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The catechol-O-methyltransferase and monoamine oxidase B polymorphisms and levodopa therapy in the Iranian patients with sporadic Parkinson's disease

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Parkinson's disease (PD) patients vary widely in their response to levodopa treatment, and this may be partially genetic in origin. Recent studies suggest that catechol-O-methyltransferase (COMT), G1947A and monoamine oxidase B (MAOB), A644G polymorphisms might influence the risk and treatment of PD. Herein, we aimed to test the possible influence of MAOB and COMT genetic polymorphisms on the effective daily dose of levodopa administered in the fifth year of treatment. We also examined the effect of COMT and MAOB haplotypes on levodopa therapy outcome. There were 31 females and 72 males of Iranian origin diagnosed with sporadic PD included into the study. The patients were divided into two groups. Group 1: patients received daily doses of levodopa below 500 mg in the fifth year of treatment. Group 2: those patients receiving daily doses exceeding 500 mg in the fifth year of treatment. MAOB and COMT polymorphism genotyping was performed by using PCR-based restriction fragment length polymorphism (RFLP) analyses. Our data show that the first group suffered less frequently from dyskinesia than patients from the second group. No statistically significant differences were found in allele frequencies and genotype distributions of the studied genes between two groups. In addition, the incidence of the specific haplotypes between the two groups did not show any difference. The present data suggest that pharmacokinetic or pharmacodynamic factors other than the investigated genetic variants of the MAOB and COMT enzymes seem to determine the response to levodopa in the Iranian PD patients.

Key words: COMT, dyskinesia, Iranian, levodopa, MAOB, Parkinson's disease, polymorphism

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease of unknown etiology that predominantly affects the elderly (Jankovic et al. 2000). Interaction of both environmental factors and genetics has been suggested to be involved in destroying the pigmented cells of the cerebral substantia nigra (Fahn and Ciohen 1992) and development of the disease. The candidate PD pathogenic genes include those that are linked to dopamine synthesis, transport and degradation, detoxification of xenobiotics and other toxins in dopaminergic neurons. Levodopa in combination with a dopa-decarboxylase (DDC) inhibitor remains the most effective symptomatic treatment for PD (Rascol et al. 2000, Jankovic 2006). A number of studies suggested that functional polymorphisms might affect the phenomenon of 'levodopa-nonresponse' and levodopa-induced motor fluctuations, mainly levodopa-induced dyskinesia (Gilgun-Sherki et al. 2004, de Lau et al. 2012). Recent investigations suggest that polymorphism in catechol-O-methyltransferase (COMT) and monoamine oxidase B (MAOB) might influence the risk and treatment of PD (Goudreau et al. 2002, Bialecka et al. 2007, 2008). COMT inactivates neurotransmitters, hormones, potentially toxic metabolites, and xenobiotics contain-

