Comparison of antithyroid drugs efficacy on P wave changes in patients with Graves' disease

Graves hastalarında antitiroid ilaçların P dalga değişiklikleri üzerine etkilerinin karşılaştırılması

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ABSTRACT

Objective: Some precursor P wave changes on electrocardiogram (ECG) before the atrial fibrillation (AF) episodes occur in the hyperthyroidism. Our aim was to compare the effect of two antithyroid drugs (ATD) on P wave duration and dispersion (PWD) in patients with hyperthyroidism.

Methods: Fifty patients (13 men, 37 women; mean age 39.2±13.2 years) with newly diagnosed overt hyperthyroid patients with Graves' disease (GD) were enrolled in the prospective, randomized study. The maximum P wave duration (Pmax) and the minimum P wave duration (Pmin) were measured in all 12-lead surface ECGs. The patients were consecutively randomized to propylthiouracil (PTU) (n=24) and methimazole (MMZ) (n=26) groups. Electrocardiogram was repeated within euthyroid state after the 18-month ATD treatment. Student t-test, Mann-Whitney U and Pearson Chi-square tests were used for comparisons of the data between groups. The differences between pre- and post-treatment measurements within groups were evaluated by Wilcoxon Sign Rank test. The correlation of data was tested by using Spearman correlation analysis.

Results: The maximum P wave duration (Pmax) was 90 (80-110) and 90 (90-110) msec, (p=0.586), and PWD was 35 (22.5-48.7) and 40 (30-40) msec, respectively (p=0.952) in PTU and MMZ groups. After euthyroidism was achieved, Pmax was 80 (80-90) and 87.5 (80-90) msec (p=0.676), and PWD was 27.5 (20-35) and 27.5 (20-30) msec in PTU and MMZ groups, respectively (p=0.540). After ATD treatment PWD decreased (p=0.009 and p<0.001, respectively) in both of PTU and MMZ groups. However effects of ATD on PWD change were similar (p=0.486).

Conclusion: P wave duration and PWD are found to be prolonged in hyperthyroid patients with GD. Both propylthiouracil and methimazole reduce the P wave duration and dispersion. Thus, we can conclude that improvements in atrial conduction properties are not associated with the type of ATD but with only achievement of euthyroidism. (*Anadolu Kardiyol Derg 2009; 9: 298-303)*

Key words: Graves' disease, atrial fibrillation, P wave dispersion, antithyroid drugs

ÖZET

Amaç: Atryial fibrilasyonun (AF) henüz ortaya çıkmadan önce hipertiroidinin yüzey elektrokardiyogramına (EKG), P dalga parametrelerinde bazı değişiklikler ile yansıdığı düşünülmektedir. Çalışmamızda hipertiroidli hastalarda iki antitiroid ilacın P dalga süresi ve dispersiyonu üzerindeki etkilerinin karşılaştırılması amaçlanmıştır.

Yöntemler: Yeni tanı almış hipertiroidli 50 Graves hastası prospektif, randomize çalışmaya dâhil edildi (13 erkek, 37 kadın; ortalama yaş 39.2±13.2 yıl). On iki derivasyonlu yüzey EKG'den en uzun P (Pmax) ve en kısa P (Pmin) uzunluğu belirlendi. Hastalar sırayla propiltiyourasil (PTU) (n=24) ve metimazol (MMZ) (n=26) gruplarına randomize edildi. On sekiz aylık antitiroid tedavi sonrası, hastalar ötiroid halde iken EKG tekrarlandı. Gruplar arası verilerin karşılaştırması için Student t-testi, Mann-Whitney U ve Pearson Ki-kare testleri kullanıldı. Tedavi öncesi ve sonrası gruplar arası farklılıklar Wilcoxon Sign Rank testi ile değerlendirildi. Verilerin korelasyonu Spearman analizi yardımıyla test edildi.

