Non-motor symptoms associated with short term Levodopa effect in patients with early Parkinson's Disease

A pilot study

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4. oktober 2013

Abstract

Parkinson's disease (PD) is a chronic progressive neurodegenerative disorder caused by loss of nigrostriatal dopaminergic pathways.

PD is generally characterized by bradykinesia, resting tremor, rigidity and postural instability and the clinical diagnosis is based on these motor symptoms.

Non-motor symptoms (NMS) such as sleep disturbances, anxiety, depression, orthostatic hypotension and pain are however also important and common symptoms of the disease. Over 90 % of patients across all stages of the disease suffer from NMS.

Six patients were recruited and examined with focus on non-motor symptoms, such as pain and orthostatic hypotension, before and after administration of a standard dose of levodopa (100 mg). A screening for depression and anxiety and a motor examination was also performed.

The hypothesis of this pilot study is that levodopa has a positive short term effect on NMS in PD patients. The aim of this study is therefore to compare NMS, particularly pain and blood pressure, before and after medication with levodopa in a group of newly diagnosed PD patients.

The results of this study show that pain and depression are present in patient with early PD. It's not possible to draw any conclusions about the short term effect of levodopa from this material since the results were not cohesive and the patient group was too small.

1 Introduction

1.1 Parkinson's Disease

Many parts of the brain are involved in the process of a planned movement. Premotor cortex, basal ganglia and cerebellum represent important parts of the brain involved in movement. Disease and damage in these parts can result in movement disorders. Basal ganglia is a general name for some of the nucleuses in the cerebrum. Function deficit in the basal ganglia results in motor and non-motor complications. The most common cause for function deficit is neurodegenerative disorders (1).

Parkinson's disease (PD) is a chronic progressive neurodegenerative disorder caused by loss of nigrostriatal dopaminergic pathways. Dopamine is a neurotransmitter and patients with Parkinson's disease will eventually develop a dopamine deficiency caused by neuron degeneration in substansia nigra (1).

PD is generally characterized by bradykinesia, resting tremor, rigidity and postural instability and the clinical diagnosis is based on these motor symptoms. Research has consequently been focused on these characteristics and the following treatment regimes.

PD is not possible to cure but the symptoms can be relieved. There are many different treatment regimens and all must be individualized for each patient. The main goals with treatment are to treat the symptoms and to stop the progress of the disease. Most symptoms in PD are caused by dopamine deficiency. Replacement therapy of dopamine is thus a frequently used treatment regime. Dopamine can't pass the blood brain barrier so instead the patients are given Levodopa. Levodopa is absorbed in nigrostriatal neurons where it is transformed to dopamine (1). Levodopa is very effective on the motor symptoms, but the effect on non-motor symptoms is sparsely investigated. The short-term effect of levodopa on motor symptoms is well documented and has good effect but the knowledge of short term effect on NMS is limited and thus of great interest for future research.

1.2 Non-motor symptoms

Non-motor symptoms (NMS) such as sleep disturbances, anxiety, depression, orthostatic hypotension and pain are however also important and common symptoms of the disease (2). Over 90 % of patients across all stages of the disease suffer from NMS. There are two instruments developed to assess NMS in PD: the Non-Motor Symptoms Questionnaire (NMSQuest) and the Non-Motor Symptom Scale (NMSS). Studies using the NMSS suggest that NMS have a direct negative effect on quality of life (3). A study using the NMSQuest has highlighted that several non-motor issues had not been discussed with the doctor before they were flagged by the NMSQuest (4).

In a study by Chaudhuri et al it was reported that several NMS are on the top five of most troublesome symptoms in patients with early PD and a typical patient with PD can have up to 12 NMS (5). It has also been stated that NMS can occur in all stages of the disease, even before the motor symptoms. The number of NMS correlates with the duration and severity of PD (6).

