Research Article

Potential protective role of ACE-inhibitors and AT1 receptor blockers against levodopa-induced dyskinesias: a retrospective case-control study

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Abstract

Growing evidence has highlighted that angiotensin-converting enzyme (ACE)-inhibitors (ACEi)/AT1 receptor blockers (ARBs) may influence the complex interplay between dopamine and the renin-angiotensin system in the nigrostriatal pathway, thus affecting the development of levodopa-induced dyskinesia in Parkinson's disease (PD). In the present study, we analyzed whether the use of this class of medication was associated with a reduced occurrence of levodopa-induced dyskinesia, using electronically-stored information of idiopathic PD patients enrolled at Novara University Hospital "Maggiore della Carità". We conducted a retrospective case-control study identifying PD patients with dyskinesias (PwD; *n* = 47) as cases. For each PwD we selected a non-dyskinetic control (NoD), nearly perfectly matched according to sex, Unified Parkinson's Disease Rating Scale (UPDRS) part III score, and duration of antiparkinsonian treatment. Binary logistic regression was used to evaluate whether dyskinesias were associated with ACEi/ARBs use. Ninety-four PD patients were included, aged 72.18 ± 9 years, with an average disease duration of 10.20 ± 4.8 years and 9.04 ± 4.9 years of antiparkinsonian treatment. The mean UPDRS part III score was 18.87 ± 7.6 and the median HY stage was 2. In the NoD group, 25 (53.2%) were users and 22 (46.8%) non-users of ACEi/ARBs. Conversely, in the PwD group, 11 (23.4%) were users and 36 non-users (76.6%) of this drug class (Pearson chi-square = 8.824, *P* = 0.003). Concerning general medication, there were no other statistically significant differences between groups. After controlling for tremor dominant phenotype, levodopa equivalent daily dose, HY 3-4, and disease duration, ACEi/ARBs use was a significant predictor of a lower occurrence of dyskinesia (OR = 0.226, 95% CI: 0.080–0.636, *P* = 0.005). Therefore, our study suggests that ACEi/ARBs may reduce levodopa-induced dyskinesia occurrence and, thanks to good tolerability and easy management, represent a feasible choice when dealing with the treatment of hypertension in PD patients. The study was approved by the Ethics Committee of Novara University Hospital "Maggiore della Carità" (CE 65/16) on July 27, 2016.

Key Words: angiotensin-converting enzyme inhibitors; AT1 receptor blockers; dyskinesias; hypertension; levodopa; motor complications; neuroinflammation; Parkinson's disease; renin-angiotensin system

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Introduction

Levodopa represents the gold standard treatment in Parkinson's disease (PD) patients. However, after a variable time on dopaminergic therapy, patients may develop motor complications, such as motor fluctuations and levodopa-induced dyskinesias (LIDs) (Kelly et al., 2019).

Since this process may also be influenced by an inflammatory response and oxidative stress in the basal ganglia (Rocha et al., 2018; Jiang et al., 2019), identification of underlying mechanisms can be crucial for the long-term treatment of PD patients. Interestingly, the renin-angiotensin system (RAS) seems linked to cerebral blood flow and neuroprotection, and its influence has been studied in neurodegenerative conditions (Ciobica et al., 2009; Messiha et al., 2020). Angiotensin II (AII), the most important effector of the RAS, is generated by the action of two enzymes (renin and angiotensin-converting enzyme [ACE]) on the precursor angiotensinogen. The activity of AII is mediated by two main cell receptors: AII type 1 and type 2 receptors (AT1 and AT2), and previous studies have detected the presence of AT1 receptors in the substantia nigra (SN) pars compacta and presynaptically on the terminals of dopaminergic neurons in the striatum (Labandeira-Garcia et al., 2013). Sathiya and colleagues demonstrated that

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telmisartan before and after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) lesion was able to reduce cell loss and motor impairment with concurrent reduction of a-synuclein and increase of brain-derived neurotrophic factor and glial cell-derived neurotrophic factor (Sathiya et al., 2013). Moreover, the co-administration of l-dopa and candesartan in the 6-hydroxydopamine rat model determined a reduction of LIDs, and animals treated with both candesartan and l-dopa displayed significantly lower striatal levels of vascular endothelial growth factor and interleukin (IL)-1β than those treated with l-dopa alone (Muñoz et al., 2014). Evidence of protective effects in animal models has also been found for ACE inhibitors (ACEi): the administration of perindopril significantly attenuated MPTP-induced substantia nigra and striatal damage; conversely, amlodipine showed no significant effects on striatal dopamine depletion after MPTP treatment (Kurosaki et al., 2004). In another study, rats treated with captopril and 6-hydroxydopamine showed significantly less reduction in the number of dopaminergic neurons in the substantia nigra and the density of striatal dopaminergic terminals than 6-hydroxydopamine-lesioned rats not treated with captopril (Lopez-Real et al., 2005).

