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How Does Entacapon Affect Homocysteine Levels?

Entakapon Homosistein Düzeyini Nasıl Etkiler?

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Abstract

Objective: To determine homocysteine, vitamin B12, and folate levels in patients with Parkinson's disease and to investigate the effect of entacapone use on homocysteine levels.

Materials and Methods: The records of patients who were followed up in our outpatient clinic between 2009 and 2010 were reviewed retrospectively. The demographic, clinical characteristics, and laboratory findings of the patients were recorded. The control group consisted of healthy subjects with similar demographic characteristics. The patients were divided into two groups according to the treatment they received.

Results: The control group consisted of 22 healthy subjects (group 1), group 2 comprised 22 patients [entacapone (+)], and group 3 constitued 50 patients [entacapone (-)]. The homocysteine levels of the control group were significantly lower than the entacapone (-) and entacapone (+) groups. The vitamin B12 level of the control group was significantly higher than in the entacapone (-) group. The folate levels of the control group were significantly higher than those of the entacapone (-) group. There was no significant difference between the entacapone (-) and entacapone (+) groups in terms of homocysteine, vitamin B12, and folate levels.

Conclusion: Levodopa treatment affects homocysteine levels in patients with Parkinson's disease. The effect of levodopa + entacapone on plasma homocysteine levels should be evaluated together with basal vitamin B12 and folate levels and genetic features.

Keywords: Idiopathic Parkinson's disease, entacapone, homocysteine

Öz

Amaç: Parkinson hastalarında homosistein, vitamin B12 ve folat düzeylerinin belirlenmesi ve entakapon kullanımının homosistein düzeylerine etkisinin araştırılması amaçlanmıştır.

Gereç ve Yöntem: Hareket bozuklukları polikliniğimizde 2009-2010 tarihleri arasında takipli olan hastaların dosyaları retrospektif olarak incelendi. Hastaların demografik, klinik özellikleri ve laboratuvar bulguları kayıt edildi. Benzer demografik özelliklere sahip laboratuvar değerleri incelenmiş olan sağlıklı kişiler kontrol grubunu oluşturdu. Hastalar aldıkları tedaviye göre 2 gruba ayrılarak değerlendirme yapıldı.

Bulgular: Grup 1: Yirmi iki sağlıklı kişiden (kontrol grubu), grup 2: Yirmi iki hastadan [entakapon (+)], grup 3: Elli hastadan [entakapon (-)] oluşmaktadır. Kontrol grubunun homosistein düzeyi entakapon (-) ve entakapon (+) gruba göre anlamlı derecede düşük saptandı. Kontrol grubunun vitamin B12 düzeyi entakapon (-) grupa göre anlamlı olarak yüksek saptandı. Kontrol grubunun folat düzeyi entakapon (-) gruba göre anlamlı olarak yüksek saptandı. Entakapon (-) ve entakapon (+) gruplar arasında homosistein, vitamin B12 ve folat düzeyleri açısından anlamlı fark saptanmadı.

Sonuç: Parkinson hastalarında levodopa tedavisi homosistein düzeyini etkilemektedir. Levodopa + entakapon kullanımının plazma homosistein düzeylerine etkisinin plazmanın bazal vitamin B12 ve folat düzeyleri ve genetik özelliklerle birlikte değerlendirilmesi gerektiği düşünülmüştür.

Anahtar Kelimeler: İdiyopatik Parkinson hastalığı, entakapon, homosistein

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Introduction

Idiopathic Parkinson's disease (IPD) is one of the most common, progressive neurodegenerative diseases with bradykinesia, tremor, rigidity, and postural instability (1,2,3). Studies have reported that the use of levodopa in IPD is associated with an increase in plasma homocysteine (Hcy) levels (4,5,6,7,8,9,10,11,12,13). Levodopa undergoes O-methylation by the enzyme called catechol-O-methyl transferase (COMT). This reaction uses S-adenosyl methionine (SAM) as the methyl donor, and S-adenosyl homocysteine (SAH) is formed by demethylation. SAH is converted into homocysteine (8). Hcy is converted back to methionine via methylene tetrahydrofolate reductase (MTHFR) and betaine homocysteine methyl transferase. MTHFR enzyme uses folate as a cofactor (14). Increased plasma Hcy levels are due to genetic (a gene mutation encoding the MTHFR enzyme) and acquired causes (such as severe metabolic disorders, vitamin B12, and folic acid deficiency) (15). Hcy is an independent risk factor for coronary artery disease and it has been stated that hyperhomocysteinemia (HHcy) may be a risk factor for atherothrombotic vascular disease (16,17). Entacapone, a COMT inhibitor, is widely used in the treatment of IPD to control motor complications (18). Some studies showed that entacapone might reduce plasma Hcy levels (19,20,21), but others have shown otherwise (22,23). The aim of this study was to determine plasma Hcy levels in patients with IPD and to investigate the effect of levodopa or levodopa + entacapone on plasma Hcy levels.