1.2.1 Pain

One of the most frequent NMS in patients with PD is pain. A recently published review concluded that pain is observed in approximately 30 – 50% of PD patients and is most certainly an under diagnosed and/or overlooked symptom (5). The knowledge of the pathophysiology of pain in PD patients is also limited. Ford classification of pain distinguishes the following categories: 1) musculoskeletal pain, 2) neuropathic pain, 3) dystonia related pain and 4) central pain. The musculoskeletal pain is the most common pain within PD patient and the prevalence ranges from 45 to 75% (7). The cause of the pain sets the treatment therapy and the most common cause of pain is parkisonian rigidity. When the pain originates from the rigidity caused by the Parkinson disease it’s called secondary pain. When the pain is secondary to the disease the treatment is directed towards the disease and thereby indirectly the pain. Dopaminergic treatment such as levodopa is known to have good effect on motor symptoms and therefore effect on pain can be expected.

1.2.2 Orthostatic hypotension

Orthostatic hypotension is also a frequent finding in patients with Parkinson's disease but its diagnosis remains uncertain since it is difficult to distinguish between the role of the disease and that of medication (8). Antiparkinsonian medication may cause autonomic dysfunction when levodopa is transformed to dopamine, which regulates the blood pressure through vasodilation. A recent metaanalysis has shown that the prevalence of orthostatic hypotension in PD is about 30% (9).

1.2.3 Depression

The prevalence of depression amongst PD patient varies between 20 and 50% and is frequently associated with greater disability, rapid progression of motor symptoms and increased mortality (10). Depression is one of the NMS that has largest impact on quality of life and is often present before any motor symptoms (3). SSRI, tricyclic antidepressant and dopamine agonists have demonstrated antidepressant effect on depressed patients with PD (10).

1.3 Scales and instruments

The scales most frequently used in making the diagnosis of PD based on the motor symptoms are the Hoehn and Yahr scale (H&Y), the Schwab & England scale and the Unified Parkinson's Disease Rating Scale (UPDRS). The UPDRS is the most commonly used and validated to document the disease and the response to medication. UDRS is a four tiered scale that emphasizes on motor measurements (11). In this study the UPDRS part 3 was chosen to measure the motor symptoms due to its validity and frequent use.

Pain can be measured in many ways, the most common are the Visual Analogue Scale (VAS), Numeric Rating Scale (NRS), Verbal Rating Scale (VRS) and Faces and Pain Scale- Revised (FPS-R). VAS consists of a horizontal line, 100 mm in length. The end points of the VAS is "No pain" and "Worst imaginable pain". The NRS is 11- point scale from 0 through 10; 0 representing "No pain" and 10 representing "Worst imaginable pain". The VRS is a 5- point scaled consisting of five phrases (no pain, mild pain, moderate pain, intense pain and maximum pain) that describe the pain intensity. FRS-R is 6- point scale with 6 different faces

that represent different stages of pain. Each illustration represents a numeric score (0, 2, 4, 6, 8, and 10) (12).

1.4 Aim and hypothesis

The hypothesis of this pilot study is that levodopa has a positive short term effect on NMS in PD patients. The aim of this study is therefore to compare NMS, particularly pain and blood pressure, before and after medication with levodopa in a group of newly diagnosed PD patients. Degree of depression is also examined and a standard motor function test will be performed.

2 Subjects and Methods

2.1 Patients and study design

Six patients from the Akershus sykehus, Oslo, Norway were recruited to the study. The inclusion criteria were patients who had been diagnosed with Parkinson's disease during the last 5 years with no previously antiparkinsonian medication. Patients with cognitive decline and patients who could not communicate due to other illness were excluded. No age or gender limits were set. The patients were recruited when arriving for a levodopa test.

2.2 Examination

The patients were examined with focus on non- motor symptoms before (T0) and after (T1) administration of a standard dose of levodopa (100 mg). At T0 blood pressure was measured manually and the patients assessed perceived pain intensity and completed a questionnaire about anxiety and depression. The T1-examination was performed 90 minutes after levodopa administration and then blood pressure and pain was assessed once again. A standard motor examination was also carried out before and after medication.

