Dyskinetic patients show rebound worsening of affect after an acute L-dopa challenge

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Abstract

Background: Motor response complications that arise with repeated L-dopa administration for the treatment of Parkinson's disease are well understood but the relationship between motor response complications and affect are not. We proposed that patients with dyskinesias would report rebound worsening in affect during wearing-off of L-dopa effect.

Methods: Fifty Parkinson's disease patients with were assessed with the Purdue Pegboard test and rated Positive Affect and Negative Affect after overnight withdrawal of dopaminergic medications and half hourly for 6 h after a standard L-dopa challenge. Patients were carefully classified into stable responder (n = 12), fluctuator (n = 15), and dyskinetic (n = 23) groups.

Results: Positive Affect was improved by L-dopa in dyskinetics and to a lesser degree in fluctuators but not in stable responders. At T = 4–6 h, Positive Affect rebounded below baseline in dyskinetics only. On regression analysis, rebound worsening positively correlated with ratings of dyskinesia severity. Negative Affect improved with L-dopa in all groups and tended to remain below baseline for 6 h after L-dopa challenge. Peak effects of L-dopa on Positive Affect and Negative Affect occurred significantly earlier than effects on Purdue Pegboard test and were positively correlated with L-dopa equivalent daily dose.

Conclusion: There is a clinical dissociation between L-dopa effects on motor function, Positive Affect and Negative Affect. Rebound worsening in Positive Affect occurred only in dyskinetic patients and the onset of rebound worsening occurred before the end of the motor benefit phase. These observations could explain why some Parkinson patients report wearing-off symptoms despite the external impression of good motor control.

1. Introduction

The development of disabling motor response complications to L-dopa marks a critical point in the progression of Parkinson's disease (PD). Wearing-off represents progressive shortening of the duration of action of individual L-dopa doses and dyskinesias often develop soon after the onset of wearing-off symptoms [1]. One hypothesis surrounding postsynaptic factors in dyskinesias, is that repeated exposure to L-dopa induces a sensitisation to its behavioural stimulant properties [2] with consequent dysregulation of genes and proteins in downstream neurons resulting in altered neuronal firing patterns. Wearing-off symptoms may also occasionally be followed by a deterioration of Parkinson symptoms to a level below that observed at baseline. This phenomenon, called rebound worsening, is poorly understood.

Soon after L-dopa initiation, PD patients begin to experience transient elevations in "mood" with each dose [3]. The association between mood and motor fluctuations is complex. For instance, PD patients with advanced disease report lower mood in an "on" state with dyskinesias compared to an "on" state without dyskinesias [4]. However, these studies are hard to interpret because they utilised models of affect based on conceptualisations of positive ("happy") and negative ("sad") affect as diametric opposites [3]. While positive (PA) and negative (NA) affect do represent dominant dimensions in self-reported mood and from a terminology standpoint
appear to occupy opposite poles, this is not the case [5]. Divergent forms of evidence suggest that PA and NA are better represented as orthogonal dimensions [6] mediated by functionally segregated brain regions that spatially overlap and are highly interconnected [7,8].

To our knowledge, the clinical relationship between affect and motor response complications has not previously been studied. The relationship may be important because evidence from preclinical studies indicates that dyskinesias signal the emergence of broader changes in systems regulating sensorimotor and limbic system function [9], indicating a possible link between the presence of dyskinesias and the emergence of states characterised by low PA.

We therefore aimed to test the effect of L-dopa on Positive Affect and Negative Affect and its temporal relationship to motor function in PD patients who were well characterised for the presence of motor response complications. We proposed that patients with dyskinesia would show different affective responses to L-dopa; in particular, we sought evidence of rebound worsening in affect compared to patients without dyskinesias. We also aimed to assess whether rebound worsening was predicted by disease or medication variables.

2. Methods

2.1. Subjects

A sample of 50 PD patients receiving regular dopaminergic drug therapy with MMSE score > 26 was studied as part of a comprehensive study of L-dopa effects on motor and non-motor symptoms of PD [10]. Written informed consent was obtained from each patient for protocols approved by the Melbourne Health human research ethics committee.