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ing a catechol moiety by enzymatic methylation (Kopin 1985, Smit et al. 1990, Mannisto et al. 1992). In the presence of a peripheral decarboxilase inhibitor, this enzyme is responsible for peripheral levodopa degradation to 3-O-methyldopa (3-OMD). Clinical observations on effects of PD pharmacotherapy associated with administration of COMT inhibitors prompted genetic studies on COMT polymorphism. The COMT gene in humans is localized to chromosome 22, band q11.2. The Val158Met SNP within COMT (rs4680) encodes a Valine→Methionine substitution at protein residue 158 of the membrane-bound COMT isoform that predominates in brain tissue. This substitution is linked to low COMT enzyme activity and is designated the L (low activity) allele, in contrast to the H (high activity) allele (Hosak 2007). In the individuals with the L allele, the COMT protein is thermolabile. Differences in COMT activity may determine individual variations in the therapeutic response to levodopa (Rivera-Calimlim and Reilly 1984, Espinoza et al. 2012) and affect the individual susceptibility to PD. The COMT L/L variant is found in 30% of Caucasian and 10% of Asian populations. Published reports indicated higher risk for idiopathic PD in COMTL/L homozygotes (Kunugi et al. 1997). On the other hand, type B MAO is potentially involved in the pathogenesis of PD because of its role in catabolising dopamine, with the resultant production of reactive oxygen species, and in activating exogenous neurotoxins, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, a neurotoxin that is deleterious to the substantia nigra cells (Fahn and Cohen 1992). Patients with PD are reported to have higher platelet MAOB activity than control individuals (Steventon et al. 1989). Furthermore, inhibition of MAOB activity in the brains of cigarette smokers has been suggested to have a protective effect against the development of PD (Checkoway et al. 1998). Thus, there is an increasing body of evidence that MAOB may play an important role in the pathogenesis of PD. The gene encoding MAO-B is located on the X-chromosome (Xp11.4-p11.23) (Hsu et al. 1989) and contains an A644G (rs1799836) SNP in intron 13 (Kurth et al. 1993). Although this A→G substitution does not change protein sequence, it was associated with varying enzyme activity: *in vitro* and *in vivo*, it has been shown that MAOB activity is higher for carriers of allele G intron 13 as compared to allele A (Garpenstrand et al. 2000, Costa-Mallen et al. 2005). However, in the human brain the A-allele has been associated with higher messenger Ribonucleic Acid (mRNA) levels of MAOB (Balciuniene et al. 2002).

An important clinical problem in the long-term treatment of patients with Parkinson's disease (PD) is the occurrence of adverse effects induced by drugs. In patients who are on levodopa therapy and have had PD symptoms for 5 years, there are often complications of development of abnormal involuntary movements (dyskinesia), psychotic symptoms, "on-off" and "wearing-off" phenomena (motor fluctuation) (Miyawaki et al. 1997, Ahlskog and Muenter 2001, Olanow et al. 2001). Early studies showed that the prevalence of motor fluctuations and dyskinesia were 41–55% after 5–6 years of levodopa treatment (Sweet and McDowell 1975, Hely et al. 1994), while a double-blind, prospective study reported a prevalence of approximately 20% (Block et al. 1997). High levodopa doses and prolonged treatment increase the risk of these complications. One of the postulated approaches is the use of the lowest possible doses of levodopa that allow control of PD symptoms, or initiation of the disease treatment with agonists of dopamine receptors (Kitamura et al. 2002). When levodopa is given orally, concentrations in the plasma of PD patients vary greatly among individuals (Deleu et al. 2002) due to pathological and physiological factors, as well as heredity factors. The genetic factors may involve in the occurrence of the adverse effects of chronic levodopa therapy in PD patients (Goetz et al. 2001, Wang et al. 2001, Kaiser et al. 2003, Bialecka et al. 2008). Since individuals with the G/G genotype have three- to fourfold higher activity of the COMT enzyme than those with the A/A genotype (Lachman et al. 1996, Weinshilboum et al. 1999), it has been hypothesized that COMT polymorphism might affect levodopa metabolism. Only few studies have investigated the influence of COMT and MAOB polymorphisms on the effect of levodopa therapy. A clinical study on a group of polish PD patients revealed that patients carrying the MAOB genotype A may benefit from more efficient and safer levodopa therapy. Moreover, the frequency of COMT L/L homozygotes was higher in the group treated with low doses of levodopa (Bialecka et al. 2004). However, the results were not statistically significant.

In the current study, we have investigated the possible association of COMT as well as MAOB polymorphisms with the effective daily dose of levodopa in the fifth year of treatment in the Iranian population. We

have also focused on the influence of specific COMT and MAOB haplotypes on levodopa therapy outcome.

