Amino Acids (2002) 23: 141–145
DOI 10.1007/s00726-001-0119-1

Amino
Acids
Printed in Austria

# Recognition and treatment of response fluctuations in Parkinson's disease: Review article

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Received July 7, 2001
Accepted August 6, 2001
Published online September 10, 2002; © Springer-Verlag 2002

**Summary.** Patients with Parkinson's disease (PD) by definition benefit from treatment with the dopamine precursor levodopa. However, after 5 years of therapy 50% of patients experience motor response complications (MRC's): the benefit from each dose becomes shorter (wearing-off fluctuations), more unpredictable (on-off fluctuations) and associated with involuntary movements (dyskinesias). In addition these patients suffer from fluctuations in motor function that are inherent to the disease itself. Recent findings have lead to the suggestion that hyperfunction of NMDA receptors on striatal efferent neurons, as a consequence of chronic non-physiologic dopaminergic stimulation, contributes to the pathogenesis of MRC's. In PD patients blockade of striatal glutamate receptors with several NMDA-antagonists improve MRC's. With progression of PD the severity and complexity of MRC's magnify, obfuscating their pattern and their relation to the medication cycle. Only through detailed history taking and patient education will the physician be able to clarify the situation and establish a rational, targeted approach to the treatment of patients with advanced PD complicated by motor fluctuations and dyskinesias.

**Keywords:** Motor response complications – Dyskinesias – Levodopa treatment

Patients with idiopathic Parkinson's disease, (almost) by definition, benefit from the aminoacid levo-3,4-dihydroxyphenylalanine, or levodopa. While there is ongoing debate whether or not levodopa is the drug of choice to initiate antiparkinson therapy, there is no doubt that this dopamine precursor, once instituted, is the most effective drug currently available for treating the symptoms and signs of Parkinson's disease (PD). However, the initially favorable response to levodopa becomes fraught with complications after long-term treatment. With time, levodopa-associated involuntary movements (or dyskinesias) and oscillations in the performance of movement (motor fluctuations) arise and contribute increasingly to the disability experienced by patients with advanced disease. Together, these changes in the response to levodopa are called motor response complications. Recent findings suggest that hyperfunction of N-methyl-D-aspartate (NMDA) receptors on striatal efferent neurons, as a consequence of chronic non-physiologic dopaminergic stimulation, contributes to the pathogenesis of motor response complications (Chase et al., 1996). Unfortunately, these new insights have not yet led to the prevention of their development. Conservative estimation suggests that 10% of PD patients will develop motor fluctuations per treatment year, so that 50% are affected after 5 years of treatment (Marsden et al., 1981). More recent studies suggest that this 50% mark may already be reached after 2–3 years (Blanchet et al., 1996).

For the treating physician, the combination of worsening parkinsonian symptoms and changing response to levodopa can be increasingly challenging. At this point it becomes critically important to have, on the one hand, an educated patient (and caregiver) who can *document* the temporal relationship between medication administration and symptoms, and, on the other hand, a physician who is able to *recognize* the different types of response fluctuations. Without such a partnership no rational basis for the management of the advanced PD patient exists, and both patient and physician become frustrated in the process.

As always, *recognition* is facilitated by *classification* (Marsden et al., 1981; Quinn, 1998; Riley and Lang, 1993). Fluctuations in condition can be classified according to their relationship with: 1) the disease

itself versus its treatment (levodopa); 2) "high-dopa" or "low-dopa" conditions; 3) their temporal pattern (momentarily, diurnal, longer-duration); 4) the system by which they are expressed (motor, sensory, autonomic, cognitive). Admittedly, these classifications are somewhat artificial and partially overlapping, but they are conceptually useful and will be touched upon briefly.

## Fluctuations inherent to the disease

Fluctuations in motor function were recognized even before the levodopa era (Poewe, 1994; Souques, 1921). Disease-related fluctuations include both voluntary and involuntary movements.

### *A) Voluntary movements*

Most PD patients feel better in the morning after a good night's sleep and after short periods of sleep during the day. Motor symptoms can fluctuate during the day depending on concomitant activities or emotional stress. An example of the latter is that of kinesia paradoxica, which indicates sudden and brief mobility, in an otherwise severely akinetic patient (Souques, 1921). This acute mobility is usually induced by severe stress and afterwards patients return immediately to their akinetic state. On the other side of the spectrum is freezing, a temporary interruption in the execution of movement, usually gait. It occurs especially in narrow, confined spaces, door openings, or when turning (Mizuno, 1994). The mildest form of freezing occurs only at the initiation of gait and is then called start hesitation.

