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Clinical pharmacokinetics of pramipexole, ropinirole and rotigotine in patients with Parkinson's disease

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ABSTRACT

Introduction: Pramipexole (PRA), ropinirole (ROP) and rotigotine (ROT) are non-ergoline dopaminergic agonists (DAs) used to treat Parkinson's disease (PD). Clinical pharmacokinetics of DAs is poorly characterized in PD. The main purpose of our study was to investigate the effect of dose, age and sex on steady-state plasma concentrations of DAs in real life PD patients on chronic DAs therapy.

Methods: The study was single center, open and prospective. Blood samples for measurement of DAs plasma concentrations were drawn in the morning, at a median 18-h distance from the last DA dose.

Results: Ninety-one patients treated with PRA, 50 with ROP and 37 with ROT were enrolled in the study. Plasma concentration of DAs significantly correlated with weight-adjusted daily dose in all subgroups, although at a given dose, matched plasma concentrations highly varied among patients. Median PRA plasma concentration-to-daily dose ratio (C/D) [(ng/mL)/(mg/kg/d)] was 68% higher in patients > 65 years than ≤65 years (158 *vs* 94, $p < 0.001$), while was not affected by age in ROP and ROT subgroups. No sex-mediated differences in C/D ratios were observed in any group.

Conclusion: These are the first observations on DAs pharmacokinetics in PD patients' everyday clinical practice. Of relevance, patients over 65yrs may require about one third of PRA dose compared to under 65yrs to achieve the same plasma concentration. Due to the high intersubject variability in plasma concentrations at the same dosage, we speculate that monitoring of plasma DAs might be helpful in the individualization of treatment in selected patients.

1. Introduction

At present treatment of Parkinson's disease (PD) only suppresses symptoms and mainly relies on agents able to restore dopaminergic transmission in the nigrostriatal pathway. Beside the precursor of dopamine, levodopa (LD), which remains the most effective therapy [1], non-ergoline dopamine receptor agonists (DAs) are extensively used in the treatment of PD, both as monotherapy and add-on therapy to LD [2]. They are also indicated in primary restless legs syndrome [3]. Currently available agents of this class include two oral DAs, pramipexole (PRA) and ropinirole (ROP), both as immediate-release (IR) and extended-release (ER) formulations, and rotigotine (ROT) as transdermal delivery patch formulation.

Clinical pharmacokinetics of PRA, ROP and ROT is poorly characterized in PD patients. Published data are scanty, mostly available as abstracts or poster presentations, often referring to small groups of healthy young subjects, or patients enrolled in clinical trials [4–7].

Taken overall, the clinical use of DAs is largely empirical, based on standard dosages, which do not take into account the potential effects of demographic and clinical variables on DAs bioavailability and matched clinical effects. Post-marketing experience with DAs has disclosed a series of central and peripheral possibly dose-related adverse effects (AEs), including somnolence [8], impulse control disorders (ICD) (compulsive gambling, buying, and sexual behavior) [9] and risk of heart failure with PRA [10], which can hamper the use of these agents.

The main purpose of this study was to investigate the effect of dose,

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Table 1
Clinical details of patients.

Group (n)	Age (yrs)	Sex (m/f)	Weight (kg)	BMI (kg/m^2)	H&Y scale	PD symptoms duration (yrs)	DAs therapy duration (yrs)	DAs dose (mg/d) (dose/d)		Levodopa dose (mg/d)
Pramipexole (91)	68 ± 9 (41–82)	60/31	74 ± 13 (45–110)	26 ± 4 (17–37)	2 (1–4) 1 (n = 12) 2 (n = 59) 3 (n = 10) 4 (n = 10)	9.2 ± 6.7 (1–34)	5.2 ± 4.6 (0.25–16)	1.0 ± 0.7* (0.18–2.1) n = 29 1.3 ± 0.7# (0.26–3.15) n = 62	3 (1–3) 1 (1–2)	420 ± 222 (100–1300) (n = 90)
Ropinirole (50)	63 ± 11 (28–89)	32/18	74 ± 16 (41–107)	27 ± 5 (16–36)	2 (1–4) 1 (n = 8) 2 (n = 35) 3 (n = 5) 4 (n = 2)	7.9 ± 5.8 (1–25)	4.7 ± 3.7 (0.25–15)	9.1 ± 4.6 (0.5–16)	1 (1–2)	391 ± 205 (100–1000) (n = 48)
Rotigotine (37)	66 ± 11 (42–86)	23/14	71 ± 14 (45–103)	25 ± 4 (16–32)	2 (1–5) 1 (n = 5) 2 (n = 15) 3 (n = 6) 4 (n = 8) 5 (n = 3)	8.9 ± 4.7 (1–21)	5.3 ± 5.1 (0.25–21)	6.8 ± 2.9 (2–12)	1	544 ± 290 (50–1400) (n = 37)