2.2. Procedure

PD patients were examined in the morning in a practically defined “off” state after overnight withdrawal of dopaminergic medications. Baseline (t1) assessments included the Unified PD Rating Scale (UPDRS), Purdue Pegboard test (PPT) [11] and the Positive Affect Negative Affect Schedule (PANAS) (using instructions asking patients to rate feelings “right now, at the present moment”) [5]. The PANAS was initially developed to provide a reliable estimate of two broad and largely independent factors implicated in emotional experience: Positive and Negative Affect (PA and NA). The PANAS is composed of 20 self-ratings items corresponding to adjectives (e.g., Interested, Distressed) that describe different states, feelings and emotions. Each of the 10 terms linked respectively to NA and PA requires a score on a 5-point Likert scale. Each rating seeks to measure the intensity of that specific feeling or emotion during the given timeframe for the participant (1 — very slightly or not at all; 5 — extremely). The factorial structure of the 20 items version of the PANAS comprises only two orthogonal factors, each related to one of two primary dimensions of mood: Positive Affect and Negative Affect. The two scales exhibit acceptably high internal consistency (Cronbach’s coefficient alpha for NA & PA/ present: 0.85) and invariably low intercorrelations (< 0.16 for present instructions) [5]. The PPT measures finger and hand dexterity. The total number of pegs placed in 30 s with the dominant hand, non-dominant hand, and hands simultaneously was measured, similar to previously [12].

L-dopa challenge dose was given as the patient’s usual morning dose plus an additional 50 mg. PPT and PANAS were repeated every 30 min for 6 h, and the UPDRS part III, PPT, and PA to evaluate the effects of group membership, time after L-dopa dose, and their interaction. T-tests were used for post-hoc analyses using LSD. The following values were calculated: 1. Percentage change from t1 to peak value for PPT (i.e., the highest value achieved after baseline), 2. Percentage change from t1 to “on” state UPDRS part III, 3. Percentage change from t1 to peak value of PA, 4. Percentage change from t1 to trough value of NA and 5. Percentage change from baseline to T = 6 h of PA (rebound worsening). Potentially predictive variables of percentage change in PPT, PA, NA and rebound worsening were entered into a forward stepwise logistic regression model. The following explanatory variables were used in the regression analyses: age, disease duration, sex, LEDD, and modified AIMS score. Percentage change in UPDRS part III was used for the regressions for affect. Data for NA were not normally distributed due to a strong floor effect. Therefore, NA data were dichotomised according to proportion scoring > 10 and data were analysed with a generalised linear mixed models in Genstat.

3. Results

3.1. Patient characteristics

Patient characteristics are shown in esupp 1. As expected, the groups differed in LEDD intake and disease duration. 4 of the 23 patients with dyskinesias reported no symptoms of wearing-off.

3.2. Practically defined “off” state

Scores for PPT, PA and NA after overnight withdrawal of medication, i.e. in a practically defined “off” state, are given in Table 1. Fluctuators performed better on PPT compared to dyskinesics (P = 0.009) and trended to performing better than stable responders (P = 0.077) — broadly consistent with “off” UPDRS III ratings in each group (esupp 1). No significant differences in PA or NA were found at baseline.

3.3. L-dopa effects by group

Fig. 1 depicts the effects of L-dopa on motor performance and subjective state (PA and NA) in 1A. stable responders, 1B. fluctuators and 1C. dyskinesics. L-dopa effects were typical of those reported in several other recent studies [11,12]. For PPT [F(24,564) = 1.949; P = 0.005] and PA [F(24,564) = 2.073; P = 0.002], there was a significant group-by-time interaction.

In stable responders, (Fig. 1A) the change in PPT or PA after L-dopa did not achieve significance compared to baseline. However, NA was reduced between 3 and 4.5 h. In fluctuators, PPT was significantly increased at 2.5 and 3.0 h. PA did not significantly differ at T = 0.5—6.0 h from baseline. However, for the fluctuators, PA at T = 2.0 h, T = 2.5 h, and T = 3.0 h was significantly higher compared to PA at T = 0.5 h (P = 0.029, 0.020 and 0.032, respectively). NA was significantly reduced to below baseline from 0.5 to 6.0 h. Dyskinesics showed significant motor benefit from 1.0 to 4.0 h. PA was significantly improved at 1.5 h compared to baseline but was significantly lower than baseline from 4.0 to 6.0 h. NA was reduced between 1.0 and 4.0 h.

3.4. Maximum effects of L-dopa on PPT, PA and NA and rebound effects

The maximum effect of L-dopa was measured by comparing the percentage change from baseline to peak values of PPT and PA and trough values of NA. Dyskinesics showed greater percentage change in PPT compared to fluctuators and stable responders. No differences were found between groups in rebound effects as measured by percentage change from baseline to values at T = 6 h (Table 1).

3.4.1. Regressions

On multivariate analysis LEDD was the only variable to independently predict percentage change in PPT from baseline to peak.
(P = 0.002), PA from baseline to peak (P < 0.001) and NA from baseline to trough (P < 0.001). Score on modified AIMS was the only variable to independently predict rebound worsening (P = 0.025).

