

# The effects of thiazide and thiazide-potassium sparing diuretics on fibrinolytic system parameters

## *Tiazid ve tiazid potasyum tutucu diüretik kombinasyonlarının fibrinolitik sistem parametreleri üzerine etkileri*

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### ABSTRACT

**Objective:** This study investigates whether the combination of thiazides with an aldosterone antagonist can decrease their negative effects on the fibrinolytic activity.

**Methods:** Twenty-eight hypertensive patients (20 men, 8 women) visiting our hypertension unit were included in the study. The control group consisted of age- and gender-matched 9 normotensive healthy individuals. The patients in the 1st group (7 men, 2 women, mean age 48.55±6.14 years) were given 50 mg hydrochlorothiazide (HCT), whereas patients in the 2nd group (7 men, 2 women, mean age 48±6.3 years) received a combination of 50 mg HCT and 5 mg amiloride and the 3rd group (7 men, 3 women, mean age 48.2±7.25 years) took 50 mg HCT and 50 mg spironolactone for a period of 2 weeks. The plasminogen activator inhibitor (PAI)-I, tissue plasminogen activator (t-PA) and PAI-I/t-PA ratio were assessed before and after treatment.

**Results:** Treatment with HCT-spirolactone caused an increase in PAI-I (p<0.001) and t-PA (p<0.001), while no changes were observed in PAI-I/t-PA (P>0.05). In patients treated with HCT-spirolactone, PAI-I increase rate was lower than in those treated with HCT and HCT-amiloride (p<0.001). Hydrochlorothiazide, HCT-amiloride and HCT-spirolactone treatments caused a significant decrease in the baseline blood pressure values (p<0.001). Uric acid levels had increased after treatment with HCT (p<0.01) and HCT-amiloride (p<0.001), but no changes were observed in individuals receiving HCT-spirolactone (p>0.05).

**Conclusion:** Thiazides have a negative effect on the endogenous fibrinolytic activity, which is already impaired in the hypertensive patients. Their use in combination with an aldosterone antagonist such as spironolactone can decrease their hypofibrinolytic effects and metabolic side effects. (*Anadolu Kardiyol Derg 2006; 6: 143-7*)

**Key words:** Hypertension, fibrinolytic activity, spironolactone, thiazide

### ÖZET

**Amaç:** Bu çalışmada tiazidlerin aldosteron antagonistleri ile kombine edilmelerinin, fibrinolitik aktivite üzerine tiazidlerin yaptığı olumsuz etkileri azaltabileceğinin araştırılması hedeflenmiştir.

**Yöntemler:** Bu çalışmaya hipertansiyon ünitemize başvuran 28 hipertansif hasta (20 erkek, 8 bayan) dahil edilmiştir. Kontrol grubu hastalara uygun yaş ve cinsiyetle eşleştirilen 9 normotansif sağlıklı bireyi içeriyordu. Birinci gruba (7 erkek, 2 kadın, ortalama yaş 48.55±6.14) 50mg hidroklorotiazid (HCT), 2. gruba (7 erkek, 2 kadın, ortalama yaş 48±6.3) 50mg HCT ve 5mg amilorid kombinasyonu, 3. gruba (7 erkek, 3 kadın, ortalama yaş 48.2±7.25) 50mg HCT ve 50mg spironolakton kombinasyonu iki hafta süreyle verildi.

**Bulgular:** Hidroklorotiazid tedavisi plazminojen aktivatörü inhibitörü (PAI)-I ve PAI-I/doku plazminojen aktivatörü (t-PA) oranında artışa yol açmıştır (p<0.001 ve p<0.05) ancak t-PA seviyesinde değişiklik gözlenmemiştir (p>0.05). Hidroklorotiazid-spirolakton tedavisi verilenlerde PAI-I ve t-PA artmıştır (p<0.001) ancak PAI-I/t-PA oranı değişmemiştir (p>0.05). Hidroklorotiazid-spirolakton tedavisi verilenlerde PAI-I artış oranı HCT ve HCT-amilorid verilenlerden daha düşük olmuştur (p<0.001). Hidroklorotiazid HCT-spirolakton ve HCT-amilorid tedavileri kan basıncının bazal değerine göre belirgin bir düşme sağlamıştır (p<0.001). Ürik asit düzeyleri HCT ve HCT-amilorid alanlarda artmış (p<0.01 ve p<0.001), HCT-spirolakton alanlarda değişiklik gözlenmemiştir (p>0.05).