m, male; f, female; BMI, Body Mass Index; H&Y, Hoehn & Yahr; PD, Parkinson's disease; DAs, dopaminergic agents. *Immediate-release formulation; # Extended-release formulation. Data are expressed as mean ± standard deviation (range), with the exception of H&Y scale and DAs dose/d, expressed as median (range).

age and sex on steady-state plasma concentrations of DAs in a population of real life PD patients on chronic DAs therapy. Preliminary data were also collected about the potential pharmacokinetic interaction between PRA and amantadine [11] and the effect on ROP pharmacokinetics of cigarette smoke and caffeine, inducer and substrate, respectively, of the cytochrome P450 CYP1A2 isoenzyme [12] primarily involved in the metabolism of ROP [13].

2. Materials and methods

2.1. Patients

The study was single center, prospective and open (protocol number CE 15128, Ethics Committee of the Bologna-Imola Local Health Trust). The protocol was proposed to patients with PD receiving chronic DAs therapy. Written informed consent was obtained from each subject.

Inclusion criteria were:

a) age ≥18 years;
b) PD diagnosis according to Gelb [14];
c) chronic therapy with DAs for at least one month, also in cotherapy with other antiparkinsonian drugs;
d) no change in dosage of DAs and concomitant antiparkinsonian drugs over the preceding week.

Clinical and therapeutic information was collected for each patient by one of the authors (G.L.) during ambulatory visit by means of an *ad hoc* case report form, at the time of blood sampling. The case report form included anamnestic records (PD symptoms onset, recognition of therapeutic history, ongoing antiparkinsonian and non-antiparkinsonian treatment, lifestyle and dietary habits, including smoking and caffeine consumption, evidence of AEs, with special reference to ICD, seemingly related to the introduction of DAs to therapeutic regimen).

To assess the compliance with medication, the physician asked the patients and their caregivers whether they had taken their usual DA therapy the previous day and the time of the last dose. All questions were made in a simple way to avoid misinterpretation.

2.2. Blood sampling and analytical methods

Venous blood samples were drawn between 8 and 10 a.m., before the first morning dose of DAs, when administered. Blood specimens (4 mL) were transferred into heparinized tubes (16 IU heparin/mL blood) and centrifuged at 1700 *g* for 10 min at 4 °C. Plasma was separated and stored at −80 °C until analysis of DAs, within 3 months. Plasma concentrations of DAs were determined by ultra high pressure liquid chromatography - tandem mass spectrometry method (UHPLC-MS/MS) as previously reported [15,16]. The lower limit of quantification was 0.08 ng/mL for PRA and ROP, and 0.05 ng/mL for ROT. The limit of detection was 0.04 ng/mL for PRA and ROP, and 0.02 ng/mL for ROT. Intra- and interassay imprecision and inaccuracy were ≤15% at all quality control concentrations, over a calibration range of 0.08–4 ng/mL for PRA, 0.2–10 ng/mL for ROP and 0.05–2.5 ng/mL for ROT.

2.3. Data and statistical analysis

The main study outcome was the DAs plasma concentration-to-weight-adjusted daily dose ratio (C/D) [(ng/mL)/(mg/kg/d)]. Plasma drug concentrations were normalized for weight-adjusted daily dose to allow for comparisons among differently weighted subjects.