### *B) Involuntary movements*

Curling of the toes, inversion of the foot, or painful cramps usually in the lower extremities, may be heralding symptoms of Parkinson's disease, especially in younger individuals. Initially this dystonia may be present only during specific tasks or actions, such as bicycling or jogging, but it usually progresses to be present at rest as well (Purves Stewart, 1898, LeWitt, 1986). Institution of dopaminergic therapy largely eliminates this problem.

## Fluctuations associated with levodopa treatment

Long term treatment with levodopa leads to fluctuations in the execution of voluntary movement as well as the development of involuntary movements (Marsden et al., 1981).

### *A) Voluntary movement*

The initial phase of levodopa treatment is characterized by the absence of motor fluctuations. The antiparkinson effect of levodopa outlasts the half-life of the drug, enabling a stable motor state even when patients skip a levodopa dose. The first fluctuation to surface is usually a shortening of the response to levodopa. This can be experienced as slowness in the morning before the first dose is taken, or during the day when symptoms recur before the next scheduled dose is due. This predictable fluctuation is called "wearing-off". This situation can be improved relatively easily by increasing the frequency of medication administration, or by adjuvant therapy with mono-amine-oxidase (MAO) inhibitors and especially catechol-O-methyl-transferase (COMT)-inhibitors, both of which interfere with levodopa metabolism.

With unrelenting progression of the disease and continuation of levodopa treatment, further shortening of the benefit occurs and the fluctuations loose their predictability. Patients can switch "on" from an "off" state, and vice versa, in a matter of seconds. These unpredictable motor fluctuations, called "on-off" phenomenon by the neurologist, are often referred to as riding "on a roller-coaster" or "yo-yoing" by the patient (Marsden et al., 1981). Patients and caregivers are no longer able to determine the relationship between timing of medication and symptomatology. Individual doses may be ineffective (dose failure) or lose their efficacy seemingly at random. This may occur because, in order to compensate for more frequent levodopa intake, the individual levodopa dose has been lowered. The levodopa dose-response curve, however, is no longer graded, and responses occur in an "all-or-nothing" fashion, once a certain threshold level of levodopa is exceeded (Hardie et al., 1984). Thus, at least part of the unpredictability is only apparent and caused by subthreshold levodopa levels. Another important contribution to the unpredictability of the response to levodopa comes from the diet. Large neutral amino acids from dietary protein compete with levodopa

for the same carrier for their transport across the intestinal wall (Wade et al., 1973). A similar competition exists at the level of the blood-brain barrier. Therefore, protein-rich meals, through their effect on levodopa levels, can have a major impact on fluctuations of motor symptoms. Conversely, limiting protein intake during the day may decrease fluctuations during times that patients are most active. They have to make up for this in the evening, a strategy referred to as a protein redistribution diet (Pincus and Barry, 1988).

By increasing an individual levodopa dose the response often resumes its predictable character. This suggests that wearing-off and on-off phenomena are not two separate entities, but variants of the same phenomenon (Verhagen Metman, 1997). The treatment of the on-off phenomenon therefore consists foremost of adequate dopaminergic stimulation. An appropriate dose of *regular* levodopa should be prescribed, while adjuvant therapy with agonists, amantadine and COMT-inhibition all play a supporting role. Decreasing "off" time may also be achieved by using faster acting levodopa preparations and by "rescue" therapy with the very quick and short acting dopamine agonist apomorphine, administered either subcutaneously, sublingually or intranasally. Alternatively, frequent ingestion of liquid levodopa by mouth or even by gastrointestinal infusion has been applied as well (Djadetti and Melamed, 1998; Tolosa et al., 1994).

### *B) Involuntary movements*

By the time fluctuations in motor response start to appear, patients usually also start to develop another major change in response to levodopa: involuntary movements or dyskinesias (Marsden et al., 1981). When they first arise they are usually associated with high levodopa levels and may be prevented or minimized by lowering levodopa intake. Later on, however, the therapeutic window of levodopa (difference between the dose of levodopa required for a beneficial effect and that causing side effects, i.e. dyskinesias) narrows progressively and dyskinesias become the obligatory counterparts of the beneficial effects of levodopa ("interdose", "on" or "square-wave" dyskinesias). At this point lowering levodopa intake is no longer advantageous as patients will suffer increased immobility as a result. A less common, but more confusing, phenomenon is that of *di-or biphasic* dyskinesias. This is most frequently seen in patients with young onset Parkinson's disease, and the term refers to the fact that involuntary movements do not occur at the time that levodopa levels peak, but when they quickly rise or fall, i.e. at the beginning and/or end of a levodopa dose. Diphasic dyskinesias may be violent and ballistic in character, with a predilection for the legs. The leg movements can also consist of rhythmic, alternating kicking or bicycling movements. Some patients exhibit fixed dystonia, leading to bizarre postures often associated with pain and generalized distress (Marsden et al., 1981).

