Comparison of Desipramine and Citalopram Treatments for Depression in Parkinson’s Disease: A Double-Blind, Randomized, Placebo-Controlled Study

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Abstract: Depression is one of the most common psychiatric disturbances in Parkinson’s disease (PD). Recent reviews have highlighted the lack of controlled trials and the ensuing difficulty in formulating recommendations for antidepressant use in PD. We sought to establish whether antidepressants provide real benefits and whether tricyclic and selective serotonin reuptake inhibitor (SSRI) antidepressants differ in their short-term efficacy, because the time to onset of therapeutic benefit remains an important criterion in depression. The short-term efficacy (after 14 and 30 days) of two antidepressants (desipramine, a predominantly noradrenergic reuptake inhibitor tricyclic and citalopram, a SSRI) was assessed in a double-blind, randomized, placebo-controlled study of 48 nondemented PD patients suffering from major depression. After 14 days, desipramine prompted an improvement in the Montgomery Asberg Depression Rating Scale (MADRS) score, compared with citalopram and placebo. Both antidepressants produced significant improvements in the MADRS score after 30 days. Mild adverse events were twice as frequent in the desipramine group as in the other groups. A predominantly noradrenergic tricyclic antidepressant induced a more intense short-term effect on parkinsonian depression than did an SSRI. However, desipramine’s lower tolerability may outweigh its slight short-term clinical advantage.

Key words: depression; Parkinson’s disease; antidepressant treatment; serotonin; norepinephrine

The reported prevalence of depression (according to the DSM IV criteria) in Parkinson’s disease (PD) ranges from 7 to 70%, 1 although the mean value is generally around 40% for depression and 25% or less for major depression. 2,3 Depression can be observed throughout the course of the disease, that is, soon after onset but also in advanced PD. 4,5 The clinical efficacy of antidepressants in treating PD depression remains largely unknown. Indeed, despite the high prevalence of depression, the latter’s major impact on quality of life and the extensive use of antidepressants in PD, very few controlled drug trials in this field have been reported. Two recent reviews identified just three randomized, controlled trials on a total of 106 patients, with assessment taking place after a very long treatment period (between 16 and 52 weeks). 6,7 However, the trials’ results were undermined...
by methodological bias (i.e., the lack of statistical analysis; a nonvalidated, in-house depression scale; an open-label paradigm). Last, two very old, double-blind, placebo-controlled studies revealed the efficacy of tricyclic antidepressants (imipramine and desipramine) but again did not use validated scales. This lack of data makes it difficult to formulate recommendations.

The fact that depression in PD cannot be satisfactorily treated with dopaminergic medication alone suggests the simultaneous involvement of other neurotransmission systems. It is believed that the neuronal circuitry of the serotonergic and noradrenergic systems and their connections to the prefrontal cortex and the mesolimbic system are involved in depression. Furthermore, our understanding of the mechanisms of antidepressant action has changed over time. The strong antidepressant activity of the tricyclic antidepressants argues in favor of a role for norepinephrine and serotonin in both depression and the mechanisms involved in antidepressant action. Next-generation antidepressants include the selective serotonin reuptake inhibitors (SSRIs, such as citalopram) and further support the role of serotonin, whereas the features of selective norepinephrine reuptake inhibitors (e.g., desipramine) underline the relevance of norepinephrine. Given (i) the fact that the acute effects of selective reuptake inhibitors often predict their long-term effects, (ii) the lack of studies confirming long-term differences between antidepressants in PD, and (iii) the fact that time to onset of therapeutic benefit remains an important therapeutic criterion in major depression, we sought to establish the drugs’ short-term effects (relative to placebo) at 14 and 30 days in PD patients with major depression but receiving optimal dopamine treatment.

**PATIENTS AND METHODS**

**Patients**

Outpatients from our active case file were consecutively included if they were under 80 and had been suffering from PD for over 2 years (excluding de novo PD). All were receiving optimal dopaminergic treatment (Table 1), the doses of which were strictly maintained throughout the study. The dopamine agonists were equally distributed across the three arms: three patients on ropinirole in the desipramine arm and two in the others, one to three patients on bromocriptine, piribedil, and pergolide in each arm and none on pramipexol. Furthermore, all met the DSM IV criteria...
for an ongoing, major depressive episode\textsuperscript{22,23} (i.e., to exclude cases of isolated dysthymia without depression) and had to score at least 20 on the overall Montgomery Asberg Depression Rating Scale (MADRS) score.\textsuperscript{24,25} The exclusion criteria were as follows: serious or unstable medical conditions, dementia (Mini-Mental State Examination $< 27$; Mattis Dementia Rating Scale Score $< 130$), psychotic disorders, and suicidal thoughts. Psychotherapeutic drugs, anticholinergics and antipsychotics (including clozapine), were not allowed during the study. Anxiolytic or hypnotic drugs were only allowed if maintained at the prestudy dose. Patients receiving subthalamic nucleus stimulation were only eligible after a minimum postsurgery period of 6 months and as long as they displayed good motor outcomes and stable parameters. The study was approved by Lille University Hospital’s Investigational Review Board. All patients gave their written, informed consent to participation.