Materials and Methods

Seventy-two patients [38 (52.8%) men, 34 (47.2%) women] and 22 healthy individuals [4 (18.2%) men, 18 (81.8%) women] were included. Patients with severe metabolic disorders, vitamin use history or signs of secondary parkinsonism were excluded from the study.

In our study, clinical staging of IPD was evaluated using the Hoehn-Yahr scale and clinical severity was evaluated with the Unified Parkinson's Disease Rating Scale (UPDRS). Patients with IPD were divided into two groups according to the type of treatment received. Group 1 consisted of 22 healthy people (4 men, 18 women), group 2 comprised 22 patients (12 men, 10 women) treated with levodopa + entacapone (11 patients) and levodopa + entacapone + dopamine agonist (11 patients), and group 3 constituted 50 patients (26 men, 24 women) treated with levodopa + entacapone (29 patients) and levodopa + entacapone + dopamine agonist (21 patients).

Approval for the study was obtained from the University of Health Sciences Turkey, İstanbul Haseki Training and Research Hospital Ethics Committee (date: 23.06.2009, decision no: 14) and it was performed according to the Declaration of Helsinki.

Statistical Analysis

The SPSS, version 21.0 package program was used in the statistical analysis of the data.

Numerical variables are shown using mean ± standard deviation and median [minimum (min)-maximum (max)], and qualitative variables using numbers and percentages. As a result of the analysis using the Kolmogorov-Smirnov test, it was shown that variables except for age, folate, and entacapone dose did not show normal distribution. One-Way ANOVA was used to compare groups showing normal distribution, and Tukey's honestly sigificant difference test was used to determine the group that caused the difference. The Kruskal-Wallis test was used to compare groups that did not show normal distribution, and the Mann-Whitney U test was used to determine the group that caused the difference. Student's t-test was used for the comparison of two groups with normal distribution, and the Mann-Whitney U test was used for comparisons between two groups that did not show normal distribution. The chi-square test was used to compare qualitative data. In multivariate analysis, logistic regression analysis was performed by using possible factors determined in previous analyzes. The Hosmer-Lemeshow test was used for model adaptation.

Spearman's correlation coefficient was calculated for the analysis of the relationship between parameters. Results were evaluated at 95% confidence intervals and a significance level of $p<0.05$.

Results

Demographic data, and laboratory and clinical characteristics are given in Table 1.

There was no significant difference in terms of age between the groups (p=0.09). When the groups were compared in terms of the women/men ratio, it was found that the rate of women was higher in the control group (group 1-group 2; p=0.028) (group 1-group 3: p=0.015).

A statistically significant difference was found between the groups in terms of Hcy, vitamin B12, and folate levels (p=0.009, p=0.016, and p=0.032, respectively) (Table 1).

The Hcy level of the control group was found to be significantly lower than in the entacapone (-) and entacapone (+) groups (p=0.003 and p=0.034, respectively) (Figure 1a). The vitamin B12 level of the control group was found to be significantly higher than in the entacapone (-) group (p=0.003) (Figure 1b). The folate level of the control group was found to be significantly higher than in the entacapone (-) group (p=0.043) (Figure 1c).

There was no statistically significant difference between the entacapone (+) and entacapone (-) groups in terms of patients with HHcy according to the use of entacapone (p=0.615). In 31 patients with HHcy, vitamin B12 and folate levels were 223.81 (range, 92-475) pg/ml and 5.82 (range, 1.4-10.2) ng/ml, respectively, depending on the use of entacapone. Vitamin B12 and folate levels did not differ according to entacapone use (p=0.94 and p=0.22, respectively).

There was no statistically significant difference between entacapone (+) and entacapone (-) groups in terms of age of onset, duration of disease, levodopa dose, and duration of levodopa use (p=0.638, p=0.184, p=0.825, and p=0.196, respectively). There was no statistically significant difference in terms of the use of dopamine agonists between the entacapone (+) and entacapone (-) groups (p=0.710).