Bulgular: Tedavi öncesi PTU ve MMZ tedavi gruplarında Pmax (sırasıyla 90 (80-110) ve 90 (90-110) ms, p>0.05) ile P dalga dispersiyonu (PWD) değerleri (sırasıyla 35 (22.5-48.7) ve 40 (30-40) ms, p>0.05) benzerdi. Tedavi sonrası PTU ve MMZ gruplarındaki Pmax (sırasıyla 80 (80-90) ve 87.5 (80-90) ms, p=0.676) ve PWD değerleri (sırasıyla 27.5 (20-35) ve 27.5 (20-30) ms, p=0.540) idi. Ötiroidizmin sağlanması ile PWD değerlerinde hem PTU grubunda, hem de MMZ grubunda istatistiksel olarak anlamlı düşüş tespit edildi (sırasıyla p=0.009 ve p<0.001). Ancak antitiroid ilaç gruplarının PWD değişiklik oranları benzerdi (p=0.486).

Sonuç: Hipertiroidili Graves hastalarında P dalga süresi ve PWD artmaktadır. Propiltiyourasil ve metimazol tedavileri P dalga süresi ve dispersiyonunu azaltmaktadırlar. İlaç tedavisi ile ötiroidizm sağlandığında, atriyal ileti parametrelerinde ilacın cinsinden bağımsız olarak düzelme görülmektedir. *(Anadolu Kardiyol Derg 2009; 9: 298-303)*

Anahtar kelimeler: Graves hastalığı, atriyal fibrilasyon, P dalga dispersiyonu, antitiroid ilaçlar

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Introduction

Atrial fibrillation (AF) is associated with increased cardiovascular morbidity and mortality (1). Hyperthyroidism is associated with risk of worsening of a preexisting heart disease, but hyperthyroidism can also cause cardiac disease (2, 3). Atrial fibrillation in thyrotoxicosis is associated with significant mortality and morbidity resulting from embolic events (4). Atrial fibrillation occurs in 10-15% of patients with hyperthyroidism (5). Hyperthyroidism is associated with shortening of action potential duration that triggers the development of AF. In a study on the effects of thyroid hormones on cardiomyocytes, action potential duration was shorter in hyperthyroid than in euthyroid myocytes (6). Thyroid hormone also potentiates the effect of adrenergic system on heart. Facilitation of action of catecholamines is by increasing tissue sensitivity, which is the result of increased transcription of beta adrenergic receptor. The structural similarity to catecholamines also contributes to these effects (7). Therefore, electrocardiogram (ECG) may be helpful in identifying hyperthyroid subjects at risk for developing atrial fibrillation. Maximum P wave duration (Pmax) and P wave dispersion (PWD) were higher in both subclinical and overt hyperthyroidism (8).

Antithyroid drugs, specifically thionamides (either propylthiouracil (PTU) or methimazole (MMZ)), are most often used as the primary treatment for persons with Graves' disease, in whom "remission," which is usually defined as remaining biochemically euthyroid for one year after cessation of drug treatment, is possible (9). There is only one study reported in the literature on effects of antithyroid drugs on P wave changes in patients with hyperthyroidism. This study showed that PTU treatment of three months has effectively decreased P wave duration and P wave dispersion at levels measured in healthy control subjects (10). There is no study examining the effect of MMZ on P wave changes.

In this study, our aim was to evaluate the effects of hyperthyroidism on P wave duration and dispersion, as well as to compare the effects of propylthiouracil and methimazole on P wave duration and dispersion in patients with Graves disease (GD).

Methods

Study design and patients

We planned a prospective, randomized study. We enrolled 60 patients with clinical hyperthyroidism referred to Endocrinology and Metabolism outpatient clinic. The diagnosis of GD was established by the presence of signs and symptoms of thyrotoxicosis, accompanied by a diffuse goiter, an increased radioiodine uptake, and biochemical evidence of hyperthyroidism and high circulating thyroid-stimulating hormone (TSH) receptor antibody. None of the subjects had history of coronary artery disease, valvular heart disease, hypertension, diabetes mellitus, arrhythmia, pulmonary disease, or other systemic diseases and were not taking any medication. All patients signed an informed consent form, and the study was approved by the Ethics Committee of our institution. The patients were consecutively randomized to one of the following treatment groups: PTU group (n=30), propylthiouracil 4-8 mg/kg daily and propranolol 40 mg daily; MMZ group (n=30), methimazole 0.5-1 mg/kg daily, and propranolol 40 mg daily. However, a total number of 10 patients (6 from PTU group and 4 from MMZ group) were outside the scope of this study. The reasons for exclusion from the analyses were as following: P wave could not be precisely evaluated on ECG in 3 patients (2 from PTU group and 1 from MMZ group), remission could not be ensured for 5 patients (3 from PTU group and 2 from MMZ group) during the follow-up period, medical treatment was ended and surgical or radioiodine treatment was applied, and 2 patients failed to attend the control examinations (1 from PTU group and 1 from MMZ group) during the 18-month follow-up period. Patients were followed monthly by blood cell counts, liver and thyroid function tests. Propranolol treatment was ended after euthyroidism was enhanced in patients. Antithyroid treatment of the patients continued for 18 months to ensure remission. Minimum P wave duration (Pmin), Pmax and PWD were re-evaluated in euthyroid state following the 18-month ATD treatment.

