Acta neurol. belg., 2002, **102**, 163-166

Should levodopa be used anymore ?

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Abstract

Levodopa is the most potent dopaminergic oral drug available in clinical practice. After chronic treatment, many patients with Parkinson's disease develop dyskinesia and motor fluctuations which are difficult to manage. It was hoped that introduction of dopaminergic agonists could diminish these side effects while keeping the same efficacy as levodopa. Prospective clinical data do not support this idea with the present drugs. Levodopa remains the most useful treatment and most clinicians believe that it is wise to associate early on levodopa with one of the dopamine agonists.

Key words : Parkinson's disease ; levodopa ; dopamine agonist.

Up to today there is no placebo controlled, long term trial published to precisely assess the impact of levodopa treatment on the progression of Parkinson's disease (PD), depite the fact that levodopa has an established role as the most efficient oral antiparkinsonian drug for over several decades. Nobody questions the well established efficacy of levodopa, and the «Evidenc-Based Review» published in 2002 by the Movement Disorder Society clearly states :«*Based on one high quality long-term prospective double-blind trial each there is sufficient evidence to conclude that levovopa monotherapy is more efficacious than monotherapy with ropinirole, pramipexole or cabergoline in improving symptomatic control in de novo patients with PD*» (Goetz *et al*., 2002*)* . In the same review bromocriptine is said to be «less efficacious» than levodopa. Questions remain however about the precise mechanisms of action of levodopa, the benefit-risk ratio of it's different formulations, and the optimal combination pattern of levodopa with other more recent antiparkinsonian drugs.

Once it has penetrated into the brain levodopa exerts its antiparkinsonian effects after conversion into dopamine. This conversion occurs predominantly in the dopaminergic neurons and also at other sites (Hefti *et al.,* 1981).The scene of it's major effects on movement are the medium spiny neurons in the striatum, which account for about 90% of stiatal neurons and are the striatal projection neurons. The medium spiny neurons receive massive glutamaergic cortical excitatory inputs to the heads of dendritic spines. The nigrostriatatal dopamine neurons also project to the medium spiny neurons but predominantly to the shafts of the dendritic spines and are in the position to modulate cortical glutamaergic inputs to the striatum. Dopamine facilitates motor behavior by its action on both the direct and the indirect pathway. Although many of the motor signs of PD are shown to be the result of progressive decline of the dopaminergig neurons projecting to the striatum, it has to be kept in mind that that there is extensive dopaminergic innervation of most cortical areas, and specifically the primary motor, premotor and anterior cingulate area (Gaspar *et al*., 1991). Levodopa remains the most potent drug for the treatment of motor symptoms of PD despite vivid controversy relating to concerns that it might contribute to neurodegeneration. At the centre of this issue is the oxidant stress hypothesis of PD and the recognition that much of dopamine metabolism occurs by oxidant mechanisms. The generation of oxydoradicals and the microenvironnment of the substantia nigra, with high concentrations of iron and neuromelanin, are thought to fuel the neurodegerative process. These views, combined with intense commercial pressure in favor of more recent dopaminergic agonists, have been put in a more balanced perspective only recently with the growing consensus that levodopa is not toxic in the usual dose range (Agid *et al*., 1999).

The pulsatile nature of dopamine production from levodopa admistration differs to a large extent from the physiologic pattern of neurotransmitter secretion. Normally, there is a low but continuous release of dopamine with superimposed increases with short (phasic) and with longer (phasic) timecourses. Differences in the dopaminergic cell firing pattern are associated with different activities, various stimuli and behaviors (Walters *et al*., 2000).

Presented at the BNS meeting, Brugge, october 2002.