Alterations of the RAS pathway have also been proved in human studies: Pessoa Rocha et al. (2016) found that PD patients exhibit lower plasma levels of angiotensin I, II, and 1–7 than control individuals, and lower circulating levels of angiotensins are associated with increased severity of depressive symptoms. Furthermore, in a double-blind placebo-controlled crossover pilot study, Reardon et al. (2000) found that, after a 4-week treatment with perindopril, there was a reduction in "on phase" peak dyskinesia in seven PD patients.

Hypertension represents a common health issue and may be a risk factor for PD development as well (Hou et al., 2018). Prompt management of this condition is recommended, and among currently acknowledged treatments, ACEi/AT1 receptor blockers (ARBs) may also be beneficial against dyskinesias. Therefore, this study aimed to explore the association between LIDs and the use of this class of medication, thus determining whether prescription patterns of ACEi/ARBs may affect the development of LIDs in PD patients.

Materials and Methods

Study subjects

In this retrospective case-control study, electronically-stored information of patients with a first diagnosis of idiopathic PD (Postuma et al., 2015) established between 1994 and 2016 and with the last follow-up visit at our center for movement disorders between January 1, 2019 and January 31, 2020 was analyzed. The inclusion criteria for this study were the availability of complete clinical and medication data and levodopa use. Among exclusion criteria, we considered follow-up duration less than 4 years and patients with atypical or vascular parkinsonism, drug-naïve patients, and those with other movement disorders. Part of the same cohort of patients was included in previous studies, which were designed and conducted to explore the molecular determinants of PD progression, with a focus on genetic and immunologic markers (Corrado et al., 2018; Kustrimovic et al., 2018). During regular follow-up visits, the severity of motor symptoms and disease staging were assessed in "on" condition using the Unified Parkinson's Disease Rating Scale (UPDRS) part III–IV and the Hoehn and Yahr (HY) scale (Goetz et al., 2004, 2008). Detailed information about antiparkinsonian therapies, levodopa equivalent daily dose (LEDD) (Tomlinson et al., 2010), and ongoing medication for concomitant chronic conditions were obtained, including indications of prescription and routes of administration. Drugs for non-neurological disorders (i.e. statins, antiplatelets, anticoagulants, antiarrhythmics, proton-pump inhibitors, antidepressants, antipsychotics, oral hypoglycemic drugs, thyroid drugs, alpha-adrenoreceptor antagonists/5 alpha-reductase inhibitors, and vitamin D) were prescribed by other care providers and all medications were coded according to the WHO Anatomical Therapeutic Chemical (ATC) classification (Peng et al., 2020).

After application of the abovementioned inclusion and exclusion criteria, 223 patients were available for case-control analysis. We examined data registered during patients' last appointment, and LIDs were recorded in 58 subjects according to neurological examination and UPDRS part IV score (items 4.1 and 4.2 ≥ 1). After careful removal from the analysis of those subjects already dyskinetic at the baseline visit (i.e. first evaluation at our outpatient clinic for movement disorders), 47 dyskinetic patients (PwD) were identified as cases. Peak-dose dyskinesia was the most frequent type of LID (95.7%). Using a ratio of case to control 1:1 (Thompson, 1986), we selected for each PwD a control (NoD), nearly perfectly matched according to sex, years of antiparkinsonian treatment (± 2 years), and UPDRS part III score (± 2 points). Flow diagram for the enrollment of study participants can be seen in **Figure 1**. We analyzed whether, in the time frame between the baseline and the last appointment (mean duration of follow-up = 9 years), there was an ongoing ACEi/ARBs therapy. Subjects with ACEi/ARBs initiation or discontinuation after the baseline visit were removed from the analysis (n = 6). Changes in dosage regimen or from one active substance to another were not considered as exclusion criteria.