METHODS

A non-interventional study was performed with 103 (men and women) unrelated patients of Iranian descent. The patients were all recruited from the Movement Disorders Clinic at the Hazrat Rasool Hospital in Tehran, Iran. Diagnosis of idiopathic PD was based on clinical symptoms according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria (Danil and Lees 1993) and if at least two of the four main signs of the disease, i.e. tremor at rest, rigidity, bradykinesia and postural reflex impairment, were observed. All patients were examined during the "on" state for their baseline motor function and the activities of daily living using the Unified Parkinson's Disease Rating Scale (UPDRS) in the phase of good motor activity. The severity of the disease was evaluated using the Hoehen-Yahr (H-Y) score (Hoehn and Yahr 1967). Dyskinesia was defined as drug induced hyperkinetic or dystonic movements or postures or both (Hagell and Widner 1999). Informed consent was obtained from the PD patients, according to a protocol approved by the Human Subjects Research Ethics Committee of Pasteur Institute of Iran, project No. 435.

The patients were divided into two groups. The first group consisted of 44 patients treated with daily dose of levodopa below 500 mg/24 h in the fifth year of therapy. The second group included 59 patients treated with doses of levodopa more than 500 mg/day in the fifth year of treatment. All the patients eligible for the study were taking levodopa with decarboxylase inhibitor. Eleven patients (25%) from the first group and nine patients (15.2%) from the second group were administered an additional dopamine receptor agonist (pramipexole or ropinirole).

Genomic DNA was extracted from blood samples, using the NucleoSpin® blood XL kit (Macherey-Nagel, Germany). COMT and MAOB genotypes were determined using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay, as originally described by Kunugi and coauthors (1997) and Sun and colleagues (2004). The 217 bp region of the COMT gene, incuding exon 4, which contains the polymorphism site, was amplified with the following set of primers: 5-TCGTGGACGC-CGTGATTCAGG-3 and the reverse primer, 5-AGGTCTGACAACGGGTCAGGC-3 (Yoritaka et al. 1997) under conditions previously described (Bialecka et al. 2004). The PCR product was digested with the restriction enzyme *Nla* III (Fermentase, Canada), which cleaves the Met-108 allele (COMTL – low activity) but not the Val-108 allele (COMTH-high activity), in addition to a constant cleavage site. Homozygotes for COMTH variant give fragments of 136 and 81-bp, heterozygotes fragments of 40, 81, 96 and 136-bp and homozygotes for COMTL fragments of 40, 81 and 96-bp (Wu et al. 2002).

In the MAOB study, a 232 bp DNA fragment of the MAOB containing the intron 13 polymorphism was amplified. The forward primer 5-GGAAC-CTCTTATACCACAGG-3 and reverse primer 5-GACTGCCAGATTTCATCCTC-3 were used for partial MAOB DNA fragment amplification (Reilly et al. 1980). The PCR mixture in the MAOB study contained the same reagents used in COMT amplification and under previously described conditions (Bialecka et al. 2004). To determine the MAOB polymorphism, the PCR amplified DNA product was digested with the restriction enzyme *Tsp* 45I. MAOB allele 1 (containing A and therefore the *Tsp* 45I restriction site) was detected as two bands of 146 and 86 bp, whereas allele 2 (containing G and no *Tsp* 45I restriction site) was detected as a single 232-bp band (Wu et al. 2002).

The characteristics of patients, i.e. age, mean duration of PD, levodopa daily dose administered and occurrence of dyskinesia were compared using unpaired Student *t*-test. Chi-square and odds ratio were used to compare either allelic frequencies or the genotype frequencies of MAOB or COMT in the first and second groups. When more than 20% of the cell numbers, or when the expected number of cases was less than 1.0 in a cell, Fisher's exact test was performed (SPSS, version 11.5). Since the MAOB gene is located on the X chromosome, the MAOB genotype was assessed separately in men and women.