There was no statistically significant difference between the entacapone (+) and entacapone (-) groups in terms of disease severity (UPDRS total/motor/daily life activity/cognitive score, HY stage) (p=0.797, p=0.932, p=0.722, p=0.333, and p=0.432, respectively).

No statistically significant correlation was found between Hcy, vitamin B12, and folate levels and entacapone dose and duration of entacapone use in patients with IPD using entacapone ($p>0.05$) (Table 2).

Table 1. Demographic, laboratory and clinical characteristics of the groups				
	Group 1 (control) n=22	Group 2 entacapone (+) n=22	Group 3 entacapone (-) n=50	p
Age (years)	62.36±9.78	67.59±9.21	67.28±9.36	NS*
Women/men	18/4 (81.8%/18.2%)	10/12 (45.45%/55.45%)	24/26 (48%/52%)	0.017‡
Homocysteine (µmol/l)	10.22 (5.31-16.70)	14.17 (2.66-32.40)	16.36 (4.72-50.00)	0.009†
Vitamin B12 (pg/mL)	406.591 (191-847)	304.636 (83-739)	265.080 (98-880)	0.016†
Folate (ng/ml)	7.90±3.44	7.39±3.63	5.99±2.54	0.032*
Disease onset age (years)	-	63.5 (38-75)	62.5 (28-74)	NS§
Duration of illness (months)	-	60 (8-204)	72 (12-300)	NS§
Levodopa dose (mg)	-	400 (50-1500)	400 (100-1200)	NS§
Levodopa usage time (months)	-	42.5 (6-180)	48 (7-168)	NS§
Entacapone dose (mg)	-	800 (200-1400)	-	-
Entacapone usage time (months)	-	24 (6-63)	-	-
Dopa agonist (yes/no)	-	11/11 (34.4%/27.5%)	21/29 (65.6%/72.5%)	NS‡
UPDRS total score	-	29 (5-66)	26 (1-62)	NS§
UPDRS motor score	-	17.5 (2-36)	16.5 (0-51)	NS§
UPDRS DLA score	-	7 (0-26)	6 (0-20)	NS§
UPDRS cognitive score	-	2 (0-8)	2 (0-8)	NS§
HY stage	-	2 (1-4)	3 (1-4)	NS§

*One-Way ANOVA test, †Kruskall-Wallis test, ‡Chi-square test, §Mann-Whitney U test, DLA: Daily life activities, UPDRS: Unified Parkinson's Disease Rating Scale, HY: Hoehn Yahr, NS: Not significant

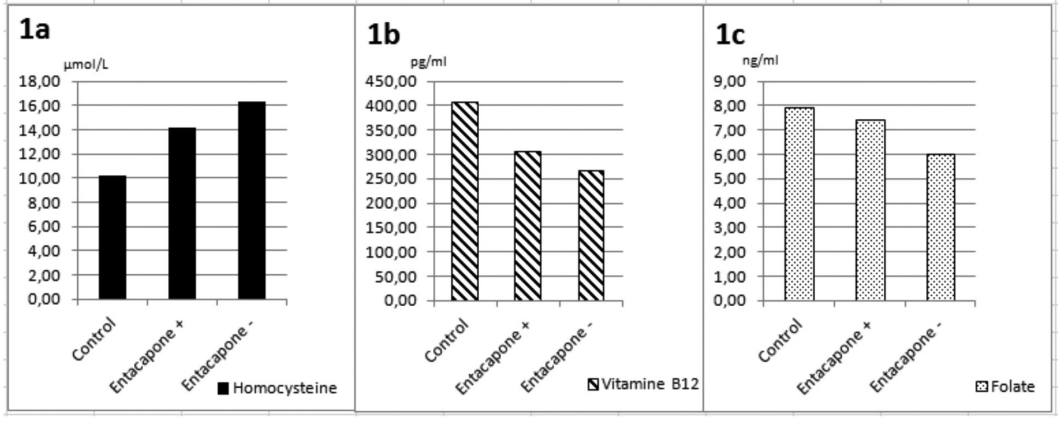

Figure 1. a) Control-entacapone (+) (p=0.034), control-entacapone (-) (p=0.003), entacapone (+)-entacapone (-) (p=0.517) (Mann-Whitney U test). b) Control-entacapone (+) (p=0.087), control-entacapone (-) (p=0.003), entacapone (+)-entacapone (-) (p=0.616) (Mann-Whitney U test). c) Control-entacapone (+) (p=0.845), control-entacapone (-) (p=0.043), entacapone (+)-entacapone (-) (p=0.180) (One-way ANOVA test-Post-hoc analysis)

