Overview of Present Day Treatment of Parkinson’s Disease*

M. D. Yahr

Department of Neurology, Mt. Sinai School of Medicine, New York, U.S.A.

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Summary

In the light of present day knowledge, augmenting striatal dopaminergic activity is the most effective means for controlling the symptoms of parkinsonism. This is best accomplished by the administration of levodopa with a peripheral decarboxylase inhibitor. However, limitations in its benefits develop after long-term administration in a substantial number of patients. In an attempt to overcome these a number of pharmacological agents acting on striatal dopaminergic mechanisms have undergone clinical trial. Of those tried Deprenyl, an MAO-B inhibitor, given with levodopa and carbidopa has shown the most promise. Preliminary results in 35 patients indicate that it is useful in diminishing the incidence of “on-off” phenomena—one of the most limiting reactions to levodopa—as well as enabling some patients to recoup their loss of therapeutic benefits. Though far from resolving all of the therapeutic difficulties encountered with prolonged use of levodopa, it appears to be a valuable adjunctive agent for the long-term problem patient.

A considerable number of reports are now available regarding the long-term therapeutic effects of levodopa administered alone or in combination with a peripheral decarboxylase inhibitor (PDI) on the symptoms of parkinsonism [1, 2]. In general there is agreement regarding the following:

1. As many as 75—80 % of patients are benefited in varying degrees from its use.

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2. Therapeutic effects are optimal during the first 2—3 years of its administration.
3. Long-term usage results in a loss of therapeutic efficacy which not infrequently occurs in association with an increasing number of side effects, particularly adventitious movements (AIM) and the so-called “on-off” phenomena.

Considerable debate exists as to the underlying basis for this altered response. Some attribute it to the progression of the disease, others to the attendant metabolic consequence of long-term dopa administration. Undoubtedly, both play a role but we have been impressed that the time course of responses obtained in patients with advanced disease show similarities with those less severely involved. This would support an alteration in pharmacokinetics after prolonged administration of levodopa.

Though less than a consensus exists regarding the mechanisms by which levodopa produces its beneficial effects, the prevailing opinion is that of replenishment of the dopaminergic deficiency in the striatum [3]. Presumably the attendant side effects relate to the pharmacodynamic action of this neurotransmitter as well. The involuntary movements have been attributed to an interaction of dopamine with receptor sites in various phases of denervation hypersensitivity while the “on-off” phenomena to receptors that become temporarily unresponsive. This explanation is less than completely satisfactory. From a theoretical standpoint it does not take into consideration the role of other neurotransmitter agents whose activity might be altered by a number of factors including an excess supply of unstored dopamine or its production in non-nigral neurons. Clinically, it is difficult to fully explain the considerable variability and differing nature of these phenomena. Certainly, the “on-off” response, the most limiting aspect of the long-term treatment with levodopa, is difficult to fit into this concept. At least two forms are evident. One, dose related in that “on” periods occur following an ingested dose but the beneficial effects wane and an “off” period ensues prior to the next scheduled dose. The other is non-dose related, occurring capriciously with “on-off” periods appearing randomly throughout the day. Conceivably, a lack of continuing availability of levodopa in the striatum for conversion to dopamine or the latter's rapid degradation may play a role. One factor to be considered is whether an altered ability to maintain a uniform blood level of levodopa develops. That marked variability in blood levels occur in some patients after long-term therapy with levodopa has previously been reported from our laboratory [4]. As shown in Fig. 1, a significant rise in blood dopa is maintained for less than one hour during which in some patients