**Experimental Design**

We performed a double-blind, placebo-controlled study with three parallel arms. The study aimed at comparing desipramine and citalopram with placebo for treatment of a major depressive episode. Depression and anxiety scales were scored at baseline and on days 14 and 30 (i.e., the D0, D14, and D30 scores). Cognitive, motor, and overall acceptability were assessed at D0 and D30. The same team of investigators [a neuropsychologist (SD), a neurologist (CM), and a psychiatrist (IP)] assessed each patient to avoid interrater variation. The psychiatrist was blinded to any side effects noted by the neurologist. After the study, patients were referred to an independent psychiatrist for standard follow-up. Patients on placebo who had not responded to treatment were offered active drugs.

**The A Priori Estimated Sample Size**

Before the study and on the basis of previously published work in PD,\textsuperscript{19,26} we estimated that the mean MADRS score of depressed PD patients at baseline would be $30 \pm 5$. With treatment, we expected to see a 50\% decrease in that score in the treated groups and a 30\% decrease in the placebo group. Considering an alpha risk of 0.05 (for an analysis of variance), the expected mean MADRS scores at day 14 (21 with the placebo and 15 with the active drug) and an estimated standard deviation of five, the target sample size for achieving a power of 90\% was 15 subjects per arm.

**Randomization**

All eligible PD patients were randomly assigned to one of three parallel treatment arms. Randomization was independently stratified using a randomization table by Lille University Hospital’s Clinical Investigation Centre, and the list was transmitted to an independent contract research organization (LC2, Lentilly, France) for preparation of the study tablets (allocating treatment in blocks of six). All double-blind procedures were checked by an independent third party.

**Dosage Schedule**

For all treatments, three indistinguishable tablets were taken once a day, in the morning. For each drug, the recommended dose for depression was used (i.e., 75 mg for desipramine\textsuperscript{27} and 20 mg for citalopram\textsuperscript{28}). The low end of the therapeutic range was chosen to minimize patient withdrawals due to adverse events. The desipramine treatment consisted of two 25 mg tablets and 1 placebo tablet for the first 2 days and then three 25 mg tablets for the last 28 days. The citalopram treatment consisted of one 20 mg tablet and two placebo tablets for all 30 days. The patients in the placebo group received three placebo tablets.

**Efficacy Criteria**

The primary endpoint was a change in the MADRS score at D14 and D30 (relative to D0) as judged by an analysis of variance (ANOVA) for repeated measures. The short-term depression remission rate (DRR) was considered as an achievement of a MADRS score below 10,\textsuperscript{25} a good short-term response (GR) corresponded to a decrease in the MADRS score of at least 50\% and the lack of a short-term response (LR) corresponded to a decrease in the MADRS score of less than 20\%.

MADRS items were grouped according to a three-factor model for the analysis of depressive symptoms.\textsuperscript{29,30} The first factor (labeled “psychic anxiety/dysphoria”) includes pessimistic and suicidal thoughts and reported sadness; the second factor (“dysphoric apathy/retardation”) includes lassitude, inability to feel, apparent sadness, and concentration difficulties; the third factor (“vegetative symptoms”) includes reduced sleep, reduced appetite, and inner tension.

Drug effects on anxiety were also studied by comparing the mean Hamilton Anxiety Rating Scale (HARS) scores.\textsuperscript{31}
Acceptability Criteria

Neuropsychological tests included the MMSE score, the Mattis Dementia Rating Scale score, and the Frontal Assessment Battery score. The motor assessment included UPDRS parts III and IV. Adverse events were reported spontaneously and verbally to the investigators and via a self-questionnaire (which listed the side effects typically observed with antidepressants) that all subjects had to fill out. General health status, weight, prone and standing arterial blood pressures, heart rate, an electrocardiogram, and a standard blood biochemistry profile were also assessed.