Table 2. Relationship between entacapone dose and duration of use and biochemistry measurements				
	Entacapone dose		Duration of entacapon use	
	r	p	r	p
Homocysteine (µmol/l)	0.288	0.194	0.281	0.205
Vitamin B12 (pg/ml)	-0.233	0.297	-0.304	0.169
Folate (ng/ml)	0.169	0.452	0.055	0.809

r: Spearman's rho correlation coefficient

Table 3. Logistic regression analysis results		
Risk factors	**RR (95% CI)**	**p**
Sex	2.428 (0.932-6.329)	0.070
Low vitamin B12	0.995 (0.991-0.999)	0.010
Low folate	0.862 (0.720-1.032)	0.107
Use of entacapone	0.849 (0.276-2.605)	0.774

RR: Estimated relative risk and 95% confidence interval shown by odds ratio, CI: Confidence interval

Sex, low vitamin B12, low folate, entacapone use status were evaluated in terms of high Hcy levels using logistic regression analysis. Among the parameters examined, low vitamin B12 was found to be significant in terms of high Hcy ($p<0.05$) (Table 3).

Discussion

Our study showed that the use of entacapone in patients with IPD did not affect plasma Hcy levels. Studies have shown that adding entacapone to levodopa treatment in patients with IPD does not have a consistent effect on plasma Hcy levels in accordance with our results (10,2121,22,23,24). However, there are studies showing that plasma Hcy levels of those using levodopa + entacapone are found to be lower than in patients only receiving levodopa treatment (19,20,25). In our study, the mean plasma homocysteine level of the group using entacapone (min: 2.66 µmol/l, max: 32.4 µmol/l) was found to be lower than the mean plasma homocysteine level (min: 4.72 µmol/l, max: 50 µmol/l) of the group not using entacapone without reaching statistical significance. The low number of patients in the entacapone group was also thought to contribute to the result. In the group using entacapone, it was observed that the patient who had the highest Hcy level used entacapone at a dose of 600 mg/day for 12 months, and the patient who had the lowest Hcy level used entacapone at a dose of 800 mg/day for 12 months. Although the duration of use was the same, it suggested that this difference in Hcy levels might depend on the entacapone dose used, basal vitamin levels, and genetic characteristics. There was no significant difference between the mean plasma vitamin B12 and folate levels of the group using entacapone and the group not using entacapone. In addition, when patients with HHcy were evaluated between themselves, no difference was found in terms of vitamin B12 and folate levels.

Zesiewicz et al. (26) examined publications on the subject and published a comparison. In the study, it was suggested that the use of levodopa + entacapone in patients with IPD prevented levodopa-induced HHcy in the presence of folate and vitamin B12 deficiency (26). In a study conducted by Postuma et al. (24), it was found that levodopa increased plasma Hcy levels, and a decrease in plasma Hcy levels was found in the patient group that was supplemented with folate and vitamin B12 compared with placebo. In a study conducted by Nevrly et al. (27), it was suggested that the addition of entacapone to the treatment had no significant effect on plasma Hcy levels; however, HHcy occurred in those who received long-term levodopa treatment and that combined therapy in the form of levodopa + entacapone in the early stages of IPD could be protective from HHcy. Our study suggested that there might not be any difference in terms of Hcy levels between the entacapone (-) and entacapone (+) groups due to the lack of significant difference in terms of vitamin B12 and folate levels between the groups.

Sex is considered as an independent factor affecting Hcy levels in healthy individuals of all age groups (28). In the literature, it has been shown that men have higher Hcy concentrations than women, but the difference decreases after menopause (29). Similarly, studies revealing that serum vitamin B12 and folate levels are significantly higher in women compared with men in the healthy population show that sex factor is also important in terms of the levels of these vitamins (30,31). In addition, it has been reported that there are significant differences between male and female patients in terms of both Hcy levels and the functional areas (motor/cognitive) affected by Hcy levels in diseases in which HHcy is thought to be an important risk factor (32,33). In our study, the plasma Hcy levels of our patient group were found to be higher than in the control group. It has been suggested that HHcy in IPD may be associated with the use of levodopa and the C677T genotype of the MTHFR enzyme (34). Homocysteine is formed by the transformation of SAM, which is a methyl donor in the metabolic pathway of levodopa, to SAH (35). Studies have shown that there is an increase in plasma Hcy levels in IPD (6,13,34). These findings coincide with the idea that the elevation of Hcy observed in patients with IPD is mainly caused by the use of levodopa (19,31,36). The high number of female patients in the control group (even in the postmenopausal period) was one of the limitations of our study, which may make our results questionable. However, the logistic regression analysis performed in terms of high Hcy levels showed that sex was not effective.