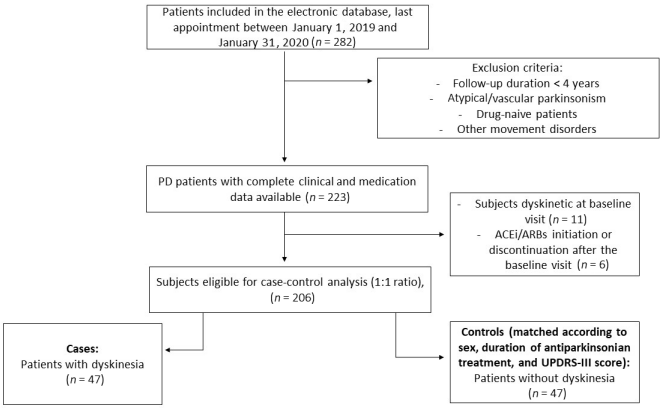

Figure 1 | **Flow diagram for the enrollment of study participants.**
ACEi: Angiotensin-converting enzyme inhibitor; ARBs: AT1 receptor blockers; UPDRS: Unified Parkinson's Disease Rating Scale.

Ethics statement

Written informed consent was obtained from all subjects (**Additional file 1**) and the study was approved on July 27, 2016 by the Ethics Committee of Novara University Hospital "Maggiore della Carità" (CE 65/16; **Additional file 2**), in compliance with national legislation and the *Declaration of Helsinki*.

Statistical analysis

Variables were expressed as counts and percentages when categorical and as mean ± standard deviation or medians (interquartile range) when continuous. Normality was assessed using the Shapiro-Wilk test. Since continuous variables were not normally distributed, group comparisons were analyzed using the non-parametric Mann-Whitney U test. Associations between categorical variables were assessed through Pearson chi-square or Fisher's exact test, as appropriate. Binary logistic regression with "enter" method was used to determine the odds ratios and their relative confidence intervals. The outcome variable was dichotomized as 0 = absence of dyskinesias and 1 = presence of dyskinesias. The goodness of fit was confirmed using the Hosmer-Lemeshow test. The significance level was set to P-value < 0.05. All analyses were performed using SPSS Version 25 (IBM, Armonk, NY, USA).

Results

Characteristics of patients with and without dyskinesia

47 PwD and 47 NoD were identified. Demographic, clinical, and medication data of PD patients can be seen in **Table 1**. There were no statistically significant differences regarding sex, age, disease severity (as assessed by UPDRS part III), age at PD onset, type and duration of antiparkinsonian treatment, and medication for non-neurological disorders. Nevertheless, as expected, in the PwD group disease duration (P = 0.029) and LEDD were higher (P = 0.012) and there was a higher prevalence of HY stages 3–4 (P = 0.019), whereas tremor dominant patients were more frequent in the NoD group (P = 0.007).

Table 1 | **Demographic, clinical and medication data of PD patients (*N* = 94) stratified according to presence or absence of dyskinesias**

	PwD (*n* = 47)	NoD (*n* = 47)	*P*-value
Age (yr)	73 (67–79)	73 (65–79)	0.964
Sex (F/M, *n*)	19/28	19/28	1
Age at PD onset (yr)	62.5 (53–68.25)	66 (55.5–71)	0.35
Side of onset (left/right, *n*)	15/32	20/27	0.286
Disease duration (yr)	10 (7–13.25)	8 (6–11)	0.029
Treatment duration (yr)	9 (6–12)	7 (5–11)	0.109
Interval baseline-dyskinesia onset (yr)	5 (3–8)	NA	NA
Tremor dominant phenotype	16 (34)	29 (61.7)	0.007
Hoehn and Yahr stage			
Stage 1	3 (6.4)	8 (17)	0.109
Stage 2	21 (44.7)	27 (57.4)	0.216
Stage 3–4	23 (48.9)	12 (25.5)	0.019
Antiparkinsonian therapy			
Levodopa/levodopa+COMTi	47 (100)	47 (100)	1
Dopamine agonists	6 (12.8)	7 (14.9)	0.765
MAOi	32 (68.1)	33 (70.2)	0.823
Amantadine	4 (8.5)	0	0.117
Trihexyphenidyl	1 (2.1)	2 (4.3)	1
LEDD (mg daily)	800 (518–1183)	652 (450–720)	0.012
UPDRS part III	18 (13–25)	17 (13–23)	0.898
ACEi/ARBs (C09)	11 (23.4)	25 (53.2)	0.003
Other antihypertensives (C02)	21 (44.7)	28 (59.6)	0.215
Statins (C10AA)	11 (23.4)	9 (19.1)	0.614
Antiplatelets (B01AC)	14 (29.8)	17 (36.2)	0.51
Anticoagulants (B01AA)	9 (19.1)	2 (7.4)	0.172
Antiarrhythmic drugs (C01BD)	15 (31.9)	15 (31.9)	1
Proton-pump inhibitors (A02BC)	12 (25.5)	15 (31.9)	0.494
Antidepressants (N06A)	19 (40.4)	15 (31.9)	0.391
Antipsychotics (N05A)	4 (8.5)	4 (8.5)	1
Oral hypoglycemic drugs (A10B)	2 (4.3)	3 (6.4)	1
Thyroid drugs (H03AA)	5 (10.6)	1 (2.1)	0.203
Alpha-adrenoreceptor antagonists/5-alpha-reductase inhibitors (G04C)	2 (4.4)	3 (7)	0.478
Vitamin D (A11CC)	5 (10.6)	5 (10.6)	1