Laboratory assay

After an overnight fast, blood samples were collected from all the study subjects for determination of serum TSH, free triiodothyronine (FT_3), free thyroxine (FT_4), anti-TSH receptor antibody (TR-Ab), anti-thyroperoxidase antibody (TPO-Ab) and anti-thyroglobulin antibody (Tg-Ab) levels. Serum TSH, FT_3 and FT_4 levels were evaluated using the Abbott Architect 2000 device and chemiluminescence microparticle immunoassay (CMIA) method. Patients who have TSH level lower than 0.35 μIU/ml and FT_3 and FT_4 levels above normal ranges (>3.71 pg/ml and >1.48 ng/dl; respectively) were accepted as having hyperthyroidism. Serum Tg-Ab and TPO-Ab values were evaluated by immunoradiometric assay (IRMA) methods (ICN Pharmaceuticals, USA). The TR-Ab auto-antibodies were measured in patients with the use of a radioreceptor assay (Radim, Italy). Normal ranges in our laboratory are as follows: Tg-Ab <50 IU/ml; TPO-Ab <10 IU/ml and TR-Ab <9 U/l (9-14 U/l borderline, >14 U/l positive).

Assessment of 12-lead ECG

The 12-lead surface ECG was obtained from each subject in the supine position after 15 minutes rest. The surface electrocardiogram was recorded at a speed and amplitude of 50 mm/sec and 2 mV/cm for two consecutive cycles. All ECGs were analyzed by a single cardiologist blinded to thyroid status and patient details. To improve accuracy, measurements were obtained with calipers and magnifying lens for defining the ECG deflection. The onset of the P wave was defined as the junction between the isoelectric line and the beginning of the P wave deflection. The offset of the P wave was defined as the junction between the end of the P wave and isoelectric line. P wave duration was defined as the time measured from the onset to the offset of the P wave. The leads in which the onset and the offset of the P wave were unclear were excluded. The Pmax and the Pmin were measured in all 12-lead surface ECGs. The PWD was defined as the difference between the Pmax and the Pmin. Intra-observer variability was found to be 4.3 % for Pmax, and 4.2 % for PWD.

Sample size estimation

The primary aim of this study was to compare treatment groups by means of actual difference in PWD according to the pre-treatment. A total sample size of 38 cases (19 for Group I, 19 for Group 2) was required to detect at least 10 msec (SD=12.5) difference with a power of 85% at the 5% significance level using a two-sided Mann-Whitney test assuming that the actual distribution is double exponential. The difference of 10 msec was taken from both pilot study and clinical experience.

Statistical analysis

Data analysis was performed by using SPSS for Windows, version 13.0 (Chicago, IL, USA). Whether the distributions of continuous variables were normal or not was determined by using Shapiro-Wilk test. Continuous variables were expressed as mean ± standard deviation or median (25^{th}-75^{th}) percentiles, where applicable. While mean ages were compared by Student's t test, Mann Whitney U test was applied for the comparisons of the median values of the thyroid function tests and P wave parameters. The differences between pre- and post-treatment measurements within groups were evaluated by Wilcoxon Sign Rank test. In addition, the actual differences in P wave parameters were calculated for each treatment group. Nominal data were analyzed by Pearson Chi-square test. The degrees of associations between continuous variables were calculated by Spearman's "rho" correlation coefficient. A p value less than 0.05 was considered statistically significant.

