

Viewpoint

Levodopa in the Treatment of Parkinson's Disease: A Consensus Meeting

Y. Agid, E. Ahlskog, A. Albanese, D. Calne, T. Chase, J. De Yebenes, S. Factor, S. Fahn, O. Gershanik, C. Goetz, W. Koller, M. Kurth, A. Lang, A. Lees, P. Lewitt, D. Marsden, E. Melamed, P. P. Michel, Y. Mizuno, J. Obeso, W. Oertel, W. Olanow, W. Poewe, P. Pollak, S. Przedzorski, N. Quinn, R. Raisman-Vozari, A. Rajput, F. Stocchi, and E. Tolosa

Members of the Consensus Meeting

Levodopa (in combination with a peripheral dopa-decarboxylase inhibitor) substantially improves the quality of life of patients. However, physicians are not always comfortable prescribing it, and its administration is often delayed to retard the development of motor complications or is restricted to patients with relatively advanced disease, because there is a fear that the decreased response of parkinsonian symptoms may result from a self-limiting effect of the drug. Moreover, long-term treatment with levodopa is claimed by some to induce the degeneration of dopaminergic neurons, thereby accelerating disease progression. Whether long-term administration of levodopa in patients may result in the irreversible appearance of side effects or accelerate the neurodegenerative process is a crucial question, and it is therefore legitimate to ask whether one should delay the introduction or limit its use in patients. To address these questions, a meeting of experts was held in Paris (January 8–9, 1998) to see whether general agreement could be reached concerning the interpretation of studies of levodopa toxicity in tissue culture, in animal models of parkinsonism, and in patients. Most of the experts agreed that the administration of levodopa was not dangerous for patients. Nevertheless, there are still conflicting results and unanswered questions. This is why this consensus on levodopa treatment of patients with Parkin-

son's disease (see below) is followed by additional comments made by some of the experts.

IN VITRO STUDIES

Levodopa can induce cell death in vitro when high concentrations ($>100 \mu\text{M}$) are used in pure cell cultures, but this is not observed at low concentrations ($<50 \mu\text{M}$). In the presence of glial cells, an in vitro situation closer to in vivo conditions, neurons appear to be protected against the deleterious effects of levodopa.

The relevance of these in vitro findings to Parkinson's disease remains uncertain. More in vitro studies in diseased cells are required.

ANIMAL AND HUMAN STUDIES

In normal animals, there is no convincing evidence that levodopa promotes cell death. In animals rendered parkinsonian by lesions of the nigrostriatal dopaminergic system, the results are conflicting, but there is no conclusive evidence that levodopa promotes cell death.

There is no evidence that levodopa promotes nerve cell death in healthy people or in those with Parkinson's disease.

CLINICAL STUDIES

Levodopa is the most effective antiparkinsonian drug and reduces the mortality rate of Parkinson's disease.

The fact that levodopa treatment seems to become progressively less effective with time largely reflects the appearance of symptoms that are relatively unresponsive to levodopa, probably resulting from the progression of nondopaminergic brain lesions. There is no available evi-

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Dr. G. Cohen, who attended the consensus meeting, was not in agreement with the conclusions.

Address correspondence and reprint requests to Yves Agid, INSERM U 289 & Fédération de Neurologie, Hôpital de la Salpêtrière-47, Bd de l'Hôpital-75651 Paris, Cedex 13, France.

dence that supports the involvement of long-term levodopa administration in this process.

Levodopa-associated motor complications result from the combination of increasing loss of dopamine neurons (which unavoidably worsens with time and cannot so far be prevented) and postsynaptic changes resulting from long-term intermittent administration of levodopa. The repeated administration of levodopa triggers alterations in function which may explain the development of motor adverse reactions. As yet, there is no hard evidence that this phenomenon is irreversible.

There is no convincing evidence that levodopa causes or accelerates neuronal cell death. The decision of when and how to prescribe levodopa should be based only on consideration of its efficacy and side effect profile.