Continuous variables are expressed as medians (interquartile range, IQR), categorical variables as counts and percentages unless stated otherwise. The Anatomical Therapeutic Chemical (ATC) codes of ongoing non-antiparkinsonian medication are shown in parentheses. Significant *P* values are in italics. ACEi: Angiotensin-converting enzyme inhibitors; ARBs: AT1 receptor blockers; COMTi: catechol-O-methyltransferase inhibitors; LEDD: levodopa equivalent daily dose; MAOi: monoamine oxidase inhibitors; NA: not applicable; PD: Parkinson's disease; UPDRS: unified Parkinson's disease rating scale.

ACEi/ARBs use and LIDs

Concerning antihypertensive drugs, we found that among PwD 11 (23.4%) were users, and 36 (76.6%) non-users of ACEi/ARBs; conversely, in the NoD group, 25 (53.2%) were users and 22 (46.8%) non-users of this drug class (Pearson chi-square = 8.824, P = 0.003; **Additional Figure 1**). In particular, among ACEi/ARBs users, treatment with ramipril (n = 10, 27.8%), perindopril (n = 5, 13.9%), zofenopril (n = 3, 8.3%), enalapril (n = 2, 5.5%), valsartan (n = 6, 16.7%), olmesartan (n = 3, 8.3%), candesartan (n = 2, 5.5%), irbesartan (n = 2, 5.5%), telmisartan (n = 2, 5.5%), and losartan (n = 1, 2.8%) was recorded. During regular follow-up visits none of the patients reported major side effects requiring medical attention.

These results suggested an association between the reduced occurrence of dyskinesia and concomitant treatment with ACEi/ARBs. Therefore, binary logistic regression was performed considering the remaining confounders (i.e. tremor dominant phenotype, LEDD, HY stages 3–4, and disease duration). The use of ACEi/ARBs was a significant predictor of lower dyskinesia occurrence (odds ratio [OR] = 0.226, 95% CI: 0.080–0.636, P = 0.005), whereas LEDD was significantly associated with a higher occurrence of dyskinesia (OR = 1.237, 95% CI: 1.045–1.463, P = 0.013). The Hosmer-Lemeshow test was not statistically significant (P = 0.203), which indicated a good fit of the model.

Discussion

ACEi/ARBs are commonly used in the management of increased blood pressure, which is associated with brain atrophy, gray matter atrophy, white matter injury, and an increased risk of dementia (McGrath et al., 2017; Doiron et al., 2018). Moreover, in PD patients inadequate control of hypertension may reduce resting cerebral blood flow, which subsequently affects the oxygen delivery to the SN and promotes dopaminergic neurodegeneration (Hou et al., 2018).

In this scenario, it should be highlighted that the RAS plays a key role in the perpetuation of inflammation (Gironacci et al., 2018; Parga et al., 2018; Diaz-Ruiz et al., 2020), which can lead to dopaminergic cell death through different mechanisms. Firstly, AII may act on neurons directly via AT1 receptors and indirectly stimulating the production of reactive oxygen species. Secondly, AII can act on microglia with subsequent production of high concentrations of reactive oxygen species and activation of other microglial signaling pathways involved in the inflammatory response. In animal models, dopamine deficiency seems to induce compensatory overactivation of the RAS, which further enhances dopaminergic degeneration: this mechanism can be prevented by angiotensin receptor blockers and inhibitors of the angiotensin-converting enzyme (Labandeira-Garcia et al., 2013).

Recent evidence in a hemilesioned rat model of PD (Rivas-Santisteban et al., 2020) confirmed that AT1 and AT2 receptors can form heterodimers, expressed in striatal neurons and microglia, and their coactivation reduced the signaling output of angiotensin. Intriguingly, candesartan antagonized the detrimental effects of central AT1 receptor activation increasing at the same time the beneficial effects of the AT2 receptor, thanks to an antagonist-mediated cross-potentiation mechanism. In addition, the AT1/2 heterodimer expression was markedly higher in animals that were not made dyskinetic by l-dopa treatment compared to dyskinetic animals.