Data and Statistical Analysis

In view of the non-Gaussian distribution of the parameters, results are presented with medians and quartiles. Intergroup comparisons were performed using a nonparametric ANOVA for repeated measures. The effects of treatment (placebo, citalopram, desipramine) and time (D0, D14, D30) were studied, along with the interaction between these two factors (via Bonferroni post hoc tests). A significance level of 0.05 was chosen. Comparisons at D14 and D30 were always made relative to the baseline (i.e., D0 values).

RESULTS

From a total of 160 consecutive primary and secondary PD patients referred to our center for mood disorders over a period of 3 years, only 48 met the DSM criteria for major depression (see flowchart below). The remaining 112 had minor depression or dysthymia. Hence, 48 patients were included in the study: 16 in the placebo group, 15 in the citalopram group, and 17 in the desipramine group (Table 1). At baseline, the three groups did not differ significantly.

Effect on the MADRS Score (Table 2, Fig. 1)

No main effect of time or treatment was noted ($F_{(2,11)} = 0.8, P = 0.9; F_{(2,11)} = 1.7, P = 0.2$, respec-
A treatment × time interaction was observed for the MADRS score (F(4,9) = 4.5, P = 0.03). Post hoc comparisons revealed an improvement at D14 in the desipramine group (compared with the citalopram (P = 0.005) and the placebo groups (P = 0.003), as well as an improvement at D30 for both the citalopram (P = 0.03) and desipramine groups (P = 0.002), compared with placebo. The same profile was observed for the GR (χ^2 = 6, P = 0.05) and LR (χ^2 = 7.9, P = 0.001) parameters. The DRRs differed significantly at D14 (χ^2 = 6, P = 0.05) and D30 (χ^2 = 6.5, P = 0.03), with a greater improvement on desipramine at D14 and D30, compared with the citalopram and placebo groups.

**Effect in a Three-Factor Analytic Model of Depression Using the MADRS Score (see Fig. 2)**

There was no main effect of time or treatment on any factor. A significant treatment × time interaction (F(4,9) = 4.8, P = 0.02) was observed for the dysphoric apathy/retardation factor. Post hoc comparisons revealed an improvement at D14 in the desipramine group, compared with the other two groups, and an improvement at D30 in both treated groups, compared with the placebo group. We observed a treatment × time interaction for the psychic anxiety/dysphoria factor (F(4,9) = 5.4, P = 0.005) and the vegetative symptoms factor (F(4,9) = 7.1, P = 0.007). Post hoc comparisons revealed an improvement in the treated groups (compared with the placebo group) at both D14 and D30.

**Effect on Anxiety (Table 2)**

We observed a main effect of time (F(2,11) = 45.3, P = 0.0001) and a treatment × time interaction for the HARS score (F(4,9) = 3.7, P = 0.006). Post hoc comparisons did not reveal any significant differences between the three groups at D14. The treated groups

![FIG. 1. Percentage decreases in the Montgomery Asberg Depression Rating Scale (MADRS) scores at day 0 (D0), day 14 (D14), and day 30 (D30) in the citalopram and desipramine groups, compared with the placebo group. ‘＋’ indicates a significant decrease (P < 0.05) in the desipramine group at D14, compared with the citalopram and placebo groups and relative to D0. ‘∗’ indicates a significant decrease (P < 0.05) in the desipramine and citalopram groups at D30, compared with the placebo group and relative to D0. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
showed an equivalent improvement at D30 compared with the placebo group.

Acceptability (Table 3)

There was no significant worsening in cognitive and motor symptoms. Overall, acceptability was not significantly modified in any of the groups. Three patients dropped out between D14 and D30 due to the occurrence of severe adverse events (which resolved after treatment discontinuation): worsened bradykinesia on citalopram, induction of erectile dysfunction on citalopram, and worsened orthostatic hypotension on desipramine. Mild adverse events were twice as frequent in the desipramine group as in the other two groups.

DISCUSSION

In this study, major depression in PD was greatly improved by 1 month of antidepressant treatment, compared with placebo. In the very short term (14 days), there was a better response (in term of the MADRS score and the good response/lack of response/remission rates) with desipramine than with citalopram. At 30 days, the efficacy criteria had not changed, except for a slightly better remission rate on desipramine. However, citalopram’s acceptability was twice as high as that of desipramine.