Results

Baseline clinical characteristics of patient groups are presented in Table 1. The PTU and MMZ groups consisted of age and sex matched subjects. There were no significant differences in smoking status, systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) between two groups. There were no significant differences with regard to FT_3, FT_4, TSH, Tg-Ab, TPO-Ab and TR-Ab levels and P wave paraemters before treatment between PTU and MMZ groups (Table 1).

The Pmax and PWD significantly decreased after treatment in PTU and MMZ groups (p=0.008 and p<0.001; p=0.009 and p<0.001 respectively) (Table 2). When we compared the patients taking

Table 1. Clinical and laboratory features of the groups

Variables	PTU (n=24)	MMZ (n=26)	p
Age, years	37.7±12.3	40.3±14.2	0.494[a]
Female/Male	17/7	20/6	0.624[b]
Smoking -/+	12/12	17/9	0.271[b]
FT3, pg/ml	5.7 (4.0-13.7)	5.0 (3.7-20.0)	0.946[c]
FT4, ng/dl	2.4 (1.9-6.0)	3.4 (1.4-6.0)	0.625[c]
TSH, µIU/ml	0.01 (0-0.08)	0.01 (0-0.07)	0.381[c]
TPO-Ab, IU/l	123 (20.7-169.5)	130 (29-227.2)	0.683[c]
Tg-Ab, IU/l	33 (14.2-145)	22 (16.5-113)	0.770[c]
TR-Ab, IU/l	16.0 (9.5-24.9)	17.5 (11-24.9)	0.170[c]
SBP, mmHg	120 (110-125)	115 (110-120)	0.656[c]
DBP, mmHg	70 (70-80)	70 (70-80)	0.671[c]
HR, beat/minute	100.9±9.9	98.2±10.1	0.342[a]

[a]Student's t test, [b]Pearson Chi-square test., [c]Mann Whitney U test.
Data are represented as mean±SD and median (interquartile range)
DBP- diastolic blood pressure, FT3- free triiodothyronine, FT4- free thyroxine, HR- heart rate, MMZ- methimazole, PTU- propylthiouracil, SBP- systolic blood pressure, Tg-Ab- anti-thyroglobulin antibody, TPO-Ab- anti-thyroperoxidase antibody, TR-Ab- anti-TSH receptor antibody, TSH- thyroid-stimulating hormone

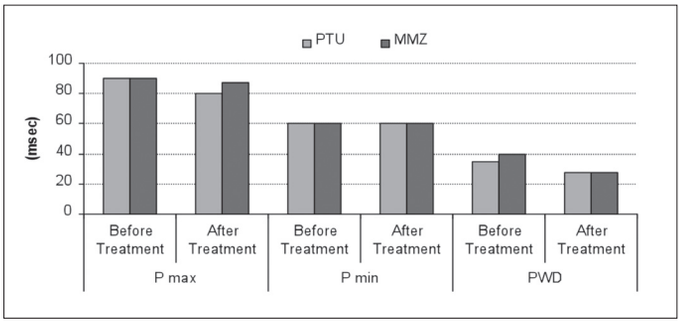

Figure 1. Comparison of P wave parameters within and between groups before and after treatment
MMZ - methimazole, PTU - propylthiouracil

Table 3. Comparison of the actual differences in P wave parameters in PTU and MMZ groups

Variables	PTU	MMZ	p[a]
Pmax, msec	-5 (-18.7 - 0)	-10 (-12.5 - 0)	0.879
Pmin, msec	0 (-5 - 7.5)	0 (-6.2 - 10)	0.809
PWD, msec	-7.5 (-20 - 0)	-10 (-16.2 - -5)	0.486

[a]Mann Whitney U test.
MMZ- methimazole, Pmax- maximum duration of P wave, Pmin- minimum duration of P wave, PTU- propylthiouracil, PWD- P wave dispersion

Table 2. Comparison of P wave parameters within groups before and after treatment

Variables	PTU			MMZ		
	Before treatment	After treatment	p[a]	Before treatment	After treatment	p[a]
Pmax, msec	90 (80-110)	80 (80-90)	0.008	90 (90-100)	87.5 (80-90)	<0.001
Pmin, msec	60 (50-70)	60 (50-65)	1.000	60 (50-62.5)	60 (58.7-65)	0.513
PWD, msec	35 (22.5-48.7)	27.5 (20-35)	0.009	40 (30-40)	27.5 (20-30)	<0.001