Prior to statistical comparisons, deviations from a gaussian distribution were tested for each assessed variable by the Kolmogorov-Smirnov test and Bartlett's test. When data were consistent with a normal distribution, means and standard deviations (SD) were calculated and the statistical significance of differences between two groups assessed by the Student's t-test. When deviation from a normal distribution was found, medians and 25th-75th percentiles were calculated and comparisons were performed by the Mann-Whitney rank sum test. Correlations between variables were assessed by Pearson's product moment coefficient. Sex distribution was compared between patients' subgroups by chi-square test. Significance was set at $p < 0.05$. Analyses were carried out by SigmaPlot 12.5 software (Systat Software, San Jose, CA, USA).

3. Results

Between February 18, 2016 and September 30, 2017, 91 patients on PRA, 50 on ROP and 37 on ROT met the inclusion criteria and were

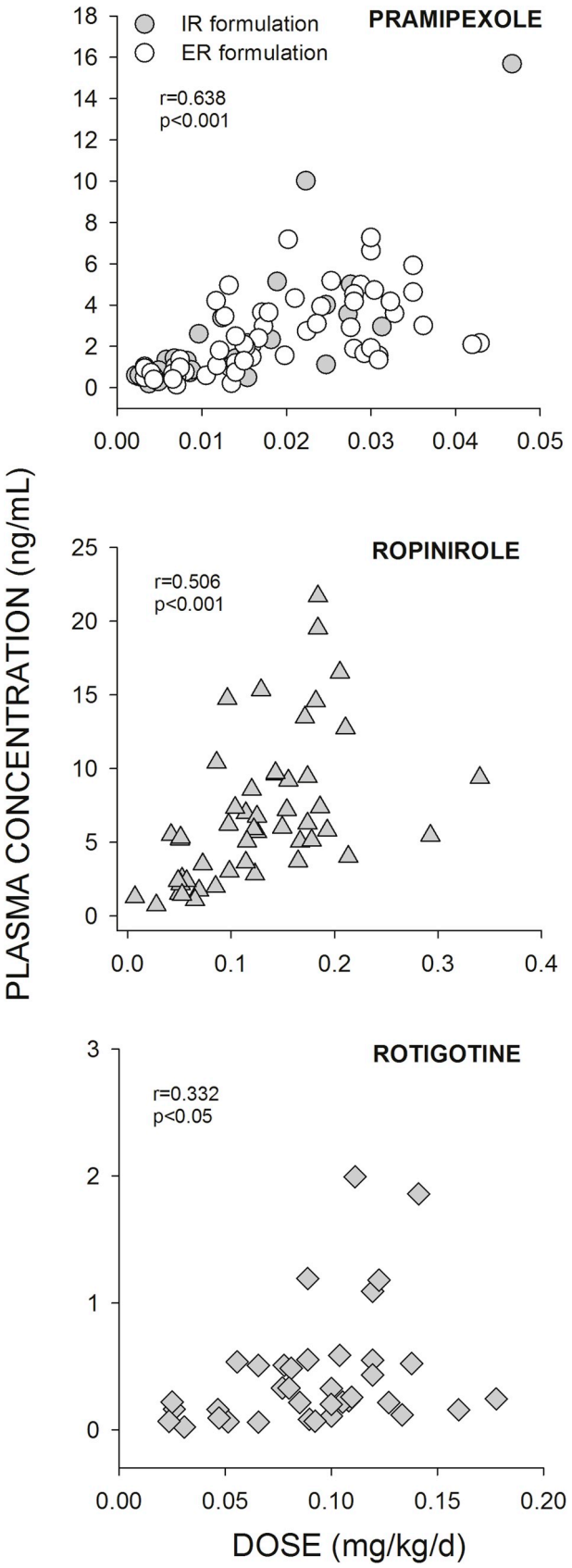

Fig. 1. Correlations between dopamine agonists plasma concentration and matched weight-adjusted daily dose. IR, immediate-release; ER, extended-release.

enrolled in the study. Clinical details of patients grouped according to different DAs are reported in Table 1.