**Sonuç:** Çalışmamız tiazidlerin etkin antihipertansifler olduğunu göstermiştir. Ancak hipertansif hastalardaki bozuk endojen fibrinolitik aktivite üzerine negatif etkileri vardır. Spirolakton gibi aldosteron antagonisti bir ajanla kombine kullanımı hipofibrinolitik ve metabolik yan etkilerini azalttığı sonucuna varılmıştır. (*Anadolu Kardiyol Derg 2006; 6: 143-7*)

**Anahtar kelimeler:** Hipertansiyon, fibrinolitik aktivite, spironolakton, tiazid

### Introduction

Cerebrovascular and cardiovascular complications are major causes of morbidity and mortality in hypertension (HT). In

hypertensive patients, impaired fibrinolysis and increased platelet aggregation are risk factors with regard to cardiovascular disease (1,2). Intensive drug therapy for HT has decreased the risk for coronary artery disease.

Endogenous fibrinolytic balance is regulated by the plasminogen activator inhibitor-1 (PAI-I) and tissue plasminogen activator (t-PA). Both are synthesized in the vascular endothelium and the two are mostly found together as a complex. The increase in PAI-I decreases the effect of the fibrinolytic system, whereas the increase in the t-PA increases the activation of the fibrinolytic system. The imbalance of these proteins in association with vascular diseases causes a sensitivity to thrombotic events (3-5).

The renin-angiotensin system (RAS), which has an important role in the pathophysiology of HT, plays a role in the regulation of the fibrinolytic functions. A prospective study in hypertensive patients has demonstrated that RAS activation is associated with an increased risk of myocardial infarction (6). The blockade of RAS via pharmacological route causes a decrease in the cardiovascular diseases. Angiotensin converting enzyme (ACE) inhibitors and angiotensin (Ang) II receptor blockers that block RAS have been shown to improve fibrinolysis by inhibiting Ang II, which is thought to be the actual molecule triggering PAI-I release (7,8). In addition, Ang II also stimulates aldosterone synthesis (9). Aldosterone contributes to the unwanted effects of RAS stimulation by increasing sodium and water reabsorption. On the other hand, regardless of the hemodynamic effects of aldosterone, there is strong evidence indicating that this substance plays a direct role in vascular toxicity and fibrosis (10-13).

The fact that endogenous fibrinolytic activity can be corrected by angiotensin II blockade suggests that the inhibition of aldosterone synthesis is also beneficial and anti-aldosterone treatment can correct the impaired fibrinolytic balance in HT patients.

In the new guidelines, thiazide group diuretics are recommended in the first line treatment of hypertension as monotherapy or in combination with other drugs (14). In ALLHAT study, ACE inhibitors and calcium channel blockers were compared, and these two drugs were not found to be superior to thiazides in efficacy and mortality (15). The results of this study show that thiazide group diuretics should have priority in the pharmacotherapy of hypertensive patients. High efficacy and low cost make thiazides the drug of choice. However, in addition to their metabolic side effects such as hyperuricemia and hypertriglyceridemia, RAS activation due to volume depletion and hypofibrinolytic effect due to PAI-I raise question marks with regard to the use of thiazide diuretics (16).

Studies using spironolactone alone have shown that spironolactone has favorable effects on the impaired fibrinolytic balance (17,18).

This study investigates whether the combination of thiazides with an aldosterone antagonist can decrease their negative effects on the fibrinolytic activity.

## Material and Methods

Twenty-eight hypertensive patients (20 men, 8 women) visiting our hypertension unit were included in the study. All patients had high blood pressure without any underlying diseases. No patients had been treated for their hypertension before the initiation of the study.