Sex, low vitamin B12 level, low folate level, and entacapone usage status were evaluated in terms of high Hcy levels. In our study, among these parameters, only low vitamin B12 levels were found to be significant in terms of high Hcy levels. In other studies, it was observed that low folate levels were associated with higher Hcy levels (26).

HHcy damages the vascular structure by destroying vascular endothelial cells. In addition, inflammatory reactions and oxidative stress caused by HHcy may cause non-vascular neurotoxicity (37,38,39). HHcy is an independent risk factor for cerebrovascular diseases (40) and it can cause the progression of neurodegenerative diseases, including exacerbating IPD through apoptosis (41) and excitotoxic amino acid toxicity (39,40,41,42). In another study, HHcy seen in patients with IPD under levodopa treatment was shown to be associated with dementia and cognitive impairment (43). In the study conducted by Zhang et al. (44), HHcy was found to be associated with structural changes in the substansia nigra (SN) in IPD. It was shown that with the progression of IPD, the increased structural changes in the SN made motor symptoms more severe and treatment more difficult, and that these findings

were reported to be more prominent in patients with early-stage IPD and HHcy (44). Therefore, it is important to control plasma Hcy levels during IPH treatment (45).

In the advanced stages of PD, oral levodopa treatment has been shown to cause motor fluctuations due to its narrow therapeutic window (46). As the disease progresses, patients begin to require device-assisted therapies such as apomorphine pumps, deep brain stimulation, and levodopa/carbidopa intestinal gel (LCIG) (1). Studies have shown that LCIG is effective in the treatment of IPD (47,48,49,50,51). In addition, in a study comparing oral and LCIG treatments, it was found that Hcy levels were high in both groups and did not differ depending on the type of treatment, but a correlation was found between daily levodopa dose and Hcy levels in the LCIG treatment group (52).

In our study, no significant relationship was found between Hcy leveld and entacapone use status, dose, and duration of use. In the recent study of Corvol et al. (53), the COMT Val158Met polymorphism was found to be effective in the response to entacapone treatment. It was shown that entacapone treatment in patients with IPD with the COMTHH genotype increased the effect on levodopa pharmacokinetics and pharmacodynamics. It was found that entacapone made more COMT inhibition in patients with the COMTHH genotype compared with patients with the COMTLL genotype (53). When a general evaluation is made in light of this study, the fact that Hcy levels do not decrease in some patients with entacapone treatment can be explained by their COMTLL genotype. For this, COMT Val158Met polymorphism screening should be performed and the effect of entacapone on plasma Hcy levels should be investigated in large series.

It has been reported that administration of levodopa + entacapone + carbidopa provides stabilization in levodopa response, improvement in functional capacity, and increase in daily activities and quality of life in patients with IPD (53). In our study, there was no significant difference between UPDRS scores and Hoehn-Yahr stage according to the use of entacapone.

In addition, there was no significant relationship between the duration and dose of entacapone use and Hcy, folate, and vitamin B12 levels. Although Zesiewicz et al. (26) suggested that the duration of entacapone use affected plasma Hcy levels, it was stated that more studies were needed.

Study Limitations

The limitations of our study were its retrospective nature, the small number of patients, the high number of female patients in the control group, the lack of baseline vitamin levels, and not searching for genetic polymorphisms.

Conclusion

Levodopa treatment affects Hcy levels in patients with PID. It was thought that the effect of levodopa + entacapone use on plasma Hcy levels should be evaluated together with basal vitamin B12 and folate levels, and the COMT Val158Met polymorphism.

Ethics

Ethics Committee Approval: University of Health Sciences Turkey, İstanbul Haseki Training and Research Hospital Ethics Committee (date: 23.06.2009, decision no: 14) and it was performed according to the Declaration of Helsinki.

Informed Consent: Since the study was in the form of a retrospective file scan, patient consent could not be obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: G.A., F.Ö., Design: G.A., F.Ö., Ö.Ç., Data Collection or Processing: G.A., M.B., G.G., Analysis or Interpretation: G.A., F.Ö., B.P.B., Literature Search: G.A., F.Ö., Writing: G.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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