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Fifty Years of Levodopa: Pitfalls and Outlook

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Mini Review

Parkinson's Disease (PD) is a complex neurodegenerative condition manifested by characteristic motor impairment and non-motor symptoms. Levodopa represents the most effective treatment of PD. However, despite providing in the early stages of the disorder an efficacious control of the symptomatology, the beneficial effects of the treatment gradually decline. That determines the development of a wide array of motor complications which should be recognized by the physician for an optimization of the treatment over time. Nevertheless, the clinical management of complicated PD still results controversial, and the development of specific guidelines remains an unmet need. Since its introduction in 1967, levodopa has represented the most effective treatment in Parkinson's Disease (PD). However, with the advancing of the disease, factors concerning the central and peripheral pharmacokinetics and pharmacodynamics affect the optimal response observed at the beginning of the treatment.

In particular, the development of the end-of-dose deterioration and disabling dyskinetic movements determines a significant decrease in patients' quality of life. However, the pathophysiology underlying the occurrence of motor complications is still questioned. Many attempted to identify factors associated with the development of motor fluctuations. In particular, the age at the onset of the disease and at the initiation of levodopa therapy, duration of the treatment and total daily dose have been widely explored. The Earlier versus Later levodopa (ELLDOPA) study represents the only trial investigating the development of motor complications in patients randomized to different levodopa dosages [1]. Specifically, the authors found an increased frequency of wearing-off and dyskinesia in patients treated with higher doses of levodopa, albeit the follow-up period consisted of a short-term observation of 9 months and few incident cases were reported [1-2]. Olanow and colleagues as well observed a strong relation between high levodopa doses and frequency of motor complications, with a threshold value up to 400 mg/day [3]. Moreover, the results of the study suggested a key role of levodopa dosage regardless of disease severity or other predictive factors [3]. They also asserted the correlation between the weight and the development of dyskinesia in patients with levodopa dose greater than 4 mg/kg, as previously described by Zappia and others [3-6].

Another study conducted in Ghana by Cilia and colleagues investigated the occurrence of motor fluctuations in a wide cohort of African drug-naïve PD patients compared to an Italian population of PD subjects [7]. After a follow-up period of four years, the authors concluded that disease duration at the occurrence of motor complications and dyskinesias did not differ between the two study populations [7]. Thus, the duration of levodopa treatment should not influence the development of motor fluctuations. Besides, disease duration and levodopa daily dose resulted to be associated with motor fluctuations and dyskinesias [8]. Consistently with previous findings, the individual levodopa regimen then represents the major risk factor for developing motor fluctuations in relation to disease severity and extent of striatal degeneration. Since the concern to the individual PD case raised, the need for a personalized approach has started to be regarded as significant factor for delaying and decrease the impact of motor fluctuations on patient's quality of life.

The initiation of levodopa treatment in early stages, albeit with an appropriate dosage, has been suggested according to Cilia's study [9]. The subsequent therapeutic decision making is then tailored on changes in the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS-III), and patient report during the medical counselling [10]. In particular, the practical OFF score has been demonstrated to be a reliable measure of motor deterioration [11]. Despite less performed,

the progressive monitoring of the response to levodopa also in ON-state is advisable to explore the presence of dyskinetic movements, and to verify the responsiveness to the treatment when patients are not able to report it. Short-cut methods of evaluation might be relevant for selecting complicated patients who need more advanced interventions.

Specifically, a prolonged evaluation through a Waking-Day Motor Assessment (WDMA) has been demonstrated to be a reliable method to modulate the treatment on each PD case [12,13]. Indeed, daily evaluations present the limit of the time-consuming approach. Therefore, only selected patients might undergo the prolonged monitoring in dedicated centers with an expert personal. In conclusion, the development of a standardized method of evaluation to optimize levodopa treatment since the beginning is required. Prolonged method of evaluations to tailor therapeutic interventions should be indicated after an appropriate screening.

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