The main finding of this study is based on the association between ACEi/ARBs treatment and dyskinesias. Consistent with previous evidence (Kelly et al., 2019), in our cohort LEDD was a significant predictor of this motor complication. However, after controlling for relevant confounding variables, the use of ACEi/ARBs was significantly associated with a reduced occurrence of dyskinesias. Moreover, no serious side effects were ever reported in our cohort, suggesting easy management due to good tolerability. Similar findings were previously published (Reardon et al., 2000), but only perindopril was evaluated in a small group of patients. The novel contribution from our research is the possibility that

both ACEi and ARBs may prevent dyskinesias development, probably by influencing the complex interplay between dopamine and the RAS in the nigrostriatal pathway. Interestingly, the RAS has also been explored in PD non-motor symptoms: Pessoa Rocha et al. (2016) found an association between lower circulating levels of angiotensins and the severity of depression, thus suggesting the role of RAS-related neuroinflammation in other key features of PD.

However, several limitations of the present study should be mentioned, in particular its retrospective design, the small sample size, and lacking data about previous time exposure and exact dosage of ACEi/ARBs, which prevented time- and dose-related analysis. Moreover, additional variables should be considered for future logistic regression analysis, i.e. dopaminergic medication response or body mass index. Nevertheless, the limited number of patients recruited was due to the rigorous matching procedure performed to control for epidemiological and clinical variables: for each PwD we selected a matched NoD with similar features. Furthermore, even though our study cannot establish any dose-effect relationship, it highlights how prescription patterns of ACEi/ARBs may affect the development of LIDs, thus suggesting new implications for this class of therapeutics.

Despite the abovementioned limitations, we found that ACEi/ARBs are manageable antihypertensive medications and may lower dyskinesia occurrence among PD patients. Further studies with careful separation of data by different RAS-targeting drugs and prospective, randomized, and controlled designs, are therefore warranted to confirm our preliminary results.

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Conflicts of interest: *The authors declare that there are no conflicts of interest relevant to this work.*
Financial support: *None.*
Institutional review board statement: *The study was approved by the Ethics Committee of Novara University Hospital "Maggiore della Carità" (CE 65/16) on July 27, 2016.*
Declaration of patient consent: *The authors certify that they have obtained all appropriate patient consent forms. In the forms, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.*
Reporting statement: *This study followed the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.*
Biostatistics statement: *The statistical methods of this study were reviewed by the biostatistician of Novara University Hospital "Maggiore della Carità"*

Data sharing statement: *Individual participant data that underlie the results reported in this article will be available, after deidentification and upon reasonable request, for 5 years following article publication. Proposals should be directed to the corresponding author. Raw data (including personal information and participant codes) will be stored at the University Hospital "Maggiore della Carità" for this period before being destroyed. If requested, the study protocol will also be available.*
Plagiarism check: *Checked twice by iThenticate.*
Peer review: *Externally peer reviewed.*

Additional files:
Additional file 1: *Model consent form (Italian).*
Additional file 2: *Ethical Approval Documentation (Italian).*
Additional Figure 1: *Angiotensin-converting enzyme (ACE)-inhibitors (ACEi)/AT1 receptor blockers (ARBs) therapy in patients with (PwD) and without (NoD) dyskinesia.*

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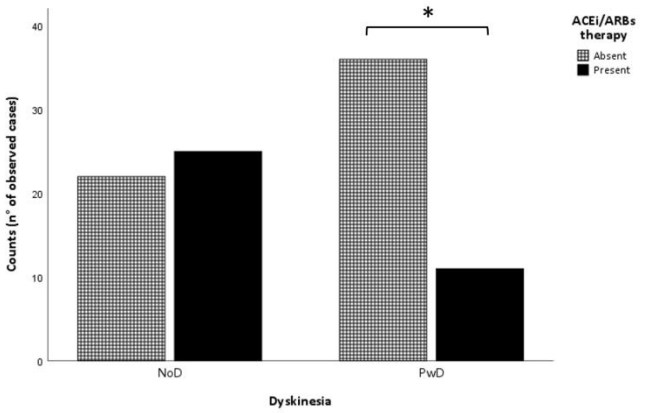

Additional Figure 1 Angiotensin-converting enzyme (ACE)-inhibitors (ACEi)/AT_1 receptor blockers (ARBs) therapy in patients with (PwD) and without (NoD) dyskinesia.
*Pearson chi-square = 8.824, $P = 0.003$.