RESULTS

One hundred and three patients with PD were included (72 men and 31 women) in the study. The

Table I

Clinical and demographic characteristics of our samples

Feature	Group 1 (n=44) Range Mean (± SD)	Group 2 (n=59) Range Mean (± SD)	P–value
Age	36–83 58.59 ± 12.3	40–77 56.62±8.6	0.34
Age at onset	30–81 50.63 ± 13.2	22–72 47.79 ± 10.8	0.234
Duration of the disease (years)	5.20 8.1 ± 3.7	5–20 9.3 ± 4.2	0.148
L–dopa dosage per 24 h at the fifth year of therapy (mg)	150–500 381.4 ± 103.9	562–11250 1183.45 ± 1421.3	0.001
UPDRS	8–68 29.5 ± 15.5	3–84 27.62 ± 15.95	0.552
H–Y	1–5 2.41 ± 0.78	1–5 2.41 ± 0.72	0.98
Fluctuation [n (%)]	12 (27.3%)	29 (49.2%)	0.025

Data are presented as mean (± SD)

first group consisted of 44 patients, aged 58.59 ± 12.3 years, treated with ≤500 mg/ 24 h of levodopa, and the second group included 59 patients, aged 56.6 ± 8.6 years, with ≥ 500 mg/ 24 h of levodopa in the fifth year of therapy. The mean duration time of the disease was 8.1 ± 3.7 years in the first group and 9.3 ± 4.2 years in the second group (P>0.05). The patients from the first and second groups were administered an average of 381.4 ± 103.9 and 1183 ± 1421.3 mg/24 h of levodopa in the fifth year of therapy (P<0.001), respectively.

Dyskinesia was diagnosed in the fifth year of levodopa therapy in twelve of 44 patients from the first group (27.3%). In the second group of 59 patients motor disturbances were found in 29 patients (49.2%) (P<0.05). The UPDRS and H-Y score differences between the two groups were not statistically significant (Table I).

Table II shows the allelic and genotype frequencies for COMT polymorphism. The allelic frequency of COMTL (Met) was 54.5% in the first group and 57.6% in the second group with no statistically significant value. There were also no significant differences between the two groups in the frequencies of either the homozygous (H/H or L/L) or heterozygous (H/L) genotypes. However, there was an insignificant higher incidence of LL genotype in the second group treated with high doses of levodopa when compared with the first group.

The distribution of MAOB genes in displayed in Table III. No statistically significant differences were found in total A and G allele frequencies of the studied gene in the first (77% and 23%) and second (79.5% and 20.5%) group. A higher frequency of the MAOB AG genotype was seen in patients treated with doses of levodopa below 500 mg/day in the fifth year of treatment. Since MAOB gene is located on chromosome X, both sexes were also analysed separately. We did not find any difference in MAOB A and G allele frequency distribution between men and women from the first and second group (P>0.05) (Table III).

Table IV shows the haplotypes of MAOB and COMT in both groups of the study. No significant differences were found in the incidence of the specific haplotypes of the studied genes between the two groups. However, the A, AA,LL haplotype predominated in the group of patients treated with

Table II

COMT genotype frequencies					
Genotype	Group 1 (*n*=44)	Group2 (*n*=59)	χ^2	*P*–value	OR (95% CI)
Total genotype					
HH	9 (20.5%)	11 (18.6%)	0.053	0.818	1.12 (0.42–2.99)
HL	22 (50%)	28 (47.5%)	0.065	0.798	1.10 (0.50–2.41)
LL	13 (20.5%)	20 (33.9%)	0.219	0.640	0.81 (0.35–1.89)
Women					
HH	4 (23.5%)	3 (21.4%)	0.019	0.889	0.12 (0.20–6.16)
HL	7 (41.2%)	5 (35.7%)	0.097	0.756	1.26 (0.29–5.41)
LL	6 (42.9%)	6 (42.9%)	0.185	0.667	0.72 (0.17–3.1)
Men					
HH	5 (18.5%)	8 (17.8%)	0.006	0.937	1.05 (0.30–3.6)
HL	15 (55.6%)	23 (51.1%)	0.134	0.715	1.19 (0.45–3.11)
LL	7 (25.9%)	14 (31.1%)	0.22	0.639	0.77 (0.26–2.25)
Total alleles					
H	40 (45.5%)	50 (42.4%)	0.195	0.659	1.07 (0.78–1.46)
L	48 (54.5%)	68 (57.6%)			0.94 (0.74–1.21)
Women					
H	15 (44.1%)	11 (39.3%)	0.147	0.701	1.12 (0.61–2.03)
L	19 (55.9%)	17 (60.7%)			0.92 (0.60–1.4)
Men					
H	25 (46.3%)	41 (44.6%)	0.041	0.839	1.03 (0.72–1.49)
L	29 (53.7%)	51 (55.4%)			0.96 (0.71–1.31)

Figures in parentheses indicate percentage or 95% CIs

higher daily doses of levodopa when compared with the same haplotype in the group of patients treated with lower daily doses of levodopa.

