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Short report Texto

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Cannabidiol for the treatment of psychosis in Parkinson's disease

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Abstract

The management of psychosis in Parkinson's disease (PD) has been considered a great challenge for clinicians and there is a need for new pharmacological intervention. Previously an antipsychotic and neuroprotective effect of Cannabidiol (CBD) has been suggested. Therefore, the aim of the present study was to directly evaluate for the first time, the efficacy, tolerability and safety of CBD on PD patients with psychotic symptoms. This was an open-label pilot study. Six consecutive outpatients (four men and two women) with the diagnosis of PD and who had psychosis for at least 3 months were selected for the study. All patients received CBD in flexible dose (started with an oral dose of 150 mg/day) for 4 weeks, in addition to their usual therapy. The psychotic symptoms evaluated by the Brief Psychiatric Rating Scale and the Parkinson Psychosis Questionnaire showed a significant decrease under CBD treatment. CBD did not worsen the motor function and decreased the total scores of the Unified Parkinson's Disease Rating Scale. No adverse effect was observed during the treatment. These preliminary data suggest that CBD may be effective, safe and well tolerated for the treatment of the psychosis in PD.

Key words

cannabidiol; CBD; Parkinson's disease; psychosis; treatment

Introduction

Psychosis is common in Parkinson's disease (PD), affecting nearly one-third of patients particularly in later stages of the disease (Naimark, *et al.*, 1996). The pathophysiology of psychosis in PD remains unknown and seems to be multifactorial (Ravina, *et al.*, 2007). Levodopa and other antiparkinsonian medications have been incriminated as the main cause, and the psychosis is frequently referred as drug induced. However, it was recognised as an integral part of the disease process even before the introduction of L-dopa (Thanvi, *et al.*, 2005). Furthermore, it is interesting to note that hallucinations appear to be correlated with the severity of cognitive decrease independent of the dopamine precursor treatment (Fenelon, *et al.*, 2000). It has been hotly debated that dopamine and its functional interactions with other neurotransmitters may play an important role (Birkmayer and Riedere, 1975). There is also evidence of the involvement of Lewy Body pathology in the ventral temporal regions of the brain in PD psychosis (Williams and Lees, 2005).

The management of psychosis in PD remains problematic and has been considered a great challenge for clinicians. Reduction in drug dosage or elimination of one or more antiparkinsonian agents is recommended as the first line therapy, but it is not always possible to apply it effectively. Otherwise, an add-on therapy with most conventional antipsychotics can produce unacceptable side-effects with further worsening of the motor symptoms and thus must be avoided. The atypical antipsychotic, clozapine, is considered to be the most effective drug in the treatment of psychosis in PD, with no worsening of

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motor symptoms, but requires mandatory monitoring of haematology. Furthermore, clozapine can cause unacceptable cardiovascular and neurological side-effects (Thanvi, *et al.*, 2005). Therefore, there is a need for a safe and effective pharmacological intervention for PD psychosis.

Studies in animal models and in healthy volunteers clearly suggest an anxiolytic and antipsychotic-like effects of cannabidiol (CBD), a *Cannabis sativa* (cannabis) component, which is devoid of the typical psychological effects of cannabis in humans Zuardi, *et al.*, 2006a. Open case studies of patients with schizophrenia treated with CBD (Zuardi, *et al.*, 1995, 2006b) and a preliminary report of a controlled clinical trial comparing CBD with amisulpride (Leweke, *et al.*, 2007) have suggested that CBD may be a safe and effective alternative possibility to be developed as an antipsychotic drug.

CBD's neuroprotective effects have recently been reported in animal models of PD (Lastres-Becker, *et al.*, 2005; Garcia-Arencibia, *et al.*, 2007). These results suggest that CBD has antioxidant properties providing neuroprotection against the progressive degeneration of nigrostriatal dopaminergic neurons occurring in PD.

Considering the relevance of these preclinical data and the antipsychotic effect of CBD, the aim of the present study was to directly evaluate for the first time the efficacy, tolerability and safety of CBD on PD patients with psychotic symptoms, in an open-label pilot study with flexible dose.

Methods

Study population

The study was conducted at the movement disorder outpatient clinic of the University Hospital of the Faculty of Medicine of Ribeirao Preto, Brazil. A diagnosis of PD was taken according to the United Kingdom Parkinson's Disease Society Brain Bank criteria (Gibb and Lees, 1988). Patients were eligible if they had psychosis for at least 3 months immediately before entry into the study that could not be controlled with reduction of antiparkinsonian medications and that were in stable doses of anti-PD medication for at least 7 days. Exclusion criteria included: diagnosis of a primary psychotic disorder, atypical Parkinsonism, presence of dementia, motor symptoms that would require increased anti-PD medication during the study period or unstable medical and other neurological or psychiatric condition.