Inclusion criteria for the study were as follows: (1) adults between 25-65 years of age, (2) systolic blood pressure > 140 mm Hg and/or diastolic blood pressure >90 mm Hg, measured by the

same person on at least two different days and with the same device (mercury sphygmomanometer). Exclusion criteria: (1) Presence of secondary hypertension, including renovascular hypertension, (2) presence of clinical cardiovascular diseases, including previous stroke or myocardial infarction, angina, arrhythmia or heart block, cardiac failure or left ventricle hypertrophy detected with echocardiography, (3) diabetes mellitus, (4) renal failure (serum creatinine >1.5mg/dl) or proteinuria (urinary protein excretion >150 mg/day) (5) alcohol consumption, (6) use of sedatives, tranquilizers, oral contraceptives, statin group antilipemic agents, aspirin or non-steroidal anti-inflammatory drugs.

Systemic physical examinations and arterial blood pressure measurements were performed for all patients in the baseline and during the control visits. Informed consent forms were completed and local ethics committee approval was obtained before the study. All patients were followed at the outpatient clinic; they were not hospitalized.

The control group consisted of age- and gender-matched 9 normotensive healthy individuals (6 men, 3 women, mean age-47.00±3.17 years). There was no history of old or newly diagnosed hypertension, cardiovascular disease or other systemic disease and none of them were receiving medication. The systolic blood pressure of normotensive individuals was <120 mm Hg and their diastolic blood pressure was <80 mm Hg.

Causes of secondary hypertension, metabolic abnormalities and presence of end organ damage, electrocardiography, echocardiography, protein content in the 24-hour urine samples, creatinine, Na excretion, plasma creatinine and electrolyte levels were investigated with physical examination and laboratory tests. For the healthy controls, physical examinations were performed, medical history data were obtained and routine biochemical tests and urine analysis were performed.

Blood samples were taken from the hypertensive and normotensive control group individuals for PAI-I antigen, and t-PA antigen, in addition to the 24-hour urine samples for Na excretion. The patients in the 1st group (7 men, 2 women, mean age 48.55±6.14 years) were given 50 mg hydrochlorothiazide (HCT), whereas patients in the 2nd group (7 men, 2 women, mean age 48±6.3 years) received a combination of 50 mg HCT and 5 mg amyloride and the 3rd group (7 men, 3 women, mean age 48.2±7.25 years) took 50 mg HCT and 50 mg spironolactone for a period of 2 weeks. In the first and second weeks of treatment, blood and 24-hour urine samples were obtained.

In order to avoid the diurnal variation on hemostatic parameters, blood samples were taken while fasting and in the morning hours. Following a 30-minute rest, blood samples were drawn from the large antecubital vein and the first few millimeters of blood were discarded. Samples taken for hemostatic parameters were immediately placed in the stability tubes (Biopol Corp). Samples for other parameters were put in polypropylene tubes containing sodium citrate. The tubes were centrifuged for 25 minutes at 3500 rpm and at a temperature of 10-18°C, and following the separation of plasma compartment, the samples were maintained at -70°C until the time of analysis. PAI-I and t-PA levels were evaluated with Tintelize Kit (Biopol Corp) and were studied using a Tritutus device (Diagnostic Grifols SA, Spain).

SPSS 12.0 for Windows software was used for statistical analysis. One-way ANOVA was used in comparing normally distributed measurements among groups. In determining which group/groups is different from the others, Tukey post hoc test was

used. Kruskal-Wallis non-parametric test was used in evaluating the parameters that were not appropriate for parametric tests. A "p" value of <0.05 was considered significant. Data were summarized as X (mean) ± SD.

## Results

The baseline plasma PAI-I levels and PAI-I/t-PA ratios were higher in hypertensive patients than in the normotensive control group patients (p<0.001). The mean baseline t-PA levels were similar in hypertensive and control groups (p>0.05) Table 1.

Hydrochlorothiazide, HCT-amyloride and HCT-spirolactone treatments caused a significant decrease in the baseline blood pressure values (p<0.001).

Treatment with HCT caused an increase in PAI-I (p<0.001) and PAI-I/t-PA ratio (p<0.05), while no changes were observed in t-PA (p>0.05).

Treatment with HCT-amyloride caused an increase in PAI-I (p<0.001) and PAI-I/t-PA ratio (p<0.001), while no changes were observed in t-PA (p>0.05).

Treatment with HCT-spirolactone caused an increase in PAI-I (p<0.001) and t-PA (p<0.001), while no changes were observed in PAI-I/t-PA (p>0.05).

In patients treated with HCT-spirolactone, PAI-I increase rate was lower than those treated with HCT and HCT-amyloride (p<0.001).