3.1. Pramipexole

Twenty-nine patients were receiving IR and 62 ER formulations. Mean ± SD time interval between the last PRA dose and blood sampling was 14 ± 3 h for IR and 20 ± 6 h for ER formulation. Trough morning PRA plasma concentration was 2.47 ± 3.27 ng/mL (range, 0.19–15.68 ng/mL) for IR and 2.48 ± 1.81 (0.14–7.27 ng/mL) for ER formulations. Overall, PRA plasma concentrations were linearly related to matched daily doses, both in terms of mg/kg/d ($r = 0.638$, $p < 0.001$, Fig. 1) and mg/d ($r = 0.415$, $p < 0.001$).

Pramipexole C/D ratio was positively correlated with patients' age ($r = 0.425$, $p < 0.001$). Median PRA C/D was 68% higher in patients over 65 years (range 66–82 years) compared with patients ≤65 years (41–65 years) (158 *vs* 94, $p < 0.001$) (Fig. 2). The two age groups were comparable for sex distribution.

Serum creatinine values were available in a subset of 66 patients receiving PRA, ranging from 0.41 to 1.67 mg/dL. Glomerular filtration rate (GFR), calculated according to Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [17] was negatively related to PRA C/D ($r = -0.555$, $p < 0.001$). GFR and age were negatively correlated ($r = -0.496$, $p < 0.001$). In ten patients with mild to moderate loss of kidney function (GFR < 60 mL/min/1.73 m^2, range 39.5–56.5), all aged over 65 years, median (25th-75th percentiles) PRA C/D was nearly doubled compared with patients with normal kidney function (GFR range from 64.8 to 105.5 mL/min/1.73 m^2): 246 (167–341) *vs* 138 (83–183), $p < 0.001$.

No significant difference in PRA C/D ratio was observed between men and women, otherwise comparable for age (Fig. 2).

All but one patient were comedicated with LD (Table 1). Pramipexole was in cotherapy with ROP in two patients and with ROT in four. Other anti-PD cotherapies included amantadine (n = 10), rasagiline (n = 9), and selegiline (n = 4). No evidence emerged of a potential effect of amantadine on median PRA C/D ratio: 134 (91–203) in comedicated *vs* 131 (85–193) in non-comedicated patients, otherwise comparable for age.

Seemingly PRA-related AEs were recorded in 22 patients. The main AEs were psychiatric (ICD: compulsive eating n = 4, hypersexuality n = 2, pathological gambling n = 2), hallucination n = 1, insomnia n = 1; neurologic (drowsiness n = 3, hyperactivity n = 2); metabolic (weight increase n = 5, weight decrease n = 1); edema (n = 5). No significant difference in median PRA C/D was observed between patients with and without AEs: 140 (72–203) *vs* 132 (90–180).

Non-DAs cotherapies were taken by 57 patients. The most frequently administered agents were: cardiovascular drugs (n = 15), antidepressants (selective serotonin reuptake inhibitors-SSRI, n = 14), antihypertensives (beta blocking agents and calcium antagonists, n = 13), anxiolytics (benzodiazepines, n = 6), statins (n = 4), hypoglycemic drugs (n = 4), thyroid drugs (n = 5).

3.2. Ropinirole

All fifty patients were receiving ROP ER. Time interval between the last ROP dose and blood sampling averaged 20 ± 6 h. Plasma concentration of ROP ranged from 0.73 to 21.69 ng/mL; the mean ROP concentration was 6.86 ± 4.91 ng/mL. Ropinirole plasma concentrations were positively correlated with both weight-adjusted daily doses ($r = 0.506$, $p < 0.001$) (Fig. 1) and daily doses ($r = 0.465$, $p < 0.001$). Median ROP C/D was not significantly different between patients > 65 years *vs* ≤ 65 years (Fig. 2). No significant sex-mediated effect on ROP C/D could be appreciated (Fig. 2).