Diagnostic psychiatric interviews were conducted by one of the authors (JP), using the Portuguese version (Del-Ben, *et al.*, 2001) of the Structured Clinical Interview for DSM-IV (First, *et al.*, 1997). In the test–retest reliability study of this version, in which both psychiatrists participated as evaluators, the concordance (Kappa) was 0.90 for psychotic disorders in general.

Six consecutive outpatients (four men and two women), mean age 58.8 ± 14.9 years, with a mean of 10.6 ± 3.7 years of disease and a median of 1050 mg/day of L-dopa treatment were included. No patient was on psychiatric medication.

Ethical considerations

All subjects and their responsible relatives (caregivers) gave written informed consent after being fully informed of the research procedure, following approval by the local ethical committee.

Data collection

The subjects received CBD in addition to their usual therapy for 4 weeks. CBD in powder, approximately 99.9% pure (supplied by THC-Pharm, Frankfurt, Germany), was dissolved in corn oil. The same amount of corn oil was used as a placebo. The drug and placebo were packed inside identical gelatin capsules. All subjects were started on one 150 mg CBD tablet and the dose was increased weekly by 150 mg depending on the clinical response. Capsules (in a light-resistant glass vial) were dispensed on a weekly basis and the patients were asked to return with the glass vial for the next drug supply. Family members were also involved in the monitoring of adherence to treatment. Subjects were evaluated before receiving CBD and at the end of weeks 1, 2, 3 and 4 under the drug, at the same time of the day and by same unblinded neurologist and psychiatrist. Assessments included neurological and physical examinations, vital signs and clinical assessments of adverse events. The main outcome measure of efficacy and health was the Bech's version of the Brief Psychiatric Rating Scale (BPRS; Bech, *et al.*, 1986) translated and adapted to Portuguese (Zuardi, *et al.*, 1994) with the interviews performed using a Structured Interview Guide (SIG), which has been shown to enhance test–retest reliability of the BPRS (Crippa, *et al.*, 2001) and the Parkinson Psychosis Questionnaire (PPQ, Brandstaedter, *et al.*, 2005). The secondary outcomes were the Unified Parkinson's Disease Rating Scale (UPDRS, Fahn, *et al.*, 1987), the Clinical Global Impression – Improvement scale (CGI–I, National Institute of Mental Health, 1976), the Mini-Mental Status Examination (MMSE, Folstein, *et al.*, 1975) and the Frontal Assessment Battery (FAB, Dubois, *et al.*, 2000). Comparisons of the rating scale scores were made by using the non-parametric Friedman test and the Wilcoxon Signed Rank test. All tests were two-tailed, and a probability of $P \leq 0.05$ was taken as significant.

Results

Table 1 shows the median [minimum–maximum] scores of the rating scales before and during the 4 weeks under CBD added to patients' treatments.

Significant improvement with CBD in the total scores of BPRS as well as in the four BPRS factors' scores, including the ones specifically related to positive (thinking disorder) and negative (withdrawal-retardation) symptoms (Crippa, *et al.*, 2002) were observed. Moreover, a questionnaire developed to assess psychotic symptoms in PD, which quantifies the frequency and severity of sleep disturbances, hallucinations/illu-

Table 1 Rating scale scores (median [minimum–maximum]) at the different assessment times

