Fluoxetine does not impair motor function in patients with Parkinson's disease: correlation between mood and motor functions with plasma concentrations of fluoxetine/norfluoxetine

Fluoxetin ne remeti motornu funkciju kod bolesnika sa Parkinsonovom bolešću: korelacija raspoloženja i motorne funkcije sa koncentracijom fluoksetina/norfluoksetina u plazmi

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Abstract

Background/Aim. Selective serotonin reuptake inhibitors are the most commonly chosen antidepressants in patients with Parkinson's disease (PD). The aim of our study was to assess the influence of fluoxetine (Flu) on motor functions in patients with PD. Methods. In this prospective, controlled, open-label study, 18 patients with PD and mild depression [(10 ≤ Hamilton Rating Scale for Depression (HDRS) ≤ 23)] without dementia [(25 ≤ Mini-Mental State Examination (MMSE)] were treated with Flu. Both single and repeated dose effects of Flu were assessed on days 1–80. Plasma concentrations of Flu and norfluoxetine (NORFlu) were correlated with the results of selected motor function performance scores: The Unified Parkinsons Disease Rating Score (UPDRS), Finger Tapping Test (FTT) and Purdue Pegboard Test (PPT). Severity of PD, depression and dementia were evaluated using standard tests [(Hoehn and Yahr stages (HY), activity of daily living (ADL), UPDRS, HDRS, MMSE)]. Results. Steady-state for Flu/NORFlu was reached after 18 days of treatment. Such a plateau correlated with significant improvements in both scores of depression and Parkinson's disability (HDRS, UPDRS and ADL, respectively). In addition, FTT and PPT scores also increased until day 18, with further slight fluctuations around the plateau. Optimal motor performances correlated with Flu concentrations of approximately 60–110 µg/L. Conclusion. Flu (20 mg/day) significantly reduced depression in PD patients while it did not impair their motor performances. Because substantial placebo effects may arise in studies of PD and depression, large, prospective, randomized, placebo-controlled clinical trials are warranted.

Key words: parkinson disease; motor activity; depressive disorder; fluoxetine; treatment outcome.

Apstrakt

Uvod/Cilj. Selektivni inhibitori ponovnog preuzimanja serotonina su antidepressivi koji se najčešće koriste u lečenju obolelih od Parkinsonove bolesti (PB). Cilj ovog istraživanja bio je da se proceni uticaj fluoksetina (Flu) na motorne funkcije bolesnika sa PB. Metode. U ovom prospektivnom, kontrolisanom, otvorenom kliničkom ispitivanju, 18 bolesnika sa PB i blagom depresijom [10 ≤ Hamiltonova skala za depresiju (10 ≤ HDRS) ≤ 23], bez demencije [(25 ≤ Mini mental test (MMSE))] lečeni su primenom Flu. Procjenjivana su dejstva kako pojedinačno, tako i poravnotežene doze Flu od prvog do osamdesetog dana. Plazma koncentracije Flu i norfluoksetina (NORFlu) korelirane su sa rezultatima određenih testova za motorne funkcije: skala za procenu težine PB (UPDRS), test spretnosti kucajanja (FTT) i Purdue pegboard Test (PPT). Izraženost PB, depresije i demencije procjenjivane su korišćenjem standardnih testova [(test dnevnih
akтивности (ADL), Hoehn-Yahr. stadijumi (HJ), HDRS, MMSE]). Rezultati. Ravnovesno stanje za Flu/NORFlu postignuto je 18. dana lečenja. Takav plato u koncentraciji Flu/NORFlu bio je praćen značajnim poboljšanjem rezultata, kako testova za depresiju, tako i za izraženost PB (HDRS, UPDRS i ADL, sledstveno). Dodatno, rezultati FTT-a i PPT-a bili su u porastu do 18. dana, sa blagim fluktuacijama oko plota. Optimalna motorna postignuća zabeležena su pri koncentraciji Flu od oko 60–110 μg/l. Zak-
tives, hypnotics or other antidepressants, as well as drugs with potential extrapyramidal adverse effects.

The study was approved by the Ethical Committee of the Faculty of Medicine, University of Belgrade, Serbia. Before entering the study patients gave written informed consent.

All the tests were performed in 18 out of 18 patients on days 11 and 18. Afterwards, 9 out of 18 patients were tested on day 50, and 8 out of 18 patients on day 80 (dropout rates of 50% and 56%, respectively). Therefore results were shown only until day 50.