[a]Wilcoxon Sign Rank test
MMZ- methimazole, Pmax- maximum duration of P wave, Pmin- minimum duration of P wave, PTU- propylthiouracil, PWD- P wave dispersion

Table 4. Correlation of age, thyroid functions and antibodies with P wave parameters

Variables	Pmax		Pmin		PWD	
	rho	p	rho	p	rho	p
Age	-0.399	0.004	-0.161	0.263	-0.250	0.080
FT3	0.035	0.808	0.071	0.623	-0.034	0.815
FT4	0.099	0.493	0.064	0.657	-0.044	0.762
TSH	0.151	0.296	0.075	0.606	0.042	0.770
TPO-Ab	-0.127	0.381	0.113	0.434	-0.227	0.113
Tg-Ab	-0.124	0.391	0.000	0.998	-0.190	0.187
TR-Ab	0.232	0.105	0.208	0.129	0.032	0.825
SBP	-0.001	0.994	0.022	0.879	0.030	0.837
DBP	0.006	0.968	-0.128	0.376	0.086	0.554
HR	-0.027	0.853	-0.039	0.790	-0.039	0.790

Spearman correlation analysis

DBP- diastolic blood pressure, FT3- free triiodothyronine, FT4- free thyroxine, HR- heart rate, MMZ- methimazole, Pmax- maximum duration of P wave, Pmin- minimum duration of P wave, PTU- propylthiouracil, PWD- P wave dispersion, SBP- systolic blood pressure, Tg-Ab- anti-thyroglobulin antibody, TPO-Ab- anti-thyroperoxidase antibody , TR-Ab- anti-TSH receptor antibody, TSH- thyroid-stimulating hormone

PTU and MMZ for P wave parameters, there was no significant difference after ATD treatment (Table 3). Effects of ATD on PWD change were also found to be similar (p=0.486) (Fig. 1).

Although there was a correlation between age and Pmax (r=0.442, p=0.001), we did not detect any correlation between SBP, DBP, HR, FT_3, FT_4, TSH, Tg-Ab, TPO-Ab and TR-Ab levels and P wave parameters (Table 4).

Discussion

In present study, we determined that P wave duration and PWD significantly decreased after treatment in PTU and MMZ groups. We found the effects of propylthiouracil and methimazole on P wave duration and PWD to be similar.

Atrial fibrillation is the most common chronic cardiac arrhythmia in clinical practice and it frequently coexists with organic heart diseases. In epidemiologic studies, incidence of AF is found to be 4% but it increases with age (11). It is well known that hyperthyroidism is an important risk factor for AF. The prevalence of AF in hyperthyroidism has been estimated as 5-15% (5).

In hyperthyroidism, increased thyroid hormones contribute to arrhythmogenic activity of cardiomyocytes by altering the action potential duration, enhancing automaticity and triggered activity (6). Thyroid hormone is known to affect cardiovascular function and has been shown to affect the gene expression of ionic currents of cardiac cells (12, 13). The thyroid hormone responsive genes encode both structural and regulatory proteins in the heart, such as myosin heavy chain, sarcoplasmic reticulum calcium adenosine triphosphatase, beta-adrenoreceptors, sodium-potassium adenosine triphosphatase, and voltage gated potassium channels (14). The shortened action potential duration in the cardiac myocytes is considered to be due to the modulation in gene expression of K+ channels (15). From a clinical perspective, if the atrium has a shorter action potential duration, it would provide a basis for atrial fibrillation and explain the frequent complication of AF in hyperthyroidism (3, 16, 17). From another point of view, shortening of the action potential duration in the ventricular muscle and concomitant tachycardia may render the ventricle susceptible to developing heart failure known as thyrotoxic heart (3, 17).