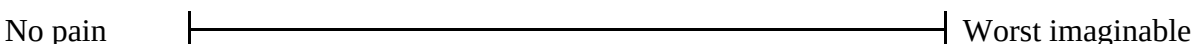
2.3 Outcome measures

Blood pressure was assessed in mmHg (manual measure). Orthostatic hypotension is defined as a systolic or diastolic blood pressure fall of ≥ 20 mm Hg and ≥10 mmHg respectively, first pressure is measured lying down and the second either standing or head- up tilt to at least 60° within 3 min (9).

Pain intensity was measured on a visual analog scale (VAS) which is considered to be a valid instrument for pain assessments (7).

The scale is validated to be used in both chronic and experimental pain (13). Most important, the VAS scale was chosen to avoid memory bias. The question asked was:

How much pain do you suffer from in this moment?



Hospital anxiety and depression scale (HADS) is a validated instrument used to screen for depression and anxiety and is the most commonly used in at Akershus Sykehus (14). The scale contains 7 questions about anxiety and 7 about depression. (Table 1)

UPDRS part 3 was chosen for assessment of motor symptoms before and after medication. The UPDRS is used worldwide and is validated to document the disease and the response to medication (11). The scale included 13 domains typical for PD (see Table 2) and each question was graded on a 5 point scale.

Table 1. HADS questionnaire where A concerns anxiety and D concerns depression.

A	**I feel tense or wound up:** Most of the time -3 A lot of the time- 2 From time to time- 1 Not at all – 0	D	**I feel as if I am slowed down:** Nearly all the time- 3 Very often- 2 Sometimes- 1 Not at all- 0
D	**I still enjoy the things I used to enjoy:** Definitely as much- 0 Not quite as much- 1 Only a little- 2 Hardly at all- 3	A	**I get a sort of frightening feeling like butterflies in the stomach:** Not at all- 0 Occasionally- 1 Quite often- 2 Very often- 3
A	**I get a sort of frightened feeling as if something awful is about to happen:** Very definitely and quite badly-3 Yes, but not too badly- 2 A little but it doesn't worry me- 1 Not at all- 0	D	**I have lost interest in my appearance:** Definitely- 3 I don't as much care as much as I should- 2 I may not take quite as much care- 1 I take just as much care- 0
D	**I can laugh and see the funny side of things:** As much as I always could- 0 Not quite so much now- 1 Definitely not so much now- 2 Not at all- 3	A	**I feel restless as I have to be on the move:** Very much indeed- 3 Quite a lot- 2 Not very much- 1 Not at all- 0
A	**Worrying thoughts go through my mind**: A great deal of the time- 3 A lot of the time- 2 From time to time, but not often- 1 Only occasionally- 0	D	**I look forward with enjoyment to things:** As much as I ever did- 0 Rather less than I used to- 1 Definitely less than I used to- 2 Hardly at all- 3
D	**I feel cheerful**: Not at all- 3 Not often- 2 Sometimes- 1 Most of the time- 0	A	**I get sudden feelings of panic:** Very often indeed- 3 Quite often- 2 Not very often- 1 Not at all- 0
A	**I can sit at ease and feel relaxed:** Definitely- 0 Usually- 1 Not often- 2 Not at all- 3	D	**I can enjoy a good book or radio/ TV program:** Often- 0 Sometimes- 1 Not often- 2 Very seldom- 3

Table 2. Unified Parkinson's disease Rating Scale, UPDRS part 3.