Thirty-four patients were caffeine consumers (1–3 cups of coffee/d); there was only one cigarette smoker. Median ROP C/D was superimposable between caffeine consumers *vs* non-consumers: 48 (31–69) *vs*

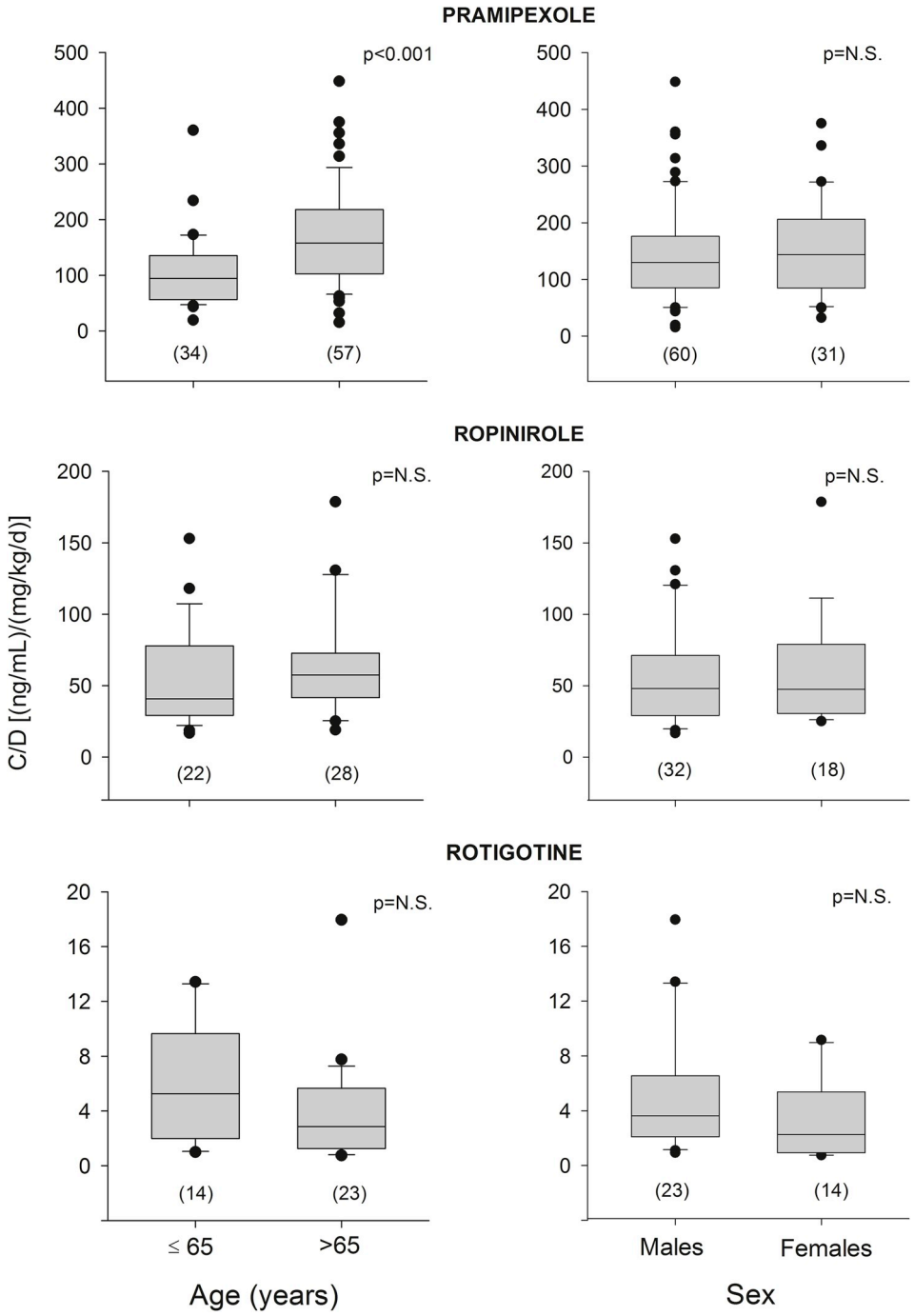

Fig. 2. Plasma concentration to weight-adjusted daily dose ratio of dopamine agonists in patients grouped by age (left panel) and sex (right panel). Box plots depict the range between the 25th and 75th percentiles of the data. The horizontal line marks the median value; capped bars indicate 10th-90th percentiles. Black circles represent outlying values. P, significance of comparison between age and sex groups by Mann-Whitney rank sum test; N.S., not significant ($p > 0.05$).