All the patients were treated with two consecutive dosing regimens.

First, acute treatment with Flu – first day, the patients received Flu, 20 mg per day, at 8 a.m. Evaluation of motor performances and blood sampling for Flu/NORFlu plasma concentration measurement were carried out immediately before the Flu treatment (day 1, 0 h), and 4 h, 6 h and 8 h after the administration of the drug. Flu was then withdrawn for three consecutive days. On the fifth day, patients received 40 mg of Flu at 8 a.m. and all the tests and blood sampling were repeated in the same order (day 5, 0–8 h after administration of the drug). The pattern of blood sampling depends on $T_{\text{max}}$ for Flu, ranging from 4 to 8 h after the single dose administration37 (Figure 1, panel A).

Second, chronic treatment with Flu – in the same patients, regular Flu treatment was initiated (20 mg per day, at 8 a.m.) on day 6 after the beginning of such a therapy, and the motor performances were evaluated on days 11, 18, 50 (steady state for Flu was reached after 18 days of Flu treatment) (Figure 1, panel B).

Two blinded refers evaluated severity of motor impairment using the Unified Parkinson's Disease Rating Scale (UPDRS) – motor score38, ADL (Schwab and England Ac-

Bioanalytical method used for determination of plasma Flu and NORFlu concentrations was high performance liquid chromatography (HPLC) coupled with mass spectrometry (MS). The method used a liquid chromatograph Therm Separation Products Spectra System (Autosampler AS3000, HPLC binary pump P 2000, Degasser SCM 1000), mass spectrometer with electro spray ionization source (Finnigan MAT SSQ 7000 LC/MS – ESI System), Computer Digital UNIX Alpha Station 255. Recovery was very high, not less than 90.8% for Flu and 80.2% for NORFlu. Limit of quantification was 2.5 $\mu$g/L for Flu and 10 $\mu$g/L for NORFlu, and limit of detection was 1 $\mu$g/L for Flu and 5 $\mu$g/L for NORFlu. Correlation coefficient was 0.9993 (concentration range of 2.5–250 $\mu$g/L), and 0.9989 (concentration range of 10–250 $\mu$g/L), for Flu and NORFlu, respectively. Coefficient of variation, calculated for precision, was not higher than 8.33% and 8.83% for Flu and NORFlu, respectively.

The results are expressed as the mean ± standard error of the mean (S.E.M.) of N observations (descriptive statistics). Comparisons between groups were analyzed using the Fisher's exact test, $t$-test, and one-way analysis of variance (ANOVA), when appropriate. In addition, correlation analysis, factor analysis, extraction method (principal component analysis), rotation method (Oblimin with Kaiser normalization) and trend analysis (fitting or least square method) were used.

Results

All the patients were right-handed. Both groups, PD0 and PD1, had similar laterality of Parkinson’s symptoms (affected right side/affected left side = 6/3).

Among 12/18 patients with the affected right side, there was no significant difference between FFT for the right hand (FTTr) and FTT for the left hand (FTTl) scores, as well as between PPT for the right hand (PPTr) and PPT for the left hand (PPTl) scores ($p = 0.66$, and 0.89, respectively).

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Among 6/18 patients with affected left side, FTTr was significantly better than FTTl (p = 0.03) and PPTl was significantly better than PPTr (p = 0.02). In addition, only PPTl score was significantly higher in the left side-affected PD patients comparing to the right side-affected PD patients (p = 0.03).

Age, gender and main clinical scores of PD0- and PDt-patients are shown in Tables 1 and 2.

## Baseline characteristics of patients with Parkinson’s disease (PD): group of de novo patients without antiparkinson’s medication (PD0) and the group with previous stable antiparkinson’s therapy (PDt)(mean ± S.E.M.)

| Group of patients | Age (years) | Duration of PD (years) | Previous levodopa therapy | Duration (years) | Dose (mg/day) | MMSE |
|-------------------|-------------|------------------------|---------------------------|-----------------|---------------|-------|
| PD0 (N = 9)       | 55.7 ± 3.0  | 2.7 ± 0.9              |                          | 3.9 ± 0.9       | 458.3 ± 55.1  | 28.0 ± 0.6 |
| PDt (N = 9)       | 56.0 ± 2.7  | 3.6 ± 1.1              |                          | 3.9 ± 0.9       | 458.3 ± 55.1  | 27.9 ± 0.9 |