Motor examination	0	1	2	3	4
Speech					
Facial Expression					
Tremor at rest					
Head					
Right arm					
Left arm					
Right leg					
Left leg					
Action or postural tremor of hands					
Right					
Left					
Rigidity					
Neck					
Right arm					
Left arm					
Right leg					
Left leg					
Finger taps					
Right					
Left					
Hand movements					
Right					
Left					
Rapid alternating movements of hands					
Right					
Left					
Leg agility					
Right					
Left					
Arising from chair					
Posture					
Gait					
Postural stability					
Body bradykinesia and hypokinesia					

Each domain is scored from 0-4 by using a verbal rating scale. Maximum score is 56.
Example of the grading for assessing rigidity:

0= Absent
1= Slight or detectable only when activated by mirror or other movements.
2= Mild to moderate
3= Marked, but full range of motion easily achieved.
4= Severe, range of motion achieved with difficulty.

2.4 Ethics

The Regional Committee for Medical and Health Research Ethics (REK), section South- East Norway granted exemption from ethical approval as the project was evaluated as a quality project (5/3-2012) Ref IRB 0000 1870. The Data Inspectorate Officer at Akershus sykehus Oslo Norway approved the study protocol (27/2-2012). A consent form was signed by each patient.

2.5 Statistics

The results of this pilot study will presented with descriptive statistics. Mean values were assessed for age and differences between T0 and T.

3 Results

3.1 Patients

Six patients, four women and two men were enrolled in this pilot-study. Gender, age and number of years with PD are presented in Table 3.

Table 3. General data of the patients

	Gender	Age (years)	Years with PD diagnosis
Patient 1	F	76	5
Patient 2	F	71	3
Patient 3	M	75	4
Patient 4	F	68	4
Patient 5	F	65	5
Patient 6	M	75	2
Mean value		71,6	3,8

3.2 Results of questionnaires and examination

Table 4. Summary of HADS scores

	Sum A	Sum D	Sum A+D
Patient 1	6	7	13
Patient 2	7	10	17
Patient 3	9	9	18
Patient 4	9	12	21
Patient 5	4	10	14
Patient 6	0	1	1
Mean value	5,8	8,1	14

Table 5. Blood pressure measurements before and after levodopa.

	T0		T0 diff	T1		T1 diff
Patient 1	160/85	155/85	-5/0	150/80	150/80	0/0
Patient 2	130/70	120/70	-10/0	125/70	120/65	-5/-5
Patient 3	140/80	115/65	-25/-15	130/80	115/70	-15/-10
Patient 4	115/65	115/60	0/-5	120/65	115/65	-5/0
Patient 5	125/70	125/65	0/-5	120/65	120/60	0/-5
Patient 6	130/85	130/80	0/-5	125/80	125/80	0/0

Table 6. VAS of pain results before (T0) and after (T1) Levodopa.

	T0	T1
Patient 1	41	38
Patient 2	0	0
Patient 3	5	3
Patient 4	19	16
Patient 5	12	21
Patient 6	0	0
Mean value	12,8	13

Table 7. Sum of UPDRS part 3 before (T0) and after (T1) Levodopa.

	Sum T0	Sum T1
Patient 1	30	23
Patient 2	27	24
Patient 3	15	10
Patient 4	28	23
Patient 5	22	20
Patient 6	18	18
Mean value	23,3	19,7

4 Discussion

4.1 Method discussion

4.1.1 Population

The number of patients is too small for drawing any conclusions. It was difficult to enroll enough patients to this pilot study since the levodopa test seldom is used. Often patient are started on levodopa without being tested first.

The patient group that was examined in this pilot study has recently been diagnosed with PD. The mean value of the patients' age was 71, 6 years and the mean value for numbers of years with PD was 3, 8 years.

4.1.2 Instruments

The problem with many of the instruments is that the patients may remember what they answered on the questions. In contrast to many other pain scales the VAS is a valid instrument to use multiple times in a short time perspective. This was an important factor involved when choosing the VAS scale for this study.