3.5. Time-to-peak L-dopa effect on PPT, PA and NA

The time from baseline to the time at which the peak response for PPT, PA and NA occurred after L-dopa (time-to-peak) was analysed. The mean time-to-peak in PPT was 2.8 h (SE = 0.2), and PA was 1.8 h (SE = 0.2). Mean time-to-rough in NA was 1.3 h (SE = 0.2). Using repeated-measures ANOVA, the main effect of time-to-peak was significant [F(2,94) = 15.14; P < 0.001]. The effect of group [F(2,47) = 2.86; P = 0.067] and time-to-peak by group interaction failed to reach significance [F(4,94) = 1.78; P = 0.139]. Post hoc analysis showed that the time-to-peak was significantly longer for PPT compared to PA (t(49) = 3.7, P < 0.001) and NA (t(49) = 5.5, P < 0.001).

4. Discussion

PD patients objectively grouped according to motor response complications were examined to establish their treatment response to a L-dopa challenge with regard to affective states and motor function. We observed differential effects of L-dopa on PA and NA according to whether patients were grouped according to a stable L-dopa response, having motor fluctuations or dyskinesias. The time course of changes in affect (PA and NA) were clearly dissociated from motor effects with a significantly earlier time-to-peak effect of L-dopa on affect compared to motor function. Moreover, rebound worsening in PA was demonstrated to occur only in dyskinetic patients and correlated with dyskinesia severity.

In a practically defined “off” state, no differences were found in affect state between the groups. In the L-dopa benefit phase, PA improved (increased) most in dyskinetics and NA improved (reduced) in all three groups. Improvements in PA did not reach significance in stable responders. This extends the findings of a previous study, in which PD patients were found to have modest improvements in “mood” with a L-dopa challenge within months of the initiation of regular L-dopa treatment and patients identified as having motor fluctuations reported greater improvements in affect from a L-dopa challenge compared to early PD patients [3]. However, these studies were limited by conceptualisations of mood with “sad” and “happy” as diametrically opposite dimensions. We found that changes in PA and NA were also positively correlated with higher LEDD, raising the possibility that in L-dopa-responsive patients, increasing total LEDD may contribute to increases in the magnitude of motor and affective responses to each individual dose of L-dopa.

Only in dyskinetic patients, did ratings of PA deteriorate to below baseline values (from 4 h after L-dopa intake), consistent with the phenomenon of rebound worsening. In contrast, NA tended to remain improved compared to baseline in stable responders and fluctuators but returned to baseline in dyskinetics. Rebound worsening in PA has not previously been reported in PD. Our cohort of dyskinetic patients had relatively short disease duration and included some patients who were not aware of end-of-dose wearing-off. We found no evidence of rebound worsening in PA in fluctuators or stable responders within the 6 h time period. While these data suggest the possibility that rebound worsening may be linked to the presence of dyskinesias there are other potential interpretations. For instance, other variables may be relevant including duration of treatment and LEDD, that may influence the emergence of dyskinesias [1]. However, importantly, we found a clear dissociation between motor state and affect – as dyskinetics demonstrated rebound worsening in PA at a time when there was still demonstrable and significant L-dopa benefits on motor function (i.e., at T = 4 h). These observations could explain why some Parkinson patients report wearing-off symptoms despite the external impression of good motor control.

We found no rebound worsening in motor function. Rebound worsening in motor function has only previously been reported in small numbers of highly selected Parkinsonian patients with prolonged disease duration [16,17].

Taken together, these observations support the notion that PA and NA are mediated by functionally segregated but overlapping and interconnected systems. The PANAS scale has been widely used to investigate and quantify changes in PA or NA states in experimental contexts aimed at either up- or down-regulating affective responses. Mood manipulations in healthy individuals can have dissociated effects on state ratings of PA and NA such that it is possible to induce mixed feelings of happiness and sadness simultaneously [18]. Consistent with this, it has also been proposed that these 2 core affective dimensions have functionally segregated neurobiological underpinnings. There is a substantial amount of research supporting a relationship between NA and the structure and function of subcortical structures including the amygdala [19].
and hippocampus, and prefrontal structures including the anterior cingulate and right dorsolateral prefrontal cortex [7]. Conversely, it is now clear that the ventral pallidum as well as the nucleus accumbens controls separate representations of the motivational components and the hedonic impact of reward [8].

Moreover, in PD, state ratings of PA and NA are acutely sensitive to medication L-dopa challenge [20,21] and are demonstrated to change within minutes of acute stimulation of the subthalamic nucleus [22]. In healthy controls and in PD, PA (but not NA) tends to associate with dopamine neurotransmission within the ventral striatum [23,24]. In contrast, Parkinson motor symptoms correlate with dopamine neurotransmission within the dorsal striatum [2].