MMSE – mini mental state examination; PD0 – de novo PD patients; PDt – PD patients with stable antiparkinsons therapy

### Changes in fluoxetine (Flu) and norfluoxetine (NORFlu) concentrations, and motor function scores (FTT, PPT) during acute treatment with Flu (day 1: 20 mg; day 5: 40 mg) (mean ± S.E.M.)

| Day of Flu treatment | Parameter | Day 1 | Day 5 of the treatment |
|---------------------|-----------|-------|------------------------|
| 0 h                 | CFlu(g/L) | 9.58 ± 1.51 | 11.44 ± 1.31 |
| 4 h                 | CFlu(g/L) | 8.83 ± 1.02 | 14.76 ± 1.88 |
| 6 h                 | CFlu(g/L) | 5.01 ± 0.35 | 7.48 ± 1.78  |
| 8 h                 | CFlu(g/L) | 3.57 ± 1.78 | 7.7 ± 2.02   |
| FTT | 4.01 ± 0.49 | 4.91 ± 0.45 | 5.17 ± 1.71 |
| PPT | 10.22 ± 0.08 | 10.33 ± 0.03 | 10.22 ± 0.81 |

## Staging of Parkinson’s disease (PD): the group of patients without antiparkinson’s medication (PD0) and the group of patients with stable antiparkinson’s therapy (PDt) (mean = steady state for Flu) (mean ± S.E.M.)

| Group of patients | HDRS | UPDRS | ADL |
|-------------------|------|-------|-----|
| PD0 (N = 9)       | 16.4 ± 2.1 | 10.4 ± 1.9* | 26.7 ± 2.9 |
| PDt (N = 9)       | 13.6 ± 0.9 | 8.2 ± 1.1*  | 29.0 ± 5.1 |

HDRS – Hamilton Depression Motor Scale; UPDRS – Unified Parkinson’s Disease Rating Scale; ADL – Schwab and England Activities of Daily Living Score.* – p < 0.05, day 0 vs. day 18 (Student’s t-test for paired data).
Of note, the raise in C_CFM between days 0 and 18 (the plateau) coincided with the increase in FTT and especially in PPT scores (Tables 3 and 4).

Factor analysis reveals that influence of Flu/NOR flu concentrations increased over time (cumulative data from both PD0 and PDt patients; plasma samples were taken on days 0, 5, 11, and 18, six hours after Flu administration). The variance explained by the concentrations of Flu and NOR flu permanently increased from 13.9% (day 5) to 29.9% (day 11) and 37.6% (day 18) of cumulative variance (values of 89.4%, 84.9% and 91.8%, respectively). At the same time, influence of motor function scores decreased over time: variance explained by PPT and FTT scores of 75.5%, 55%, and 54.1% (days 5, 11, and 18, respectively).

PPT and FTT scores significantly correlated on day 11 (r = 0.62; p < 0.01). In addition, an inverse correlation was found between Flu/NOR flu concentrations and PPT-, but not with FTT scores, on day 18 (r = -0.70 and 0.48, respectively).

Gastrointestinal, cardiovascular side effects and/or insomnia, somnolence and excessive daytime sleepness as adverse reactions to Flu were not reported in the PD patients considered in the study.

Discussion

The major results of our pilot study show that Flu treatment may alleviate depression in PD patients without deterioration of motor function scores. FTT, PPT and UPDRS-motor scores were even improved despite the parallel increase in plasma concentrations of Flu/NORflu during the first 18 days of the study.

Depression in PD must be properly diagnosed and treated. However, rare reports on the use of various antidepressants in PD patients offer controversial data on their safety regarding motor adverse reactions. Controlled clinical studies confirming the efficacy of Flu in PD patients and assessing the risk-benefit ratio of such a therapy are still lacking.

The broad therapeutic window for Flu is due to its highly variable pharmacokinetics. Flu steady state is achieved approximately after 3 weeks (concentrations of approximately 110 µg/L). If plasma concentrations increase above 110 µg/L, the dosage should be adjusted accordingly. Factor analyses indicates that mean Flu concentrations of approximately 60–110 µg/L have the most powerful effect on both PPT and FTT scores, which were significantly improved within that concentration range.

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The PPT and FTT are quantitative motor tests. While FTT more reflects motor speed, the PPT is a test for fine motor functions and coordination. Since all the patients were right-handed only among 6/18 patients with affected left side FTTr and PPTl were better than FFTl and PPTl, respectively, pointing to more efficient compensatory mechanisms in dominant hand.