Increased dopamine release is not followed by raised extracellular dopamine concentrations because of the efficacy of synaptic reuptake into presynaptic terminals (Grace *et al*., 1991). This discrete, precise tuning of dopamine at the level of the basal ganglia cannot be imitated by exogenous dopa therapy. Experimental evidence in animal studies suggests that chronic intermittent dopaminergic stimulation induces dyskinesia and motor fluctuations, which occur after prolonged levodopa treatment (Chase 1998). It is thought that plastic changes in the motor system are the consequence of repeated levodopa administration leading to dyskinesia. Continuous duodenal levodopa administration and continuous apomorphine treatment may sigificantly reduce the dyskinesia in non-controlled studies and the improvement is gradual over several weeks to months, reinforcing the idea of plastic changes rather than direct pharmacological effects (Nilsson *et al*., 2001 ; Kanovsky *et al*., 2002). Reversibiliy of levodopa induced dyskinesia has also been reported after chronic deep brain stimulation of the sub- thalamic nucleus (Bejjani *et al*., 2000). Levodopa only has a short plasma half-life (between 0.97 and 1.67 hours) (Nutt *et al*., 1984) and it is tempting to believe that a dopaminergic compound with a longer plasma half-life could prevent some of the fluctuations and reduce the motor fluctuations of chronic administration. No reduction of motor fluctuations have however been found in therapeutic trials comparing standard levodopa with sustained release levodopa (Koller *et al*., 1999).

Plasma half life however is only one aspect of the duration of therapeutic response to levodopa and clinical observation of PD patients treated with levodopa shows two types of therapeutic response, a short duration reponse (SDR) and a long duration response (LDR). The SDR lasts minutes to hours and is recognised clinically as the «on» reponse following levodopa intake in patients experiencing motor fluctuations. The long duration reponse (LDR) lasts from days to weeks and is seen as a gradual improvement with initiation of chronic levodopa treatment (Quattrone *et al*., 1995 ; Nutt *et al*., 1997). The clinical relevance of the LDR has not been well appreciated in clinical pratice, since levodopa is usually taken several times a day independent of it's long duration effect. It was commonly thought that the SDR is the result of the non-physiological synthesis of dopamine from exogenous levodopa in sites other than dopaminergic nerve terminals, and that the LDR results from exogenous levodopa in remaining dopaminergic nerve terminals that retain the capacity to store and release dopamine in a relative physiological manner. However logic and robust, recent data suggest that these ideas are wrong. In a recent prospective study the SDR was quantified in a group of PD patients *before* long term treatment was begun and the patients were followed for 4 years (Nutt *et al*., 2002). The magnitude of the SDR increased significantly over 4 years and the latency of the peak decreased, confirming that sensizitation occurs with repeated dosing. The duration of the SDR did not change over 4 years. The LDR was larger in the more affected arm, which is an argument that LDR is not dependant on residual dopamine terminals and the storage of dopamine.This is in line with the fact that dopamine agonists, whose actions are largely independant of dopamine storage, can produce an LDR (Stocchi *et al*., 2001). Eight out of 18 patients, who completed the 4 years of follow up, reported wearing off. The duration of the SDR did not differentiate the subjects with and without motor fluctuations. Therefor, these data do not support the hypothesis that fluctuations are caused mainly by shortening of the SDR to levodopa. Exactly what factors are critical to the development and maintenance of the LDR remain unknown, but it is probable that the LDR is mainly due to postsynaptic effects, either at the dopamine receptor or alterations in neuronal activity downstream to the dopamine receptor, or both. Thus the pharmacologic reponse to levodopa is very complex, and many of these aspects have only just been adresssed by recent clinical work.