46 (27–80).

All but two patients were comedicated with LD (Table 1). Other anti-PD cotherapies included amantadine (n = 5), rasagiline (n = 5), and selegiline (n = 4).

Seemingly ROP-related AEs were recorded in 14 patients. The main AEs were psychiatric (ICD: compulsive eating n = 5, pathological gambling n = 1), insomnia (n = 2); neurologic (drowsiness n = 2, headache n = 1, hyperactivity n = 1, episodes of amnesia n = 1); metabolic (weight increase n = 5, weight decrease n = 1); edema (n = 2); gastrointestinal disorders (constipation n = 1). No significant difference in median ROP C/D was observed between patients with and without AEs: 50 (30–98) *vs* 48 (30–71).

Non-DAs cotherapies were taken by 40 patients. They included: cardiovascular drugs (n = 14), antidepressants (SSRI, n = 5), antihypertensives (n = 14), anxiolytics (n = 2), statins (n = 1), prostate drugs (n = 5), thyroid drugs (n = 1).

3.3. Rotigotine

Thirty-seven patients were on ROT therapy. Twenty-nine patients applied the once-daily patch in the evening and eight patients in the morning. Time interval between the last ROT patch application and blood sampling averaged 13 ± 2 h in the first subgroup and 25 ± 1 h in the latter. Overall plasma concentration of ROT ranged from 0.02 to

1.99 ng/mL; the mean morning ROT plasma concentration was 0.43 ± 0.47 ng/mL. Mean plasma drug concentrations were similar between patients taking ROT in the evening compared with those taking the DA in the morning, at comparable daily doses.

A significant correlation was found between ROT plasma concentrations and matched drug doses, both expressed as mg/kg/d ($r = 0.332$, $p < 0.05$, Fig. 1) and mg/d ($r = 0.563$, $p < 0.001$). Median ROT C/D was not significantly different between the two patient's age subgroups (Fig. 2). No significant sex-mediated effect on ROT C/D could be appreciated (Fig. 2).

All patients were comedicated with LD (Table 1). Other anti-PD cotherapies included amantadine (n = 4), rasagiline (n = 3), and trihexyphenidyl (n = 2).

Seemingly ROT-related AEs were recorded in six patients, including: psychiatric (hallucination n = 2, insomnia n = 1); neurologic (drowsiness n = 1); metabolic (weight increase n = 1); gastrointestinal disorders (vomiting n = 1, nausea n = 1); edema (n = 2). No significant difference in median ROT C/D was observed between patients with and without AEs: 4.35 (1.58–6.49) vs 3.26 (1.37–7.75).

Non-DAs cotherapies were taken by 31 patients. The most frequently administered agents were: cardiovascular drugs (n = 9), antidepressants (SSRI, n = 8), antihypertensives (n = 6), anxiolytics (n = 3), statins (n = 4), hypnotics (n = 3), thyroid drugs (n = 4).

4. Discussion

The results of our study are the first on the effect of a series of demographic and clinical variables on DAs plasma concentrations in real life PD patients. Some observations were of relevance:

Plasma concentrations of PRA, ROP and ROT were linearly related to matched daily dose, both expressed as mg/d and mg/kg/d. It must be observed that DAs dosing in clinical practice is still based on standard dosages, which mostly do not take into account the different weight of subjects. Plasma concentration-dose linearity is an important drug characteristic in clinical practice, as it may facilitate physicians in patients' dose adjustments. However, at a given dosage, a large intersubject variation was apparent in drug morning plasma concentrations, up to five-fold for ROP, eight-fold for PRA and ten-fold for ROT. With the exception of 29 patients on PRA receiving IR formulation, the remaining 62 patients on PRA and all patients on ROP were treated with ER formulations. In line with available data from clinical trials in healthy volunteers [18], morning PRA plasma concentrations were superimposable in patients treated with a median of three daily doses of PRA IR compared with patients receiving a median one daily dose of PRA ER. Moreover, mean values of PRA trough plasma concentrations were of the same order of magnitude, at comparable daily dose, to those reported in a study exploring efficacy and safety of PRA ER *vs* IR in Japanese patients [19]. As far as ROT is concerned, eight of our patients applied the patch in the morning, the remaining 29 in the evening. We did not find a significant difference between the two subgroups in morning plasma drug concentration, in line with clinical studies showing stable steady-state 24-h plasma concentrations matched with once-daily patch administration [20].

Older age increased plasma morning concentrations of PRA but not the other agonists. Patients over 65 years receiving PRA showed an increase of almost 70% in median C/D ratio compared with under 65yrs. This finding was partly anticipated, considering that PRA is primary renally excreted, and its clearance is expected to decrease with ageing in proportion to the physiological reduction in GFR [4]. GFR calculated according to CKD-EPI equation [17] was negatively correlated with age and proved a significant predictor of PRA C/D in 66 patients for whom serum creatinine was available. Mild to moderate loss of kidney function, defined as GFR < 60 mL/min/1.73 m^2 [21], was matched to a nearly doubling of PRA C/D in a subgroup of over 65yrs patients. From a preliminary population pharmacokinetic study, a modest, i.e. 15%, decrease in ROP clearance was found in patients aged 65 years and older than patients under 65 years [6]. In line with our findings, age had no effect on mean trough ROT plasma concentrations in patients with PD enrolled in a phase I study [20].

Sex did not affect plasma morning concentrations of DAs. This finding is in line with available population pharmacokinetic data obtained in PD patients for ROP [6] and a phase I study in early PD patients for ROT [20]. The outdated evidence of a higher AUC of PRA in women than in men obtained in healthy subjects was confounded by the older age of the women group [22].

Adverse effects, seemingly related to the beginning of DAs treatment, were not associated with DAs plasma concentrations. They were registered in 24% of patients receiving PRA, 28% on ROP and 16% on ROT. In particular, ICD was reported in 9% of patients treated with PRA and 12% on ROP, percentages which are in line with those observed in cross-sectional studies on large cohorts of PD patients [23]. From clinical experience, data on the relationship between DAs dose and ICD are contradictory, as some authors reported a dose-dependent effect, with symptoms improvement or resolution by decreasing DAs dosing, while others reported recovery only after DAs withdrawal [24]. In any case our observations are preliminary and should be taken with caution, as mainly based on outpatients' or caregivers' reporting. Moreover, as DAs were generally added to existing antiparkinsonian treatment, it may be difficult to ascertain which adverse effects were caused by DAs alone or a combination of drugs.

With regard to the effect of antiparkinsonian comedication on DAs disposition, PRA prescribing information warns about a potential interaction with amantadine by competition for the same renal organic cation transport system [11], resulting in a decrease of PRA clearance. From our data obtained in a subset of ten cotreated patients, amantadine intake was not associated with a significant effect on PRA C/D ratio. The low number of patients taking this combination is insufficient to make any definite conclusion.

All but three of our patients were cotreated with LD. No mutual pharmacokinetic interaction between LD and PRA, ROP or ROT has been reported in PD patients [4–7].

From in vitro metabolic studies, the polymorphic CYP1A2 enzyme of cytochrome P450 is primarily involved in the metabolism of ROP [13]. CYP1A2 inhibitors, such as the antibacterial agent ciprofloxacin, can interact with ROP, resulting in an increase of ROP bioavailability of around 80% in healthy volunteers [6]. The potential effect on ROP pharmacokinetics of cigarette smoke and caffeine, known as inducer and substrate, respectively, of CYP1A2 [12] has not been explored so far. From our data, a modest daily consumption of 1–3 cups of coffee (around 40–120 mg caffeine) was not associated with any significant modification of ROP C/D in our patients. As for the potential interaction between PRA and amantadine, the limited number of patients coupled with the wide intersubject variability in C/D ratios make it difficult to draw any conclusion. Caffeine at a mean daily dose of 550 mg was reported to inhibit the metabolism of clozapine, another substrate of CYP1A2 isoenzyme, to an extent that may be clinically significant in certain subjects [25]. On the other hand, the effect of cigarette smoke could not be assessed, as only one smoker was documented in our ROP patients' group. In line with literature [26], smokers were under-represented in our cohort of patients.