We also found that the time courses of the different psychomotor effects of L-dopa were temporally dissociated such that the time to peak effect on affect was significantly shorter than the time to peak effect on motor function (measured by the PPT). This may reflect differential effects of L-dopa on dopaminergic neurotransmission in the ventral and dorsal striatum. Dopamine synapses in the ventral striatum and caudate-putamen share similarities in cytoarchitectural organisations but these regions receive distinct afferent inputs and send distinct efferent projections. However, there may be differential neuroplastic effects from iterative dopaminergic drug administration according to striatal topography [25]. This may be analogous to the situation in which compulsive drug wanting and change in PA (but not NA) has been linked to ventral
striatal dopamine function [24] whereas change in UPDRS has been linked to dorsal striatal dopamine systems [2].

In “off”, fluctuators performed better on the PPT compared to dyskinetics. In general, dyskinesias occur in approximately 50% of PD patients who have been treated with L-dopa for more than 5 years [1]. It has also been shown that patients take a little more than 5 years for their defined “off” state disability (i.e., motor function after overnight withdrawal of medications) to exceed their pre-treatment disability [26]. Therefore, at the time that patients develop dyskinesias, the defined “off” state would be expected to deteriorate beyond the untreated condition due to disease progression.

Significant motor effects on UPDRS after L-dopa were found in all 3 groups (esupp). Within group improvement in PPT was found in fluctuators and dyskinetics but not stable responders when compared to baseline (possibly due to the smaller sample size of the stable responders). However, percentage change in PPT from baseline to peak was significantly improved in all 3 groups (Table 1). The magnitude of L-dopa effects on motor performance (PPT) found here was comparable to other studies using similar performance measures and consistent with other findings that dyskinesics have a greater percentage change in peak PPT compared to stable responders and fluctuators [27].

Several limitations need to be pointed out. Firstly, time intervals between assessments may have been too long to detect very transient rebound worsening in motor function. In one study using 5–15 min intervals, rebound worsening in motor function was described as “transient” [16]. Another study using 30 min interval measurements reported that the duration of motor rebound worsening was between 30 and 90 min [17]. A more likely explanation for the absence of rebound worsening in motor function in our study is that disease duration in dyskinesics (mean 5.6 years) was much shorter than in the studies by Kempseter et al. and Nutt et al. where the patients had very advanced disease (mean disease duration 12 years [16] and 15 years [17]). Secondly, the 6 h duration of observation after the L-dopa challenge may have been too short to detect late rebound worsening in PA in the nondyskinetic groups although there was no suggestion of this when examining the time course effect curves. Thirdly, no significant between group effects were found for rebound worsening of PA in dyskinetics which could be explained by the smaller sample sizes in nondyskinetic groups.

In conclusion, while the negative impact of abnormal L-dopa induced dyskinetic movements in many patients is obvious, these data raise the possibility that emergence of dyskinesias may also coincide with subtle but clinically relevant changes in affective processing. Pulsatile stimulation of ventral striatal postsynaptic receptors may lead to aberrant plasticity in limbic and cognitive brain regions or alternatively could relate to broader negative effects that dyskinetics and motor response complications may have on mood and fluctuations in affective state in general [9]. It has been shown, for instance, that patients with dyskinesias score worse in quality of life subscales particularly activities of daily living, emotional well-being, communication, and bodily discomfort [28]. A high frequency of pain has been reported in PD patients with dyskinetics, and we have previously reported on a differential response to evoked pain in dyskinetic patients [10]. Dyskinesia severity has been observed to correlate with increasing depressive symptoms in PD outpatients [15]. Dyskinesias have also been linked to disabling medication-induced behavioural phenomena such as punding [29]. ICDs [30] and dopamine dysregulation syndrome [15]. Moreover, in DDS patients, the emergence of a strongly oversive withdrawal state is particularly characterised by anhedonia (low PA) [21] and this may further contribute to compulsive drug use in some patients. Clinician and patient awareness of these phenomena could lead to improved clinical management strategies in early and advanced disease.

Conflict of interest

AHE has received honoraria from Novartis for giving presentations, and providing consultancy services. He has participation in scientific advisory board meetings for Novartis, UCB Pharma, Allergan and Boehringer Ingelheim. SYL was supported by an unrestricted educational grant from Novartis. The other authors report no conflicts of interest.

Author contributions

Dr Evans participated in conception and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content.

Dr Farrell participated in conception and design, material support and drafting of part of the manuscript.

Professor Helme participated in conception and design, supervision and revision of the manuscript for intellectual content.

Professor Gibson participated in conception and design, supervision and revision of the manuscript for intellectual content.

Dr Lim participated in design, administrative, and material support, acquisition of data, and drafting of part of the manuscript and critical revision of the manuscript for important intellectual content.

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Appendix. Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.parkreldis.2012.01.020.

References