Table V shows the distribution of COMT and MAOB genotypes in patients with dyskinesia in both groups of the study. No significant differences were observed between the two groups.

DISCUSSION

Identification of the genetic factors associated with adverse effects of chronic levodopa in patients with PD is important to identify subjects at risk and prevent occurrence of the adverse effects. Several reports have been published to evaluate the association between

Table III

MAOB genotype frequency					
Genotype	Group 1 (*n*=44)	Group2 (*n*=59)	χ^2	*P*–value	OR (95% CI)
A, AA	30 (68.2%)	45 (76.3)	0.833	0.361	0.667 (0.27–1.59)
AG	9 (20.5%)	7 (11.9%)	1.417	0.234	1.910 (0.65–5.60)
G, GG	5 (11.4%)	7 (11.9%)	0.006	0.938	0.952 (0.28–3.22)
Women					
AA	8 (47.1%)	6 (42.9%)	0.055	0.815	1.185 (0.28–4.92)
AG	9 (59.2%)	7 (50%)	0.027	0.87	1.125 (0.27–4.63)
GG	0	1 (7.1%)	1.255	0.263	Undefined
Men					
A	22 (81.5%)	39 (86.7%)	0.351	0.554	1.47 (0.40–5.40)
G	5 (18.5%)	6 (13.3%)			
Total alleles					
A	47 (77%)	58 (79.5%)	0.113	0.737	1.152 (0.50–2.62)
G	14 (23%)	15 (20.5%)			
Women					
A	25 (73.5%)	19 (67.9%)	0.24	0.624	0.76 (0.25–0.41)
G	9 (26.5%)	9 (32.1%)			

Figures in parentheses indicate percentage or 95% CIs

polymorphisms of MAOB and COMT enzymes and the incidence of PD. To date, there are only few studies indicating the effect of MAOB and COMT polymorphism on effective daily dose of levodopa in the PD patients (Reilly et al. 1980, Rivera-Calimlim and Reilly 1984, Lee et al. 2001, Bialecka et al. 2004). It has been shown that controlling motor symptoms gradually diminishes after 2–5 years (Marsden and Parkes 1977), about 70% of patients ultimately develop a variety of motor manifestations, including dyskinesia in response to the treatment (Fahn and Cohen 1992). Peak-dose dyskinesia occurs before the fifth year of treatment (Nutt 1990, Cardoso and Jankovic 1997) in an estimated 30–80% of chronically treated PD patients (Nutt 1990, Peppe et al. 1993, Blanchet et al. 1996). The mechanism(s) underlying the fluctuations in response to levodopa are only partially understood. The polymorphisms in genes may at least in part affect pharmacodynamic and pharmacokinetic properties.

Our study failed to find a significant relationship between COMT and MAOB genotypes and occurrence of dyskinesia. However, a higher incidence of motor fluctuation in the second group with higher daily doses of levodopa in the fifth year of therapy was seen. This is in accordance with the study of Bialecka and coworkers (2004) and may be associated with significantly higher doses of levodopa administered. Lee and others (2008) showed that 3-OMD accumulation, the major metabolite of levodopa, from long term levodopa treatment might play a role in the drug-induced side effects including dyskinesia, on-off and