COMMENTS FROM THE PARTICIPANTS

Stewart A. Factor

Whereas the apparent toxicity of levodopa has been at issue, the more intriguing finding of late has been its possible trophic influences. In cell culture, low to medium concentrations of levodopa or the presence of glial cells provide for this effect. In pure neuronal cultures, levodopa treatment, at concentrations of 20–100 μM , leads to increasing cell numbers and processes. Astrocytes provide nutritive support, enzymatic protection, and trophic support for nerve cells. They not only provide a trophic effect in cell culture, but also can protect neurons from high concentrations of levodopa (200 μM). When levodopa is added to a mixed neuronal and glial culture, it enhances protective mechanisms against free radical damage by increasing cellular concentrations of reduced glutathione. It also provides a trophic influence through unknown (probably nondopaminergic) mechanisms. In vivo, the recent study by Murer et al. demonstrated partial recovery of dopaminergic markers in the denervated striatum of rats with a moderate lesion of the dopaminergic system who were fed levodopa for 6 months. Whether levodopa is toxic or trophic depends on a number of conditions, including levodopa concentrations at the cellular level. Dr. LeWitt (personal communication) indicated that, through the use of microdialysis techniques, levodopa concentration at the synapse in animals is in the picomolar range. According to cell culture studies, this level is not trophic or toxic.

Two other clinical issues relating to levodopa therapy include: (1) the apparent loss of efficacy of levodopa after chronic therapy, and (2) the question of reversibility of levodopa-induced motor complications. It has been noted in the consensus statement that the loss of effectiveness of levodopa with time reflects the appearance of

symptoms resulting from progression of nondopaminergic brain lesions. It should be emphasized that the effectiveness of this drug on other cardinal features of Parkinson's disease (PD), including rigidity, bradykinesia, and tremor, is not lost over time and those symptoms appear to be reasonably well controlled even in advanced states. Finally, the consensus statement indicates that there is no evidence that motor fluctuations are irreversible. In fact, Chase and colleagues have demonstrated that fluctuations may indeed be reversed in advanced patients. Their paradigm used a continuous levodopa infusion over 7–12 days. It was found that patients with simple wearing-off had complete reversibility of their fluctuations with the initiation of the continuous levodopa therapy. For those patients with more complicated motor fluctuations, such as "on-off," there was a gradual reversal of the fluctuations over time with a prolonged continuous infusion. They demonstrated decreased response variance, increased therapeutic window, increased efficacy half-time, and a shift of the dose-response curve. That would indicate the postsynaptic changes which result from intermittent oral levodopa therapy can be reversed, and the question at this time is whether we could find a simple oral therapy which could provide this continuous therapy for the duration of the patient's illness.

REFERENCE

Murer MG, Dziewczapolski G, Menalled LB, et al. Chronic levodopa is not toxic for remaining dopamine neurons, but instead promotes their recovery, in rats with moderate nigrostriatal lesions. *Ann Neurol* 1998;43:561–575.

Anthony E. Lang

"Levodopa . . . decreases the mortality rate of patients." Long-term studies consistently demonstrate that levodopa treatment is associated with a reduced mortality, and this tends to correlate with the initiation of treatment before a stage that significant disability (marked by postural instability) occurs. It should be emphasized that no similar studies have been performed in patients who have had treatment initiated with a dopamine agonist. It is likely that the effect of levodopa on mortality largely, if not exclusively, relates to a reduction in disability secondary to improvement of mobility and motor function. At this time, there is no reason to think a similar effect could not be obtained when other alternative, effective antiparkinson medication is used to initiate therapy as long as the final goal of reducing disability is obtained satisfactorily.