In our study, there was no correlation between baseline P wave alterations and serum thyroid hormone levels. Recent studies showed that low serum TSH is an independent risk factor for development of AF (18). A study showed that PWD were significantly higher in the patients with subclinical hyperthyroidism than the control group consisting of healthy subjects (19). The Pmax and PWD can be associated with the risk of development of paroxysmal AF. Furthermore, increase in the Pmax and PWD can be used as a highly specific and independent marker to determine the AF episodes (20). All of these findings support that P wave duration and PWD can be associated with increased risk of AF development in patients with hyperthyroidism. Unexpectedly, we did not find any relationship between TSH, FT_3, FT_4 levels and PWD that give rise to the opinion that further studies are needed. We can only conclude that there is an association between PWD prolongation and hyperthyroidism but there is not an exact correlation between PWD prolongation and TSH or thyroid hormone levels. When we compare two hyperthyroid patients with PWD prolongation, patient with lower thyroid hormone levels may have more PWD prolongation. These conflicting results are similar for TSH levels as well.

We found a correlation between age and Pmax (r=0.442, p=0.001). Higher prevalence occurs in elderly and in those with other coexisting risk factors for atrial fibrillation. In the study by Agner T et al. (21), 25% of hyperthyroid patients older than 60 years had atrial fibrillation compared to 5% in patients less than 60 years of age. In our study, the correlation between Pmax values and patients' ages before ATD treatment supports that older patients are affected from hyperthyroidism more than younger patients.

Antithyroid drugs are commonly used as initial therapy and primarily interfere with thyroid hormone synthesis (9). The superiority of either propylthiouracil or methimazole is not clearly established. Among patients with GD, who are treated with ATD, the average rate of remission (defined as a serum level of thyrotropin in the normal range when the patient is not receiving medication) is 30 to 50%, but relapse occurs in more than 50% of patients (9). A longer duration of ATD therapy (1 year or more) has been reported to improve remission rates, although a randomized trial showed no significant improvement in remission rates 2 years after discontinuation of therapy when treatment was continued well beyond 18 months as compared with discontinuation at 18 months (22). The thyroid hormone can also alter the function of a number of ion channels including sodium, potassium, and calcium in the cell membrane (23). Antithyroid drugs showed essentially the opposite effect on these genes to provide euthyroidism (15).

It was shown in one study (10) that prolonged P wave duration and dispersion improved with PTU treatment (10). In our study both Pmax and PWD significantly decreased after patients became euthyroid with treatment. However, when we compared the patients taking PTU or MMZ there was no significant difference between the improvement rates of P wave alterations.

In our study, as compatible with many other studies, Pmax and PWD values decreased with treatment but Pmin did not show statistically significant alteration. Thus, enhancement in PWD is responsible for enhancement for Pmax, therefore PWD values decreased with the achievement of euthyroidism with the reduction in Pmax. It is not well defined why Pmin values did not show any alterations.

Atrial fibrillation is a major risk factor for stroke, increasing the risk 5-fold compared with that in individuals with normal sinus rhythm. Randomized controlled trials have shown that prophylactic treatment with warfarin decreases the risk of stroke by 60% to 70% in patients with nonvalvular AF, and guidelines support the use of warfarin in these patients (24). The safety and tolerability of long-term oral anticoagulation therapy is not entirely clear in elderly patients, who have the highest risk for stroke (24, 25) and who may have an increased risk for bleeding complications (26). The decision to use anticoagulation in patients with nonvalvular AF should be clinically based after careful assessment of patient eligibility and the appropriateness of anticoagulation. There is no evidence showing that increase in P wave dispersion also increases thromboemboli risk, therefore anticoagulant treatment is not required for patients with hyperthyroidism.

Study limitations

It would be better to calculate PWD by 24-hour ambulatory ECG record in an aim to detect paroxysmal AF attacks. We know that, P wave duration and PWD were related with the extension of intra- and inter-atrial transmission period (Left atrium diameter (mm) = 2.47 ± 0.29 x P wave duration (mm)) (27). Echocardiography may be useful to indicate atrium diameters and to look at the correlation between other parameters in the study. However, the patients included in the study did not undergo echocardiographic analysis.

Conclusion

P wave duration and PWD are increased in hyperthyroidism and both propylthiouracil and methimazole effectively reduce the P wave duration and dispersion. The improvement in these parameters after treatment can be associated with the reduction of negative effects of thyroid hormones on atrial electrophysiology. The P wave alterations especially Pmax can return to normal with the achievement of euthyroidism status independently of antithyroid medication type

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