It is important to discuss potential bias or study limitations. We decided to study short-term efficacy because the time to onset of therapeutic benefit remains a highly valuable criterion for depressed patients. Furthermore, no studies have reported long-term differences between antidepressants in PD depres-

**TABLE 3. Transient and mild adverse events noted on a systematic questionnaire completed by all patients**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 16)</th>
<th>Citalopram (n = 15)</th>
<th>Desipramine (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry mouth</td>
<td>2</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Constipation</td>
<td>2</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>1</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Pain</td>
<td>4</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Sleepiness</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Worsened tremor</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hot flushes</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Dysuria</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Simple hallucinations</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Loss of libido</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>19</strong></td>
<td><strong>22</strong></td>
<td><strong>40</strong></td>
</tr>
</tbody>
</table>
sion or primary depression. Hence, the short duration of this trial did not enable assessment of the respective long-term efficacies of desipramine and citalopram, which are probably equivalent. Our choice of the low end of the recommended therapeutic range may explain the fact that only a few patients (n = 3) dropped out the study after 14 days due to adverse events but may also have reduced the antidepressants’ efficacy. Furthermore, we cannot rule out a possible influence of the side effects on the efficacy felt by the patients on desipramine compared with the other groups. However, this was a double-blind study, and efficacy and acceptability were separately recorded by a psychiatrist and a neurologist, respectively. The nonsignificant trend toward a lower mean age in the citalopram group may have influenced the results, although the age ranges were not significantly different. Ropinirole was equally distributed and stable during the study, which may limit its potential confounding antidepressant effect. We observed a relatively high placebo effect (a 34% decrease in depression scores and a 45% decrease in anxiety scores), which might in part be explained by patients having several consultations over a short period. Despite these limitations and the relative small sample size, our results were highly significant. Furthermore, the study was performed on a homogenous sample of PD patients and based on rigorous inclusion criteria. Interrater MADRS score variation was avoided in this single-center study, because all patients were scored by the same psychiatrist.

The noradrenergic tricyclic and SSRI antidepressants had differing effects on the various depression symptoms. A three-factor analytic model showed that (i) the dysphoric apathy/retardation factor was more improved by desipramine in the short term and (ii) the psychic anxiety/dysphoria and the vegetative symptoms factors were improved by both antidepressants, as demonstrated by the change in the HARS score.

Minor and transient adverse events were reported twice as frequently by patients on desipramine. This could also partly explain why tricyclic antidepressants are usually considered as being less well tolerated. However, the reported adverse events are commonly encountered with this drug class and were regularly monitored over the first weeks. The PD symptoms worsened in a few instances, as can be expected with SSRIs. Likewise, worsening of dry mouth and orthostatic hypotension are frequently seen in patients on desipramine. The intense short-term effect of desipramine may therefore be related to its effect on norepinephrine and dopamine systems, in view of the drug’s mechanisms of action and the known involvement of impaired norepinephrine transmission in PD depression.

After 1 month, citalopram displayed about the same intensity of effect on depression as did desipramine, suggesting (in view of citalopram’s mechanism of action) involvement of the serotonergic system. The observed time lag (15–30 days) before the appearance of therapeutic benefits with citalopram may be explained by the fact that following initiation of SSRI administration, synaptic serotonin concentrations do not increase until the 5-HT1A presynaptic receptors have been functionally desensitized (2 weeks). However, specific involvement of the serotonin system has not been confirmed in recent reports on depressed PD patients and so citalopram might enhance not only serotonergic but also noradrenergic neurotransmission.

In conclusion, we suggest that desipramine (and possibly other selective norepinephrine reuptake inhibitors) could be useful for rapidly alleviating symptoms in PD depression and that both SSRI and tricyclic antidepressants appear to have an equivalent efficacy profile after 1 month of treatment. However, given the better acceptability of SSRIs and the slight difference in efficacy compared with tricyclics, the former are also highly valuable for treating PD depression. Further studies (in a larger population and using mixed serotonergic and noradrenergic SRIs) are required to confirm our pilot study.

Acknowledgments: This work was supported by “Projet Hospitalier de Recherche Clinique” grants from the French Ministry of Health in 2002 and by the “France Parkinson” charity. The authors thank E. Pelécanos, F. Niset, P. Bocquillon, S. Duhem, N. Waucquier, B. Lucas, P. Devos, K. Ajebar, B. Thielemans, and the Fédération de la Recherche Clinique du CHU de Lille for collecting the data, the Lille University Hospital for promoting the study, and Dr David Fraser (Biotech Communication, Damery, France) for proofreading the manuscript.

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