamic and/or non-hemodynamic effect. Indeed, we supposed that regression in LVEDD due to volume control causes the regression in left ventricule mass in our patients.

It has been reported that IDWG increases by the intensity of thirst in HD patients[34]. Moreover, in a study with small and heterogeneous dialyzed patients, it has been shown that enalapril reduces thirst and drinking in dialysis patients[35]. In this study, we also confirmed the beneficial effect of RAS blockage by highly lipophilic AT-I blocker Telmisartan on IDWG% in anuric HD patients.

Conclusions

Treatment of anuric HD patients with Telmisartan at a dose of 40 mg a day reduces IDWG%,

LVEDD and IVCD measurements. Further studies investigating the long-term effect of these beneficial effects on clinical outcomes are necessary.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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