From a methodological point of view, all patients in our study were regularly followed up, at least once yearly, by the physicians of the

Movement Disorder Center of our Institute, and compliance with medication was checked at each visit by direct interview to patients' and their caregivers and its importance stressed. No evidence of poor compliance to DAs medication or overdosing emerged either from patients' medical records during routine follow-up, either during the specific visit planned for the study protocol. On the other hand, DAs overdosing did not emerge even from values of measured plasma concentrations, which were in line with those available from clinical trials, at comparable dosages. The cognitive status of the patients was not formally tested, but no major cognitive impairment emerged from ambulatory medical charts and study protocol visit. Our population of patients was mainly representative of mild to moderate stages of PD. All patients at the more severe stages were tended by caregivers.

5. Conclusion

Our results give for the first time a picture of DAs pharmacokinetics in PD clinical practice. One strength of the paper is that our findings were all obtained from a single site with uniform methodology and a single rater. This reduces the variability, but also needs verification at other sites and in other settings. Among the limitations, patients' drug therapy adherence can be less controlled in an observational setting, which, on the other hand, is more representative of day-to-day patient care compared with the artificial conditions imposed by controlled trials.

The most relevant finding was the evidence of a significant increase in systemic exposure to PRA with ageing. In practical terms, patients aged over 65yrs might require about one third of PRA weight-normalized dose compared with under 65yrs to achieve the same plasma concentration. Measurement of serum creatinine at the beginning of PRA treatment and its periodic monitoring during chronic therapy might be helpful in intrasubject longitudinal drug dosing.

From a theoretical point of view, measurement of plasma drug concentrations might be helpful in dosage adjustments when an alteration in pharmacokinetics is suspected, due for example to age-related factors, as we observed for PRA, or drug-drug interactions. In the light also of the wide intersubject variability observed in plasma DAs at the same dosages, we speculate that monitoring of plasma drug concentration might be helpful in selected cases to individualize patients' treatment. The main purpose of our study was to assess the contribution of a series of demographic variables on DAs pharmacokinetic variability in a population of real life PD patients. This was considered the first step to proper clinical protocols specifically designed to assess the relevance of plasma concentrations of DAs in terms of therapeutic and adverse effects.

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Declaration of interest

M.C. has received speaker honoraria from Chiesi Farmaceutici. G.C–B. has received speaker honoraria from Chiesi Farmaceutici, AbbVie srl and UCB Pharma S.p.A. P.C. has received honoraria for speaking engagements or consulting activities from Allergan Italia, AbbVie srl, Chiesi Farmaceutici, Eli Lilly, Novartis, Teva, UCB Pharma S.p.A and Zambon. For the remaining authors none were declared.

CRediT authorship contribution statement

Manuela Contin: Conceptualization, Formal analysis, Writing - original draft, Methodology, Supervision, Writing - review & editing. **Giovanna Lopane:** Conceptualization, Formal analysis, Data curation, Writing - review & editing. **Susan Mohamed:** Formal analysis, Writing - original draft, Data curation. **Giovanna Calandra-Buonaura:** Investigation, Writing - review & editing. **Sabina Capellari:** Formal analysis, Investigation. **Patrizia De Massis:** Investigation. **Stefania Nassetti:** Investigation. **Alessandro Perrone:** Formal analysis, Data curation. **Roberto Riva:** Formal analysis, Methodology. **Luisa Sambati:** Investigation. **Cesa Scaglione:** Investigation. **Pietro Cortelli:** Formal analysis, Investigation, Supervision.

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