Table IV

MAOB and COMT haplotype frequencies

Haplotype	Group 1 (*n*=44)	Group2 (*n*=59)	χ^2	*P*–value	OR (95% CI)
A, AA,HL	15 (34.1%)	22 (37.3%)	0.112	0.738	0.87 (0.38–1.96)
A, AA,HH	7 (15.9%)	7 (11.9%)	0.351	0.554	1.40 (0.45–4.34)
A, AA,LL	8 (18.2%)	16 (27.1%)	1.126	0.289	0.59 (0.22–1.55)
AG,HH	1 (2.3%)	2 (3.4%)	0.111	0.739	0.66 (0.05–7.55)
AG,HL	5 (11.4%)	2 (3.4%)	2.53	0.112	3.65 (0.67–19.7)
AG,LL	3 (6.8%)	3 (5.1%)	0.138	0.71	1.36 (0.26–7.11)
G,GG,HH	1 (2.3%)	2 (3.4%)	0.11	0.739	0.663 (0.05–7.55)
G,GG,HL	2 (4.5%)	4 (6.8%)	0.229	0.632	0.65 (0.11–3.74)
G,GG,LL	2 (4.5%)	1 (1.7%)	0.724	0.395	2.76 (0.24–31.46)

Figures in parentheses indicate percentage or 95% CIs

wearing off symptoms. A previous study in 121 Japanese PD patients with homozygosity for the low-activity allele showed a tendency to exhibit the 'wearing-off' phenomenon compared with controls which was not significant after Bomferroni's correction (Watanabe et al. 2003). Furthermore, another study by Contin and colleagues (2005) failed to find an association between COMT gene polymorphism and the incidence of Levodopa induced dyskinesia. However, Routtinen and others (1998) suggested that in patients with COMTL/L genotype, administration of levodopa and entacapon developed less dyskinetic symptoms. Considering the relation of dopaminergic system(s) with dyskinesia (Berthet and Bezard 2009), no association of MAOB polymorphism with dyskinesia has been reported so far. Our results also indicate that COMT and MAOB gene polymorphism might not have a great clinical significance as a predictor for the occurrence of dyskinesia.

Our present data did not show any significant differences between COMT genotype frequencies in the first and second groups. However, the L/L genotype frequency seems to be higher in the second group. In contrary, Bialecka and coworkers (2004) reported an insignificant higher incidence of COMT L/L genotype in the group which received lower doses of levodopa. Another study by Chong and colleagues (2000) found no significant difference in daily intake of levodopa and genotype during the tolcapone therapy. In a study on 73 Korean PD patients, the response to a single oral dose of levodopa (250 mg/25 mg carbidopa) was analyzed by the motor part of the UPDRS rating scale (Lee et al. 2001). The results indicated that COMT genotype does not affect the duration or magnitude of response to a single dose in PD. Furthermore, the potential effect of COMT genetic polymorphism on the pharmacokinetics and pharmacodynamics of oral Levodopa (100 mg)/benserazide (25 mg) has been investigated by simultaneous serial measurements of plasma levodopa concentrations, finger-tapping motor effects, and dyskinesia ratings at fixed times, up to 4 hours after dosing. Similarly, no significant differences emerged in the levodopa therapeutic and dyskinetic response among the three COMT genotypes (Contin et al. 2005). In contrary, there are two other reports indicating that patients with the higher erythrocyte COMT activities appear to have more adverse effect and less favourable clinical response (Reilly et al. 1980, Rivera-Calimlim and Reilly 1984). These two studies examined relatively small numbers of patients and were not able to examine different COMT genotype and allele frequencies to evaluate inherited diversities in COMT. On the other hand, there is only one study by Bialecka and coauthors (2004) considering the role of MAOB polymorphism which the results obtained, are similar to ours. Since, MAOB gene is

Table V

MAOB and COMT genotype frequencies in patients with dyskinesia

Genotype	Group 1 (*n*=44)	Group2 (*n*=59)	χ^2	*P*–value	OR (95% CI)
COMT					
HH	4 (33.3%)	8 (27.6%)	0.135	0.49	1.31 (0.30–5.59)
HL	3 (25%)	11 (37.9%)	0.631	0.33	0.54 (0.12–2.46)
LL	5 (41.7%)	10 (34.5%)	0.189	0.46	1.35 (0.34–5.39)
MAOB					
A, AA	2 (16.7%)	3 (10.3%)	0.317	0.46	1.73 (0.25–11.96)
AG	8 (66.7%)	24 (82.6%)	1.283	0.23	0.41 (0.08–1.94)
G, GG	2 (16.7%)	2 (6.9%)	0.920	0.33	2.70 (0.33–21.8)

