J Neurol (2010) 257 (Suppl 2):S247–S248
DOI 10.1007/s00415-010-5732-z

Levodopa: back to the future

Mario Zappia · Carlo Colosimo · Werner Poewe

After 50 years of clinical use, oral levodopa (LD) therapy remains the gold standard of symptomatic efficacy in the treatment of Parkinson's disease (PD) [1–3] Compared with other dopaminergic therapies, dopamine replacement with levodopa is associated with the greatest improvement in motor function as assessed by the Unified Parkinson's Disease Rating Scale (UPDRS) [4, 5]. In addition, responsiveness to oral levodopa has become a key diagnostic criterion for PD.

However, long-term treatment with LD is often complicated by the development of various types of motor response oscillations over a day as well as drug-induced dyskinesia, a complication characterized by erratic involuntary movements. Such treatment-related motor complications eventually develop in the majority of patients and are found in about one-third of patients after only 8 months of exposure [6]. Once established, motor complications are difficult to treat and can develop into a significant source of disability. In extreme cases, treatment-induced dyskinesia may completely annihilate the therapeutic benefit initially gained from the drug.

Despite an impressive body of experimental and clinical research, the precise mechanisms underlying the development of these levodopa-related motor complications remain incompletely understood. The most popular current hypothesis assumes that both motor fluctuations and dyskinesia are related to discontinuous delivery of oral levodopa to its site of action in the brain, resulting in intermittent or pulsatile dopamine receptor stimulation [7]. Indeed, after decades of clinical use and research, the best way to deliver levodopa to the brain remains elusive. Simple notions, such as the recommended starting dose, the best formulation to initiate therapy or the optimum dosing frequency, remain a matter of discussion among experts.

The development of motor complications like response oscillations and drug-induced involuntary movements in the majority of PD patients has evolved as a major limitation to long-term success of oral levodopa substitution [8]. Motor complications are believed to reflect neuroplastic changes in basal ganglia motor loops induced by chronic pulsatile dopamine receptor stimulation and, on these grounds, an important part of the research in clinical pharmacology of PD is still directed at modifying and improving the delivery of levodopa aiming for constant drug delivery. The search for strategies of continuous levodopa delivery is ongoing, including the need to optimise duodenal delivery systems in terms of convenience and hardware problems.

This supplement of the Journal of Neurology includes the proceedings of an International Symposium on Levodopa, held in Catania, Italy on 3–4 April 2009, organized by the Italian Association of Movement Disorders and PD (*DISMOV-SIN*) and endorsed by the Movement Disorder Society. All the main topics related to the current role of levodopa in the pharmacology of PD are covered in this supplement, including general issues (update on pharmacodynamic and pharmacokinetic properties), the use in clinical practice according to the different national

M. Zappia
Dipartimento di Neuroscienze, Università di Catania, Catania, Italy

C. Colosimo (✉)
Dipartimento di Neurologia e Psichiatria, Sapienza Università di Roma, Viale dell'Università 30, 00185 Roma, Italy
e-mail: carlo.colosimo@uniroma1.it

W. Poewe
Department of Neurology, Innsbruck Medical University, Innsbruck, Austria

guidelines, the many side-effects (including the dopamine dysregulation syndrome), the development of new formulations (soluble, controlled-release, gel for duodenal infusion use), the role in patients undergoing functional neurosurgery and all the main controversies still existing regarding levodopa.

Back to the future: levodopa is an old drug, but we are still searching pharmacological law and order, as attempted some years ago [9], to better understand the mystery surrounding its actions in PD.

Conflict of interest Carlo Colosimo: Consultancies and Advisory Board Membership with honoraria: Boehringer Ingelheim; Pharmaceuticals, Ipsen Pharmaceuticals, Novartis Pharmaceuticals, UCB/Schwarz; Royalties: CIC Edizioni Internazionali Publishers. Mario Zappia: Consultancies and Advisory Board Membership with honoraria: Boehringer Ingelheim, Novartis, Glaxo Smith Kline, UCB/Schwarz, Chiesi. W. Poewe has received consultancy and lecture fees from Novartis in relation to PD drug development.

References

1. Birkmayer W, Hornykiewicz O (1961) Der L-dihydrophenylalanin (DOPA)–effekt bei der Parkinson-akinese. Wien Klin Wochenschr 73:787–788
2. Barbeau A, Murphy GF, Sourkes TL (1961) Excretion of dopamine in diseases of basal ganglia. Science 133:1706–1707
3. Cotzias GC, Papavasiliou PS, Gellene R (1969) Modification of parkinsonism: chronic treatment with L-DOPA. New Engl J Med 280:337–345
4. Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE (2000) A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. 056 Study Group. N Engl J Med 342:1484–1491
5. Holloway RG, Shoulson I, Fahn S et al (2004) Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year randomized controlled trial. Arch Neurol 61:1044–1053
6. Fahn S, Oakes D, Shoulson I, Kieburtz K, Rudolph A, Lang A, Olanow CW, Tanner C, Marek K (2004) Parkinson Study Group. Levodopa and the progression of Parkinson disease. New Engl J Med 351:2498–2508
7. Olanow W, Schapira AH, Rascol O (2000) Continuous dopamine-receptor stimulation in early Parkinson's disease. Trends Neurosci (10 Suppl):S117–26
8. Colosimo C, De Michele M (1999) Motor fluctuations in Parkinson's disease: pathophysiology and treatment. Eur J Neurol 6:1–21
9. Nutt JG, Holford NHG (1996) The response to levodopa in Parkinson's disease: imposing pharmacological law and order. Ann Neurol 39:561–573