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Use of ACE-inhibitors and falls in patients with Parkinson's disease

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ABSTRACT

Falls represent a major concern in patients with Parkinson's disease (PD); however, currently acknowledged treatments for PD are not effective in reducing the risk of falling. The aim was to assess the association of use of ACE-inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) with falls among patients with PD.

We analysed data of 194 elderly with PD attending a geriatric Day Hospital. Self-reported history of falls that occurred over the last year, as well as use of drugs, including ACEIs and angiotensin II receptor blockers (ARBs) were recorded. The association of the occurrence of any falls with use of ACEIs, and ARBs was assessed by logistic regression analysis. The association between the number of falls and use of ACEIs, and ARBs was assessed according to Poisson regression.

In logistic regression, after adjusting for potential confounders, use of ACEIs was associated with a reduced probability of falling over the last year (OR = 0.15, 95% CI = 0.03–0.81; P = 0.028). This association did not vary with blood pressure levels (P for the interaction term = 0.528). Also, using Poisson regression, use of ACEIs predicted a reduced number of falls among participants who fell (PR = 0.31; 95% CI = 0.10–0.94; P = 0.039). No association was found between use of ARBs and falls.

Our results indicate that use of ACEIs might be independently associated with reduced probability, and a reduced number of falls among patients with PD. Dedicated studies are needed to define the single agents and dosages that might most effectively reduce the risk of falling in clinical practice.

1. Introduction

Despite advances in pharmacological treatment, falls still represent a major cause of disability, institutionalization, and mortality among subjects with Parkinson's disease (PD); In fact, falls occur in 35–90% of these patients, 18–65% of whom are recurrent fallers [1].

Several risk factors for falling have been identified in PD, in addition to history of falls; these include advanced age, disease duration and severity, abnormal posture and deficits of gait or balance, impairment in the activities of daily living and in mobility, cognitive impairment, and use of medications [2].

Older and frailer people are often prescribed multiple medications, and previous studies have shown that polypharmacy is associated with greater risk of falling [3]. In particular, antihypertensive agents, including ACE-inhibitors (ACEIs) have been associated with orthostatic hypotension in older populations [4]. However, other studies found that use of angiotensin system blocking agents might be associated with a reduced risk of falls in older subjects [5]. Of notice, ACEIs have been shown to slow age-related declines in muscle strength and improve exercise capacity in older people [6]; also, ACEIs and angiotensin II receptor blockers (ARBs) have been proven to exert direct neuroprotective effects, even in experimental models of PD [6,7].

The aim of the present study was to assess whether, independently of any underlying pharmacodynamics, use of ACEIs or ARBs might be associated with falls among subjects with PD.

2. Methods

This cross sectional study involved all patients with PD consecutively admitted to the geriatric Day Hospital of the Catholic

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University, Rome, between October 1st 2011, and March 30th, 2015, without exclusion criteria. PD was the first diagnosis for all participants. Diagnosis of PD was ascertained using the United Kingdom Parkinson's Disease Society Brain Bank (UK-PDS-BB) criteria [8]. Of 205 patients, 11 were excluded for missing data for the study variables. All participants were visited by the study physicians, who received specific training; the study researchers performed physical examination, and completed a questionnaire that included participants' data on socioeconomic status, lifestyle habits, and quality of life according to a standardized protocol. Information on drug therapy was collected from patients and caregivers, and further verified by inspection of medicine packs. All the drugs taken at the time of the admission interview were recorded, including over-the-counter drugs and as-needed administrations.

2.1. Standard protocol approvals, registrations, and patient consents

The Institutional Review Board of the Catholic University approved the protocol, and all the patients provided written informed consent.

2.2. Coding of drugs

Drugs were coded according to the Anatomical Therapeutic and Chemical codes/Defined Daily Dose [9]. In particular, we considered agents coded C09A (ACEIs), C09B (ACEIs in combination with diuretics or calcium channel blockers), C09C (ARBs), and C09DA, C09DB, and C09DX (ARBs in combination with diuretics, calcium antagonists, or both). No patients were on aliskiren.

2.3. Falls

Participants were asked whether they had experienced any falls during the previous 12 months, and if so how many falls occurred. A fall was defined as a sudden loss of balance causing the contact of any part of the body with the floor [10].

2.4. Covariates

Education was expressed as years of school attendance. Smoking was calculated as total lifetime pack-years for current and former smokers.