	Weeks (mean of cannabidiol dose – mg)					Statistics
	0 (0)	1 (150)	2 (250)	3 (325)	4 (400)	
BPRS						
Total score	18.5 (11–26)	10.0 (2–18)	8.0 (0–16)	6.0 (0–12)	5.5 (0–12)	$\chi^2 = 21.6$[a] $P < 0.001$
Thinking disorder	7.0 (3–10)	2.5 (0–7)	2.0 (0–5)	1.0 (0–3)	1.0 (0–2)	$\chi^2 = 17.1$[a] $P = 0.002$
Withdrawal-retardation	5.0 (4–8)	3.5 (2–8)	3.0 (0–8)	3.0 (0–7)	3.5 (0–7)	$\chi^2 = 14.1$[a] $P = 0.007$
Anxious-depression	3.0 (2–8)	1.0 (0–4)	1.5 (0–5)	0.5 (0–5)	1.0 (0–2)	$\chi^2 = 15.9$[a] $P = 0.003$
Activation	2.5 (1–5)	1.0 (0–4)	0.0 (0–4)	0.0 (0–3)	0.0 (0–3)	$\chi^2 = 14.9$[a] $P = 0.005$
PPQ						
Total score	13 (4–21)	4 (2–8)	4.5 (0–11)	2.5 (0–9)	1.5 (0–4)	$\chi^2 = 19.9$[a] $P = 0.001$
UPDRS						
Mentation, behaviour and mood	6.25 (2–9)	—	—	—	3.0 (0-9)	$Z = 1.8$[b] NS
Activities of daily living	17.0 (9–45)	—	—	—	12.5 (3-45)	$Z = 1.6$[b] NS
Motor score	44.5 (20.5–62)	—	—	—	36 (31–64)	$Z = 1.2$[b] NS
Complications of therapy	3 (1–7)	—	—	—	2.5 (0–7)	$Z = 0.4$[b] NS
Total score	67.5 (38.5–123)	—	—	—	51.5 (35–125)	$Z = 2.0$[b] $P = 0.046$
MMSE						
Total score	21 (16–26)	—	—	—	25.5 (14–27)	$Z = 1.6$[b] NS
FAB						
Total score	5.5 (3–13)	—	—	—	7.0 (4–10)	$Z = 0.3$[b] NS
CGI-I						
Very much improved = 1 No change = 4 Very much worse = 7	4	2 (1–3)	2 (1–3)	1.5 (1–3)	1.5 (1–3)	$\chi^2 = 17.9$[a] $P = 0.001$

BPRS, brief psychiatric rating scale; PPQ, Parkinson psychosis questionnaire; UPDRS, unified Parkinson's disease rating; CGI-I, clinical global impression improvement; MMSE, mini-mental status examination; FAB, frontal assessment battery; NS, non significant.

[a]Friedman test.

[b]Wilcoxon signed rank test.

sions, delusions and orientation (PPQ), has also shown a significantly decrease in the scores after CBD treatment.

The total score of the UPDRS has decreased and the CGI-I score improved significantly in the end point. The MMSE and FAB scores did not significantly change during the trial.

Discussion

These results are in accordance with the previously suggested potential antipsychotic effects of CBD (Zuardi, *et al.*, 2006a).

The observed rapid onset of the antipsychotic effect in the PD patients may be attributed to changes in dopaminergic neurotransmission. Because the psychotic symptoms of these patients were possibly associated with the use of the dopaminergic drugs, the observed antipsychotic effect of CBD may have occurred through the attenuation of dopaminergic activity in areas related to the production of psychotic symptoms. This is consistent with the preclinical evidence that CBD has previously been shown to attenuate the stereotyped behaviour and the hyperlocomotion induced by dopaminergic drugs in animal models of psychosis (Zuardi, *et al.*, 1991; Moreira, *et al.*, 2005). Indeed, the cannabinoid system seems to be involved with the dopaminergic modulation because the stimulation of

cannabinoid CB1 receptors produces an activation of dopaminergic transmission (French, *et al.*, 1997; Diana, *et al.*, 1998). Although CBD has shown low affinity with CB1 receptors (Felder, *et al.*, 1995), it seems to antagonise the CB1 agonists (Thomas, *et al.*, 2007) and the new described cannabinoid receptor GPR55 (Ryberg, *et al.*, 2007).

An important observation of this study was that CBD did not worsen the motor function. Rather, the scores of all UPDRS items decreased, but not reaching statistical significance, including the item 'motor examination', although the total score of this scale has decreased significantly. In animal model of PD, daily administration of CBD during two weeks produced a significant waning in the magnitude of toxic effects produced by a unilateral injection of 6-hydroxydopamine into the medial forebrain bundle (Lastres-Becker, *et al.*, 2005), probably by antioxidant cannabinoid receptor-independent properties (Garcia-Arencibia, *et al.*, 2007). This antioxidant action of CBD is reinforced by the observation that this cannabinoid reduced the striatal atrophy caused 3-nitropropionic acid in an animal model of Huntington's disease by mechanisms independent of the activation of cannabinoid, vanilloid TRPV1 and adenosine A2A receptors (Sagredo, *et al.*, 2007). The neuroprotective effect of CBD in the human basal ganglia was suggested by the strong positive correlation of *N*-acetylaspartate/total creatine ratio and CBD in the putamen/globus pallidum of recreational cannabis users. This could reflect an enhancement of neuronal and axonal integrity in these regions by CBD (Hermann, *et al.*, 2007).

Another important finding was that CBD did not induce any decrease in cognitive function because the MMSE and FAB scores did not significantly change during the trial. No adverse effect was observed during treatment with CBD.

The results of this pilot study showed that CBD may be effective, safe and well tolerated for the treatment of the psychosis in PD. However, randomised double-blind controlled assays would be necessary to further confirm this observation.

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