The pathophysiological profile of fluoxetine is unique among the antidepressants used in PD patients. Fluoxetine is both SSRI agent and a 5HT2c antagonist. A recent investigation confirmed that 5HT1A agonists and 5HT2c antagonists could be important features in treatment of PD. In particular, 5HT2c receptors seem to tonically inhibit dopamine release from all three major dopaminergic pathways. Accordingly, 5HT2c antagonists could block such an inhibition, especially in the terminal regions of the nigrostriatal and mesolimbic pathways.

Additionally, 5-HT2c receptors are selectively located within substantia nigra pars reticulata (SNr) and medio globus pallidus (Gpm) and 5-HT via 5-HT2c receptors is excitatory in the SNr, which may contribute to the increased activity of these regions in PD. Systemic administration of selective 5-HT2c antagonists to 6-hydroxydopamine-lesioned rodents potentiates the antiparkinsonian action of dopamine D1 and D2 agonists, which is an action mediated via 5-HT2c receptors in the SNr. Thus, 5-HT2c receptor antagonists may improve parkinsonism and drugs with 5-HT2c receptor antagonist action, such as fluoxetine, are unlikely to worsen PD.

The pathophysiological mechanisms involved in mood disturbances in PD remain complex. Serotonergic dysfunction has been postulated as such systems are involved in mood disorders in non-PD and the raphe nuclei, as well as hippocampus and prefrontal cortex, appear to be the primary sites affected. Moreover, transcranial ultrasound studies have suggested an association with reduced brainstem raphe echogenicity and nigral hyperechogenicity in patients with depression preceding PD onset compared with nondepressed patients with PD.

As the PD disease progresses, Lewy bodies occur with the rostral raphe, thalamus and limbic and cortical regions, which may result in the mediating of mood disturbances in PD.

In depression associated with PD, PD-specific pathology, with multiple transmitter deficiencies in mesocortical monoaminergic systems, plays a major role. This includes the mesocorticolimbic dopaminergic projection as well as mesocortical noradrenergic and serotonergic projections. Corticollimic noradrenergic denervation through cell loss in the locus coeruleus and serotonergic denervation via serotonin cell loss in the raphe nucleus are also likely to be important. Postmortem evidence showed lower density of neurons in the dorsal raphe nuclei in depressed versus nondepressed patients with PD and cerebro-spinal fluid measurement in vivo showed reduced serotonin metabolite (5-HIAA) levels in depressed patients with PD. A [11C]-DASB PET study in seven patients with PD with untreated depression showed elevated serotonin transporter binding in the prefrontal cortex compared with non-PD-matched controls. Recently, Politis et al. have reported that the patients with PD with the highest scores for depressive symptoms showed significantly increased [11C]-DSAB binding in the amigdala, hypothalamus, caudal raphe nuclei and posterior cingulate cortex compared with those patients with low depression scores, though not compared with healthy controls. The [11C]-DSAB binding values in other regions, including the anterior cingulate cortex, caudate, insula, prefrontal cortex, putamen rostral raphe nuclei, thalamus and ventral striatum, were similarly decreased in patients with PD, irrespective of their depressive symptoms scores, compared with the healthy controls. This study demonstrates that depressive symptoms in antidepressant-naive patients with PD are associated with relatively higher serotonin binding in raphe nuclei and limbic structures. A relative increase in serotonin transporter binding in these regions could reflect either lower extracellular serotonin levels or a disease-related loss of presynaptic serotonergic neurotransmission in contributing to the pathophysiology of PD depression.

The phenomenology of depression in PD is also different from that in patients with non-PD with less anhedonia and feeling of guilt. While etiology of depression in Parkinson’s disease is unclear (biochemical changes, psychosocial factors and situational stressors have all been implicated), it has an adverse effect on the quality of patients’ lives and doctors should ensure that they are diagnosed and properly treated.

Therefore, along with improvement on parkinsonian quality of life due to antidepressant activity of SSRI, symptoms such as bradikinesia, hypomimia, hypophonia that overlap between depression and parkinsonism could ameliorate because an improvement of mood symptoms. Evenmore, Suzuki et al. suggested that SSRIs such as fluoxetine potentially are therapeutic drugs for non-motor symptoms as well as motor symptoms in patients with PD, since fluoxetine can reverse the downregulation of cell proliferation in the subgranular zone by the unilateral 6-hydroxydopamine lesion.