Treatment with HCT caused a decrease in the serum potassium levels (p<0.001); conversely, a significant increase was observed in patients receiving HCT-amyloride and HCT spironolactone.

Uric acid levels had increased after treatment with HCT (p<0.01) and HCT-amyloride (p<0.001), but no changes were observed in individuals receiving HCT-spirolactone (p>0.05).

Treatment with HCT caused a decrease in high density lipoprotein cholesterol (p<0.01), whereas treatment with HCT-amyloride caused a slight increase in the triglyceride levels (p<0.05). Hydrochlorothiazide -spironolactone treatment did not affect the lipid profile.

## Discussion

Endogenous fibrinolytic activity is impaired in hypertensive patients (18-20). Our findings were compatible with previous studies and our results showed that patients with high blood pressure were hypofibrinolytic (compared to normotensives, PAI-I levels were significantly increased in hypertensives). Fibrinolytic balance is influenced by many factors. In addition to pharmaco-

**Table 1. The comparison of initial parameters of hypertensive patients groups and normotensive control group**

	1st group (HCT 50mg)	2nd group (HCT-Amyloride)	3rd group (HCT-Spirolactone)	4th group (Normotensives)
Age, year	48.5±6.1	48.0±6.3	48.20±7.25	47.00±3.17
BMI, kg/m <sup>2</sup>	27.67±2.85	26.68±29.32	29.32±2.93	28.00±2.38
SBP, mmHg	153.3±10.0***	155.0±13.6***	165.0±17.5***	124.0±7.8
DBP, mmHg	105.5±7.2***	101.1±5.4***	99.0±3.2***	82.0±4.3
PAI-I, ng/ml	28.04 ± 4.67***	30.14 ± 3.63 ***	29.48 ± 2.42***	20.42 ± 5.49
t-PA, ng/ml	4.99 ± 1.49	5.28 ± 0.43	5.02 ± 0.59	5.13 ± 2.27
PAI-I/t-PA	5.95±1.82***	5.75±0.93 ***	5.91±0.66 ***	4.32±2.03

\*\*\* When compared with normotensive patients p<0.001\*\*\*

BMI- body mass index, DBP- diastolic blood pressure, HCT- hydrochlorothiazide, PAI-I- plasminogen activator inhibitor-1, t-PA- tissue plasminogen activator, SBP- systolic blood pressure

**Table 2. The comparison of initial and second week treatment parameters of hypertensive patients group**

	1st group (HCT )		2nd group (HCT -Amyloride)		3rd group (HCT -Spirolactone)	
	Initial	Second week	Initial	Second week	Initial	Second week
SBP, mmHg	153.3±10.0	134.4±8.8 **	155.0±13.6	125.5±7.2***	165.0±17.5	136.0±9.6 ***
DBP, mmHg	105.5±7.2	85.5±5.2 ***	101.1±5.4	76.6±5.0***	99.0±3.2	85.0±7.0 ***
PAI-I, ng/ml	28.04±4.67	37.79±5.14 ***	30.10±3.63	39.60±4.66 ***	29.48±2.42	32.70±3.20 ***
t-PA, ng/ml	4.99±1.49	4.71±0.55	5.28±0.43	5.32±0.52	5.02±0.59	5.78±0.69 ***
PAI-I/t-PA	5.95±1.82	8.06±1.29 ***	5.75±0.93	7.63±1.52 ***	5.91±0.66	5.72±0.8
Potassium, mEq/L	4.17±0.29	3.84±0.26 **	4.36±0.31	4.93±0.26 ***	3.92±0.31	4.34±0.33 ***
Uric acid, mg/dl	5.50±1.50	6.91±0.35 **	4.93±1.55	6.34±1.02 ***	5.10±1.30	5.48±0.75
Triglyceride, mg/dl	136.7±41.0	154.8±56.8	138.5±122.7	181.4±145.2 *	178.1±104.0	180.3±106.9
HDL, mg/dl	49.8±9.7	45.7±8.8**	58.5±14.1	55.1±13.6	46.5±7.9	45.9±7.10