The timing of levodopa therapy remains controversial. Some authors advocate delaying initiation of levodopa thinking that the observed motor complications and specifically dyskinesia, are related to the duration of levodopa treatment, others prefer early treatment with levodopa to provide maximal early benefit, with the believe that motor complications simply occur because of progression of PD. A recent paper (Kostic *et al*., 2002) indicated that the disease severity appears to be the major risk factor for the development of levodopa associated motor complications, confirming the results of several earlier reports. This matter is still controversial and it is most likely from clinical observation that progressive, disease induces dopamine-receptor denervation and long term levodopa therapy both contribute to motor complications. Another issue is the fear of the levodopa *priming effect*. It has been shown that in primates with parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) levodopa induces dyskinesia almost immediately after starting therapy, whereas monotherapy with dopamine agonists usually does not. However if the primates were transiently pretreated for a few weeks with levodopa, dopamine agonists given weeks later will induce dyskinesia almost immediately- the so called levodopa priming effect (Damier *et al*., 2000). How this relates to PD in humans is not clear.

It is here that the much debated issue of initiation of PD treatment with a dopamine agonist as monotherapy comes in. The main advantage of this strategy is the lesser incidence of troublesome

dyskinesia after a few years of treatment. For example, the five yeay study on the incidence of dyskinesia comparing ropinirol monotherapy with levodopa in early PD reported at five years an incidence of dyskinesia of 45% in the levodopa group and 20% in the ropinirol group (Rascol *et al*., 2002). However only 29 out of the 179 ropinirol treated arm completed the five years on ropinirol. Thus the title of the study is misleading, as most patients do not receive ropinirol or levodopa, but ropinirol with levodopa versus levodopa alone. It should also be noted that the protocol of levodopa administration was quite different from clinical practice of most countries. Indeed the study design was that the maximal dose of levodopa was 1200 mg per day in three doses, which means up to 400 mg three times a day. Most clinicians with experience in treatment of PD are reluctant to give a dose of more than 200 mg of levodopa at a time to limit side effects. The protocol explains probably why the tolerance to evodopa was poor : 39% of patients in the levodopa group withdrew prematurely due to advers events, a percentage of intolerance well beyond the experience of most clinicians, which serves well the view that ropinirol is well tolerated in comparison to levodopa in this study.

Depite passionate views in favor of agonist monotherapy, there is little prospective clinical evidence to support it. A very systematic review on the comparison of levodopa versus Bromocriptine/-levodopa was published recently and analyzed eligible trials on about 850 patients (Ramaker and van Hilten, 2002). The authors concluded : "So, the current data show no evidence of consistent differences concerning the occurrence and severity of motor complications, scores of impairment and disability and side effects between both treatment groups". Furthermore, to quote the recent «Evidence Based Review» of the Movement Disorder Society writing about the longest known agonist, bromocriptine, which has been the object of many studies : «There is a need to assess if initial bromocriptine monotherapy, with late levodopa supplementation is equivalent regarding longstanding efficacy (10 years), safety and costs as compared to combined early L-dopa and bromocriptine treatment in de novo patients with PD (early combination strategy)» (Goetz *et al*., 2002).

Most clinicians treating patients with PD will be less interested by prospective trials comparing agonist monotherapy to levodopa monotherapy. Agonists are less potent and cause less dyskinesia. However polytherapy of levodopa with agonists is the norm and pertinent clinical studies should focus on the optimal combination and timing rather than on more theoretical monotherapy principles. From clinical experience and experimental data it seems appropriate that initial therapy should combine a dopamine agonist as a low level of continuous dopamine receptor stimulation superimposed on adeqate levodopa supplements. What the appropiate dosing and ideal combination is is not known and has to be established in long term prospective trials.

Several questions remain unanswered : What is «normal release» of dopamine at the striatal (and cortical) levels in man ? What is the nature of plastic changes induced by chronic levodopa and agonist treatment at the receptor level ? How can we modulate the short and long duration reponse to levodopa ? Until the answers to some of these questions are known, there will be no consensus on optimal treatment. It is the reponsibility of the clinician to find the most appropiate treatment for the individual patient, finding his way between animal models that are not appropriate to mimic human PD, complex pharmacologic discussions, prospective clinical trials with a design quite different from the clinical situation, and intense commercial pressure of drug companies and the increasing number of physicians paid to promote their products.

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