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Parkinson's Disease (Parkinsonism): Levodopa, a Sine Qua Non Therapeutic Agent in the Treatment of Parkinsonism

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Abstract

Parkinson's disease (PD) is a chronic neurological disorder characterized by degeneration of dopaminergic cells, which results in dopamine depletion. Pathological examination of the brain has shown widespread degenerative changes in the basal ganglia, in particular the substantia nigra and corpus striatum. Tremor, rigidity, bradykinesia, impairment gait and posture are associated with the disease symptoms. Treatment of the disease may involve brain stimulation (globus pallidus or subthalamic nucleus and thalamus respectively), surgical procedure (for patients refractive to therapeutic agents such as levodopa), transplantation of dopaminergic cells (grafting of fetal substantia nigra tissue containing dopamine neurons into the striatum of Parkinson's disease patient) and the use of therapeutic agents. The use of therapeutic agents is the mainstay of treatment. The classes of therapeutic agents employed are dopamine precursors, dopamine agonists, dopamine metabolic enzyme inhibitors, anticholinergic agents and dopamine reuptake inhibitors. Of all these therapeutic agents, dopamine precursor (levodopa) is the most effective and reliable drug in the clinical management of the disease.

Keywords: *Parkinson's Disease; Parkinsonism; Levodopa*

Introduction

Parkinson's disease (Parkinsonism) is a progressive disabling motor impairment disorder due to accelerated degeneration of brain cells (nigrostriatal dopamine neurons) in the mid brain and generally affects the elderly [1]. It is one of the neurodegenerative diseases [2]. Resting tremor, asymmetry of motor findings, loss of pigmented dopaminergic neurons of the substantia nigra, loss of dopamine in the neostriatum, good response to levodopa and presence of eosinophilic intracytoplasmic inclusions (Lewy bodies) in the residual dopaminergic neurons are the neuropathologic features of the disease [3,4].

The disease can arise from: (i) genetic mutation in three proteins namely α-synuclein (found in vesicles and synaptic regions); parkin and ubiquitin carboxy-terminal hydroxylase (both are involved in protein degradation), (ii) autosomal dominant pattern of inheritance (iii) sporadic (idiopathic)- mostly due to aging, genetic predisposition and environmental toxins. (iv) specific entities- brain trauma, chemical poisons (manganese, carbon monoxide), (v) drug-induced (iatrogenic)- antipsychotics (butyrophenones, phenothiazine) and (vi) viral inflammation [5-7].

Onset of symptoms is usually gradual. Most prevalent ones are tremor (often unilateral in onset, present at rest, ceases during voluntary movement), rigidity (increased resistance to passive limb movement), bradykinesia (extreme slowing of movement and is the most disabling feature) and impairment of gait and posture [8]. Other symptoms associated with the disease include orthostatic hypotension, cognitive dysfunction and dementia. Impairment of movement primarily affects ''automatic'' movements like those involved during handwriting, speech articulation and phonation, swallowing and walking.

The diagnosis of the disease requires the presence of distal resting tremor (3 to 6 Hz), bradykinesia, rigidity, and asymmetrical onset. Other vital signs are decreased olfaction, late-onset postural instability, micrographia and response to an adequate therapeutic challenge of levodopa or a dopamine agonist [9].

Clinically, the main objective using therapeutic agents that either increase dopaminergic actions or decrease neuronal outflow from the striatum in the treatment of Parkinson disease patients is to provide symptomatic relief.

Such therapeutic agents include

(i) Dopamine precursor (increases the level of dopamine in the brain). Typical example is levodopa.

(ii) Dopamine agonists (directly stimulate dopamine receptors). Typical examples are bromocriptine, pergolide, pramipexole and ropinirole.

(iii) Monoamine oxidase and catechol-O-methyltransferase inhibitors (prevent metabolism of dopamine). Typical example of monoamine oxidase inhibitor is selegiline while tolcapone and entacapone are examples of catechol-O-methyltransferase inhibitors.

(iv) Anticholinergic agents (reduce the excitatory activity within the striatum). Typical examples are biperiden, benztropine mesylate, procyclidine and trihexyphenidyl.