Figures in parentheses indicate percentage or 95% CIs

located on the X chromosome, we analysed the genotype and allele frequencies separately in men and women. We failed to identify a significant effect of the A644G MAOB polymorphism on the daily dose of levodopa between the first and second group. However, the frequency of the A allele was higher in the second group. There were also no differences in allele and genotype frequencies in the both men and women from the first and second groups. In both studies patients with MAOB allele A prevailed in the studied groups.

Our data shows an insignificant prevalence of COMTL/L and MAOB A allele haplotype in the patients from the second group with higher daily doses of levodopa. This may lead to an increased cumulative load of the drug which may then accelerate the neurodegenerative process and increased incidence of dyskinesia in the second group.

It could be expected that patients with AA genotype, coding for the low activity of COMT, would show a larger magnitude of response to those than with other genotypes. However, in the present study, the patients with PD showed no direct relationship between the response to daily dose and the genotypes determining COMT activity. In a study with treated PD patients, the clinical effect of a COMT inhibitor, tolcapone, did not differ between patients with different COMT genotypes (Chong et al. 2000). However, Corvol and colleagues (2011) showed that the COMTH/H genotype in PD patients enhances the effect of entacapone on the pharmacodynamics and pharmacokinetics of levodopa.

It has been also shown that the presence of MAOB G allele is related to the high activity of the enzyme, leading to a reduction in levodopa and consequently in dopamine level in the brain (Gilgun-Sherki et al. 2004). Bialecka and others (2004) suggested that the insignificant higher incidence of allele A in the group of patients with lower daily dose of levodopa, limits the rate of degradation. However, in our study MAOB genotype might not be a determinant factor in predicting the daily dose of levodopa.

We could not find differences in COMT and MAOB genotype frequencies between the first and second groups. Moreover, there was no difference in the allele frequency of each polymorphism. Furthermore, additive effects of the COMT and MAOB genes were not observed. Our results provide no evidence of association between the daily dose of levodopa and these functional polymorphisms. This suggests that functional genetic variation in the COMT and MAOB genes, alone or in combination, may not play a major role in the pharmacokinetic and pharmacodynamic of levodopa. Possible reasons why the difference in metabolism rate among the three genotypes was less significant than anticipated include the following. Although levodopa is mainly

biotransformed by aromatic amino-acid decarboxylase (AADC) and COMT, other variant forms of the COMT enzyme or metabolic pathways involving other enzymes, such as tyrosine aminotransferase, may affect the duration and amount of response to levodopa (Nutt 1992, Deleu et al. 2002). In addition, it has been reported that doses of levodopa should be considered in relation to factors such as body weight, gastric emptying rate, age of patients, long-term administration and different stages of the disease (Lin et al. 2009). Other factors including polymorphism in the genes related to dopamine metabolism and transport like DRD1 and DRD2 could be implicated in the response to levodopa after long term use (Gilgun-Sherki et al. 2004). Our results also confirm the previously reported effects of the COMT and MAOB polymorphism on pharmacodynamics and pharmacokinetics of levodopa and remains to be fully explained.

The present study, however, does have some limitations. First, although our results were negative, the findings may be restricted to the Iranian population as there may be ethnic differences. Moreover, our sample size may be small and may not be powerful enough, especially for the analysis of a combination of genotypes, as the cells in the constructed contingency tables of the combinations become many and each cell thus has relatively small counts. Thus, larger sample sizes are required to detect smaller effects, probably of minor clinical significance.

CONCLUSION

The present data suggest that pharmacokinetic or pharmacodynamic factors other than the investigated genetic variants of the MAOB and COMT enzymes seem to determine the response to levodopa in the Iranian PD patients.

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