All these various mechanisms could explain why the improvement in Parkinson’s disability scores in our patients coincided with an increase in plasma Flu and NORFlu concentrations during the first 18 days of antidepressive treatment.

Another question is to assess the possible difference between PD0 and PD+ patients’ response to Flu treatment. The beneficial effects of Flu on motor symptoms of PD patients seem to be more pronounced in PD+ group (UPDRS and ADL scores). In addition, PPT scores were mostly higher in PD+ patients during chronic treatment with Flu increasing continuously by the end of the study (day 50). However, the antidepressive efficacy of Flu was similar in both PD groups (HDRS). Also, the statistical significance was rarely observed between those groups regarding motor function scores; FTT values were even somewhat higher in PD0 patients on days 11 and 50.

According to Taylor et al., depressive symptoms precede those of motor dysfunction in 12–37% of patients with Parkinson’s disease.
paroxetine (20 mg/day) given to 33 nondemented depressed patients with PD did not alter the motor response to levodopa in patients with PD. Chung et al. in 2005, reported that the short-term paroxetine treatment did not decrease motor performance scores in PD patients, without influence on parkinsonian symptoms. In only one patient fully reversible worsening of tremor was observed. However, paroxetine frequently may induce extrapyramidal symptoms between different classes of SSRI antidepressants in patients with PD treated with dopaminergic antiparkinsonian drugs. According to the results of several studies, including our results with Flu, it seems that the benefit of SSRIs outweigh the potential problems due to adverse effects and that they may be considered to be the rational choice in the treatment of depression in PD.

There are several limitations of the study: it was an open-label study without randomization including a small number of patients. As with all non-randomized, open-label studies, our results may have influenced the results. However, the quantitative evaluations of motor functions using FTT and PPT significantly improved objectivity and validity of our findings. The observed dropout rates (50% and 56% on days 50 and 80, respectively) are high but fit to the range observed in clinical trials to depression.

Conclusion

This pilot study suggests that Flu 20 mg is effective and well tolerated antidepressant in patients with Parkinson’s disease. In addition, Flu improved motor function scores in PD patients and such improvement was observed in parallel with the increase in plasma Flu and NORFlu concentrations. Also, the effects of Flu were similar in de novo PD patients, with additional beneficial effect on anxiety, without influencing motor function. In another open-label study with paroxetine (20 mg/day) given to 33 nondemented depressed PD patients during 6 months, Ceravolo et al. in 2000, reported a significant improvement of depression, as evaluated by HDRS, without influence on parkinsonian symptoms. Chung et al. in 2005, reported that the short-term paroxetine treatment did not alter the motor response to levodopa in patients with PD. In the present study, we failed to observe any deterioration in motor performance scores of patients with PD that was related to the increase in plasma Flu and NORFlu concentrations. A slight improvement was even observed in all the scores (UPDRS, ADL, FTT and PPT). Similar results were obtained with citalopram, which improved mood but did not decrease motor performance scores in PD treated with levodopa; at the same time, citalopram improved the parkinsonian dyskinesia, bradykinesia and finger taps after one and four months of treatment, both in patients with and without depression.

In clinical trials to depression 83. Also, Weintraub et al. 44, 2006, reported that escitalopram was well tolerated, but produced only a partial response in the treatment of major depression in elderly PD patients (mean age of 72.1 years). Two open-label studies suggested that sertraline reduced depression in PD patients, with additional beneficial effect on anxiety, without influencing motor function. Additionally, Ilic et al. showed that the treatment with sertraline exerts complex modulatory effects on human motor cortex with potential behavioural usefulness. In another open-label study with paroxetine (20 mg/day) given to 33 nondemented depressed PD patients during 6 months, Ceravolo et al. in 2000, reported a significant improvement of depression, as evaluated by HDRS, without influence on parkinsonian symptoms. In only one patient fully reversible worsening of tremor was observed. However, paroxetine frequently may induce tremor as an adverse effect, with a prevalence of 1% to 2%. Chung et al. in 2005, reported that the short-term paroxetine treatment did not alter the motor response to levodopa in patients with PD.

The effects of Flu were similar in de novo PD patients and in those already treated with antiparkinsonian medications. Therefore, our results would allow an optimal design for further large, prospective, randomized, placebo-controlled clinical trials that are necessary to evaluate the efficacy and safety of SSRI antidepressants and allow the development of evidence-based guidelines.

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