\*\*\* When compared with the initial parameter of own group p<0.001\*\*\*

\*\* When compared with the initial parameter of own group p<0.01\*\*

\* When compared with the initial parameter of own group p<0.05\*

DBP- diastolic blood pressure, HCT- hydrochlorothiazide, HDL- high density lipoprotein cholesterol, PAI-I- plasminogen activator inhibitor-1, SBP- systolic blood pressure, t-PA- tissue plasminogen activator

logical agents such as ACE inhibitors, hormone replacement therapy drugs, many of the drugs used in diabetes treatment, statin class antilipemics, pathophysiological factors like hyperglycemia, hypertriglyceridemia, smoking, insulin resistance, affect fibrinolytic activity in a positive or negative way (14, 21). None of the patients included in the study or the individuals in the control group used any of those agents and they did not have a chronic disease other than HT. Effective blood pressure control was achieved in all patients taking HCT, HCT-amyloride and HCT-spiro-nolactone. The fact that all three drugs provided similar anti-hypertensive efficacy suggested that the main molecule providing anti-hypertensive effect is HCT. This result supports the view in the guidelines which favor the use of thiazides as an effective agent in the first line treatment of hypertension (14).

Thiazide usage turns out to be less common than expected, mostly due to its metabolic side effects appearing in a dose-related fashion. In addition to its metabolic side effects, the increase in PAI-I, which is thought to be due to RAS activation and hypofibrinolytic effects, causes an important problem in their usage. Hypofibrinolytic effect is mostly due to the increase in Ang II. Many in vivo and in vitro studies have shown that Ang II has stimulatory effect on PAI-I expression (22,23).

Angiotensin converting enzyme inhibitors used in combination with aldosterone antagonists decrease the risk of progressive cardiac failure and sudden cardiac death (24). The mechanism of these beneficial effects is not clear. However, there is evidence indicating that spironolactone increases fibrinolytic activity (17,18). This effect manifests itself as an increase in t-PA, decrease or no change in PAI-I and as a decrease in PAI-I/t-PA ratio. In our study, the PAI-I increase in patients taking spironolactone were lower than those using HCT and HCT amyloride; on the other hand, t-PA showed an increase only in the HCT-spiro-nolactone group. The results support the hypothesis that some benefits of the anti-aldosterone treatment are dependent on the correction of fibrinolysis. A significant difference between the potassium levels of the individuals using HCT and HCT-spiro-nolactone were observed. In order to prove that this difference in potassium levels is not related with the PAI-I level and that the fibrinolytic effect is a property of the spironolactone molecule, a third agent with a similar potassium sparing effect, amyloride, was included in the study design. Indeed, the potassium levels in the HCT spironolactone and HCT-amyloride groups were parallel, but PAI-I and t-PA levels did not demonstrate this parallelism. In another study comparing triamterene and spironolactone, the effects of the drugs on blood pressure and serum potassium were similar, but they demonstrated opposing effects on PAI-I antigen (25). Both of the studies emphasize that spironolactone influences PAI-I concentrations through mineralocorticoid receptor antagonism rather than through changes in potassium.

Angiotensin II is thought to play the most important effect on PAI-I. In humans, endogenous aldosterone plays a role in PAI regulation. Aldosterone causes myocardial, vascular and renal fibrosis in animal models and hyperaldosteronism is associated with vascular dysfunction (26).

One of the important issues in the treatment of hypertension is whether antihypertensive medication provides different levels of protection from thromboembolic complications. Anti-hypertensive treatment with diuretics provides limited protection from coronary events. The activation of RAS due to diuretics and impairment in the fibrinolytic activity due to the increase in the exp-

ression of PAI-I thereafter might be responsible for this limited effect. The anti-aldosterone effect of spironolactone contributes to the improvement in the impairment of fibrinolysis.

Hyperuricemia is an expected side effect of thiazide treatment. In our study, while this effect is not observed in individuals using HCT-spiro-nolactone, an obvious hyperuricemic effect was observed in the individuals using the two other drugs.

In conclusion, this study has shown that thiazides are effective anti-hypertensive drugs. They have a negative effect on the endogenous fibrinolytic activity, which is already impaired in the hypertensive patients. Their use in combination with an aldosterone antagonist such as spironolactone can decrease their hypofibrinolytic effects and metabolic side effects. For this reason, we think it will be more appropriate to combine thiazides with spironolactone as a choice for the first line treatment of hypertension.

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