Diagnoses were coded according to the International Classification of Diseases, ninth edition, Clinical Modification codes [11]. On admission, adjudicated disease diagnoses were based on self-reported history, clinical documentation, and medication use. Comorbidity was quantified using the Charlson score [12].

The total levodopa equivalent daily dose (LEDD) was calculated considering: standard levodopa 100 mg = controlled-release levodopa 70 mg = bromocriptine 10 mg = pergolide 1 mg = lisuride 1 mg = ropinirole 4 mg = pramipexole 0.7 mg = dehydroergocriptine 30 mg = cabergoline 1.5 mg. All LEDD were normalized for body weight [13].

Functional ability was estimated using the Katz' activities of daily living (ADLs) and the Lawton and Brody scale for instrumental activities of daily living (IADLs). Depressive symptoms were evaluated using the 15-item Italian version of the Geriatric Depression Scale (GDS) [14]. Cognition was assessed using the Mini Mental State Examination [15]. Parkinson's disease severity was assessed using the Unified Parkinson Disease Rating Scale (UPDRS) [16]. Nutritional status was evaluated using the Mini Nutritional Assessment (MNA) [17].

Body Mass Index (BMI) was calculated as weight (Kg) divided by height squared (m^2).

Appendicular lean mass was assessed using Dual X-Ray Absorpiometry (Hologic QDR 4500 W [Hologic Inc, Bedford, MA]); values were normalized by the BMI.

Muscle strength was assessed by grip strength, measured using a hand-held dynamometer (hydraulic hand BASELINE; Smith & Nephew, Agrate Brianza, Milan, Italy). Two measurements for each hand were performed, and the highest value of the strongest hand was used for statistical analyses.

The Tinetti Test was adopted to evaluate patients' ability to walk and maintain balance [18].

Ambulatory 24 h blood pressure recording was performed on the non-dominant arm with a properly calibrated Blood Pressure Monitor System 90217 from Space Laboratories (Washington DC); the dipping pattern was identified by nocturnal systolic blood pressure fall <10%.

Blood samples were obtained after overnight fasting. Glomerular Filtration Rate was estimated using the Cockcroft-Gault equation.

2.5. Statistical analysis

Data were recorded using a dedicated software with automatic coding of drugs and diagnoses. Statistical analyses were performed using SPSS for Mac 20.0. Differences were considered significant at the $P < 0.050$ level. Data of continuous variables are presented as mean values ± standard deviation (SD). Medians and inter-quartile ranges were provided for non-normally distributed variables. Analysis of variance (ANOVA) for normally distributed variables was performed according to the occurrence of falls; otherwise, the nonparametric Mann-Whitney U H test was adopted. The two-tailed Fisher exact test was used for dichotomous variables. The covariates to be entered into analyses were chosen as explanatory according to available reviews and meta-analyses from the electronic databases of PubMed (MEDLINE) and Cochrane Library, and based upon their efficiency and cheapness. Multivariable logistic regression analysis was used to assess the association of experience of at least one fall in the previous year, with age, sex, ACEIs, and all those variables, which differed significantly ($P < 0.050$) in univariate analyses. Abnormally distributed variables were analyzed after log transformation. Also, in logistic regression analysis of the interaction term "ACEIs*mean blood pressure" was performed to assess whether the association between use of ACEIs with falls varied according to blood pressure levels recorded during 24-h ambulatory monitoring. Analysis of the interaction term was also conducted to assess the dependency, if any, of the association between ACEIs and falls upon L-dopa, dopaminergic agents, and total dopa-equivalent weight-adjusted daily dosages.

Eventually, after assessing the distribution of the number of falls by the Kolmogorov-Smirnov test, we applied the Poisson regression modelling using the number of falls as dependent variable, and use of ACEIs as explanatory variable, as well as other significant covariates.

Collinearity diagnostics, estimated by correlation matrices and variance inflation factor (VIF), indicated the absence of collinearity between the covariates entered into the models (all correlation matrices <0.8 and all VIF values <3); also, in logistic regression the test of goodness of fit, performed by the Hosmer and Lemeshow Test, indicated a good fit of the model (all P values >0.050).

3. Results

Ninety one patients (47%) reported at least one episode of falling in the previous year; among these, the median number of falls was 2 [1–5].