"The repeated administration of levodopa triggers alteration in function . . . but there is no evidence that this phenomenon is irreversible." Animal studies and human

experience using methods of continuous dopaminergic stimulation suggest that many of the motor adverse reactions experienced as a consequence of levodopa may indeed be "reversible." However, one has to consider whether this reversibility is a theoretical or practical phenomenon. Generally, when patients begin to experience troublesome motor fluctuations (not simply mild "wearing off") and distressing or disabling dyskinesias, it is uncommon to obtain a substantial resolution of the problem with current practical pharmacotherapy. Although some of these patients may be markedly improved by treatments such as continuous infusions of apomorphine or newer functional surgical techniques, these are generally impractical, not widely available, still experimental, or have a risk of significant complications. Given this "practical irreversibility" of these complications, it is prudent to consider alternatives to levodopa in the early treatment of patients who may be prone to early and severe motor complications. This description particularly applies to patients with young-onset Parkinson's disease. In such patients, it is not unreasonable to choose an alternative to levodopa, not because of concerns of direct toxicity to the substantia nigra, but related to a hope that the side effects may be less in the long term. In this situation, considerable attention should be given to functional ability and quality of life, and the addition of levodopa should not be delayed beyond a reasonable time if the patient has failed to obtain useful benefit from alternative therapies.

Werner Poewe

The problem of irreversibility of levodopa-induced dyskinesias. Once primed, levodopa-induced dyskinesias will follow administration of each suprathreshold dose, that is, threshold doses do induce a full antiparkinsonian effect and dyskinetic responses become inseparable. There is consensus that patients with young-onset Parkinson's disease develop levodopa-induced dyskinesias after less than 12 months of treatment so that by 3–5 years of chronic levodopa exposure, virtually all such patients will exhibit drug-induced involuntary movements. These motor complications can be partially reversed by continuous intravenous infusions of levodopa, chronic intraduodenal levodopa infusions, continuous subcutaneous apomorphine infusions, as well as by chronic subthalamic stimulation. In this sense, they are at least partially reversible. To our current knowledge, however, they will quickly reappear once pulsatile levodopa stimulation is resumed, indicating that long-lasting and potentially irreversible plastic changes in the brain response to levodopa have developed.

C. Warren Olanow, Stanley Fahn, and Gerald Cohen Comment

We write this minority position to reflect our concern that while levodopa has not been established to be toxic to dopamine neurons in patients with PD, neither has it been established to be completely safe and to not affect the natural progression of the disease. Levodopa is toxic to dopamine neurons in cultures of rat mesencephalon, although the doses used and the defense mechanisms available may differ from those present in the human brain. There are several studies indicating that levodopa is not toxic to dopamine neurons in normal animals or people. This may not, however, be the case in PD in which there is evidence of oxidant stress and in which some defense mechanisms may be compromised. Whereas normal cells may be capable of defending against the potentially toxic effect of levodopa, nigral neurons may be rendered vulnerable by factors that have been found in PD such as mutations in α -synuclein, decreased levels of reduced glutathione, accumulation of iron, and impairment in complex I activity. Studies testing the putative toxicity of levodopa in experiments in which these factors have been altered to mirror the findings in PD have not yet been performed. We recognize that levodopa is the most potent symptomatic drug for the treatment of PD and recommend that it be used when necessary to control the signs and symptoms of this disorder, particularly in older individuals (>70 years) and those with cognitive impairment. However, it has not yet been established that the drug does not have a toxic effect on dopamine neurons in PD. Indeed, the National Institutes of Health is currently funding a clinical trial to evaluate the effect of levodopa on disease progression. Until such time as additional information is available, and in view of the propensity of levodopa to induce motor complications, we consider it prudent to use a levodopa-sparing strategy in younger patients with PD (<70 years) in which the introduction of levodopa is delayed until symptomatic control cannot be satisfactorily obtained with alternate agents.

A preliminary communication of the consensus on levodopa has been published as an editorial in *The Lancet* (Agid Y, Chase T, Marsden D. Adverse reactions to levodopa: drug toxicity or progression of disease. *Lancet* 1998;351:851–852.).

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