In general, *square-wave* dyskinesias are often more bothersome to observers than to patients themselves. Given the choice, most patients prefer to stay "on", with dyskinesias, than to be immobile and "off". However, even mild dyskinesias are aesthetically displeasing and severe dyskinesias can be exhausting, dangerous and functionally impairing. In some instances, substituting levodopa with higher doses of dopamine agonists can reduce dyskinesias. Recently, it was reported that amantadine, a mild antiparkinson agent most commonly used early on in the disease, can significantly reduce levodopa-induced dyskinesia (Verhagen Metman et al., 1998). While the antiparkinson effect of amantadine used to be explained through inhibition of dopamine re-uptake and/or enhancement of dopamine release, more recently it was shown that amantadine at therapeutically relevant concentrations antagonizes central NMDA-receptors. Since hyperfunction of striatal NMDA receptors has been proposed to play a role in the pathogenesis of motor response complications (Chase et al., 1996), NMDA receptor blockade by amantadine could well explain its antidyskinetic effect. Larger doses are more effective than lower doses. For older patients with reduced renal clearance and those who are prone to developing hallucinations, the dose needs to be adjusted (Verhagen Metman et al., 1998).

When dealing with *diphasic* dyskinesias, attempts should be made to use sufficiently high levodopa doses to assure a reasonable "on" period. If levodopa in those instances is dosed too conservatively, levodopa levels will linger around the levodopa threshold most of the time, which in fact may prolong these "low levodopa" dyskinesias. For similar reasons slow release preparations should be avoided. Conversely, using rapidly acting drugs such as the dopamine agonist apomorphine can shorten beginning-of-dose dyskinesias.

## Dystonia

After the institution of levodopa therapy, dystonia is usually associated with "off" states (Poewe et al., 1988). Early morning dystonia occurs upon awakening and end-of-dose dystonia is associated with wearing-off at the end of a levodopa dose. Curling of the toes, inversion of the foot, or cramping pain in the lower extremities are the most common manifestations, but off-dystonia can occur in the upper extremities, trunk, neck, jaw and facial muscles as well. Off-dystonia can be extremely painful and often interferes with gait. It is reversed by the next levodopa dose. If, on the other hand, no levodopa is given for several hours, the dystonic cramps will usually dissipate spontaneously, indicating that the symptomatology is somehow related to levodopa therapy. "Off"-dystonia is, obviously, best treated by reducing "off" time. This is another indication for a rapidly active drug such as apomorphine, especially if the dystonia is painful and disabling. Regular acting levodopa is preferable above slow-release preparations, and dissolving regular levodopa in CO2 containing beverages may further expedite its absorption and terminate the painful dystonia. Dystonia is not limited to the off-state but can also occur at peak-dose. In that case it usually affects the craniocervical region more than the legs, is not painful and is associated with chorea in the extremities (Poewe et al., 1988; Kidron and Melamed, 1987).

## Non-motor fluctuations

A wide array of non-motor fluctuations is commonly encountered in parkinsonian patients with a fluctuating motor response to levodopa (Riley and Lang, 1993; Hillen and Sage, 1996). Sensory complaints such as paraesthesias and pain are suspected to be due to PD if they occur predominantly on the side most affected by PD and if their severity fluctuates in cycles with the motor fluctuations. Autonomic fluctuations are common as well. Changes in bladder function, perspiration, and body temperature are the most prevalent, but other symptoms such as nausea, blood pressure fluctuations and tachycardia have been described as well. Cognitive and psychiatric fluctuations include anxiety, panic attacks, moaning or screaming, and depression. Most of these non-motor symptoms occur when the patient is in the "off" state and improve when the next dose of levodopa takes effect. Therefore, optimizing dopaminergic therapy will be beneficial. On the other hand, confusion and hallucinations are symptoms that are exacerbated in the "on" state. Gradual elimination of antiparkinson medications other than levodopa and minimizing the daily levodopa dose are usually the first steps. If that is not sufficient, atypical neuroleptics such as clozapine and quetiapine are introduced at low doses.

Recognition of this wide array of fluctuations and their temporal relation to medication ingestion will require detailed history taking by the physician and understanding of terms as well as documentation of symptoms by the patient and caregiver. Initially, this process can be extremely time-consuming. However, once the pattern of fluctuations is clarified, lasting improvement in patient management and well being can be anticipated.

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