HADS is a validated screening instrument for anxiety and depression. There are several other questionnaires that could have been used but HADS was chosen due to its validity and the fact that it is commonly used at Akershus Sykehus. It's validated for screening and not for multiple uses during a short period of time. That's why the screening was performed once and not twice as with the other instruments. It might had been a possibility to try to use a VAS scale to determine short time effect of levodopa on depression.

4.2 Result discussion

4.2.1 Motor function test

A motor function test was done before and after medication. The test was done as an indicator of whether the patients' PD diagnosis is correct. Levodopa will probably have a positive effect on the motor function if the PD diagnosis is correct. It is therefore of value to know the motor function test's response to medication when testing the non-motor symptoms. A lack of positive response to medication in the motor function test could indicate the presence of another form of movement disease that doesn't respond to levodopa. This doesn't mean that all patients that don't respond to levodopa have another disorder than PD.

The results of the UPDRS 3 demonstrate that all patients except one had a positive effect of levodopa on the motor symptoms, lowering the sum of the UPDRS 3 after medication. The one patient (patient 6) that didn't have any effect of Levodopa didn't have any non-motor symptoms to measure the effect on either. It' would have been interesting to screen this patient for non-motor symptoms with the NMSQuest or the NMSS to see whether this patient had any NMS.

4.2.2 Pain

The level of pain varied between the patients. Three out of six patients had a slight reduction in pain according to the VAS assessment. Two patients experienced no pain, neither before nor after medication and one patient experienced more pain after medication. It is impossible to say anything about a trend here since the results differ so much within the group of patients. Some patients did recognize an improvement of pain after medication so it is possible that there is an effect.

The mean value of pain before medication was 12, 8 and after it was 13. Although most patients that experienced pain before medication thought the pain was better after medication, the mean value tells us different. This indicates again that the number of patients in this study is too low.

The most common cause of pain in patients with PD is the secondary pain to parkisonian rigidity. Since the patients in this pilot study are relatively recent diagnosed their symptoms

are not very severe. This might be one of the reasons why the amount of pain in this group is not very high. The patient with the highest UPDRS score also scored highest on the pain score.

4.2.3 Depression and anxiety

The screening of depression and anxiety with the HADS questionnaire showed that all patients had some degree of depression and anxiety except one patient (patient 6). This patient didn't have any effect of Levodopa on either of the tests. Neither did patient 6 have any of the NMS asked about in this study.

Depression is a known and frequent NMS of Parkinson's disease. As described earlier in the literature we can conclude that depression and anxiety is present in early Parkinson's disease.

4.2.4 Orthostatic hypotension

The results of the blood pressure measurements indicate that one of six patients (patient number 3) had orthostatic hypotension before treatment with levodopa. Orthostatic hypotension is defined as a fall in systolic blood pressure of ≥ 20 mm Hg or in diastolic blood pressure ≥10 mmHg on either standing or head- up tilt to at least 60° within 3 min. After medication patient number 3, did not by definition have orthostatic hypotension.

When comparing the T0 and T1 results of the blood pressure measurements five of six patients have higher blood pressure before medication than after. Many patients are nervous when coming to the hospital or meeting a doctor. If this is a true result or an effect of stress is difficult to distinguish. It might also be a side effect of the medication that causes the fall in blood pressure, however this should be prevented since levodopa is prepared so it is not transformed to dopamine before reaching the neurons in the brain.

4.3 Conclusion

What can be said about the results of this study is that pain and depression are present in patient with early PD. There might be a trend that patients with pain felt an improvement of the symptoms after levodopa. It's not possible to say anything about the short term effect of levodopa on NMS from this material since the patient group is too small.
The conclusion from this study that pain and depression are present in early PD is supported by the literature.

For future research it would be beneficial to have a larger population and test more NMS before and after administration of levodopa. If possible, try the instruments on a group with a more severe PD too. As described in the literature the number of NMS correlates with severity and duration of the disease and it might be easier to see an effect if the patient group had more symptoms to measure.

5 Literature

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