(v) Adamantanes (action on dopamine release and reuptake), Typical example is amantadine.

In the present article, we will examine the properties of levodopa that make it a sine qua non therapeutic agent in the treatment of Parkinson's disease.

Dopamine

In the central nervous system (CNS), dopamine is synthesized from levodopa in dopaminergic terminals, transported into storage vesicles, and released in a spike-dependent manner following depolarization of the presynaptic neuron. The released dopamine acts on postsynaptic dopamine receptors namely D_1-like (D_1, D_5) or D_2-like (D_2, D_3, D_4). Dopamine exerts excitatory actions on D_1 receptors, whereas inhibition of neuronal activity is the action of the chemical substance on D_2 receptors. Dopamine receptors are extensively distributed throughout the CNS namely: motor striatum (D_1, D_2), mesolimbic system (D_3), frontal cortex and amygdala (D_4), hippocampus (D_5) and hypothalamus (D_3, D_5). The extensive distribution may account for the diverse pattern of pharmacological effects that occur when levodopa is administered to Parkinsonism patients. In addition to the nigrostriatal dopaminergic system, dopaminergic innervation exist in cerebral cortex and other basal ganglia regions namely: the globus pallidus pars interna (GPi), the globus pallidus pars externa (GPe), the substantia nigra pars reticularis (SNr) and the subthalamic nucleus (STN) [10,11]. Activation of dopaminergic receptors in these regions might also contribute to the pharmacological effects observed with administration of levodopa to patients suffering from the disease.

Levodopa

Levodopa (L-DOPA) is chemically defined as L-3,4-dihydroxyphenylalanine and the chemical structure is given in figure 1. It is a naturally occurring amino acid derived from tyrosine modification.

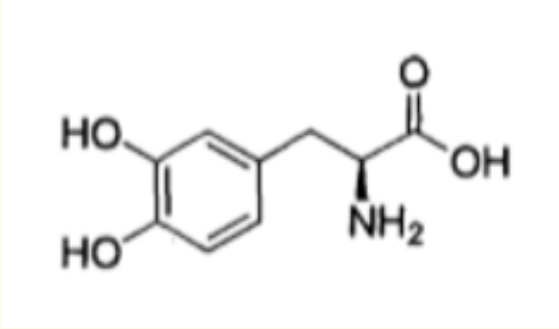

Figure 1: *Chemical structure of levodopa.*

Physicochemical properties

The physicochemical properties of levodopa show that it is a colorless crystalline powder and has a melting point of 284 - 286°C. It is slightly soluble in water, readily soluble in dilute mineral acids and alkali carbonates, practically insoluble in chloroform, ethanol, ethyl acetate, ether and benzene [12]. The logarithm partition coefficient is -2.39 (octanol/water) and pKa value of 2.32.

Physiological and pharmacological properties

Peripherally, levodopa is metabolized by two enzymatic systems namely- L-aromatic amino-acid decarboxylase and catechol-O-methyl transferase [13]. The transformation occurs in the kidney, gastrointestinal tract and liver. The peripheral metabolism of levodopa leads to only 1% of an administered oral dose reaching the brain. In the brain, levodopa is treated as if it were naturally produced by being taken up into dopaminergic nerve terminals where it is temporary stored prior to its conversion into dopamine and released following nerve stimulation. The nerve terminals therefore provide a short-term buffering of levodopa variable blood levels, permitting its pharmacological effect to be maintained between doses.

Levodopa is the most effective and reliable drug in the clinical management of Parkinson disease and provides benefits (improved mobility, reduced disability, and prolonged survival) almost to all patients with the disease [14-16].

It is widely used in the treatment of all types of the disease except that associated with antipsychotic drug therapy. The rationale for is use was based on the discovery that dopamine is depleted in the striatum of Parkinson's disease patients [18,19]. However, as dopamine cannot penetrate the central nervous system (CNS), its prodrug (levodopa) having the capability to penetrate the CNS is decarboxylated into the active product dopamine hence its utilization in the place of dopamine [19-21].

The extensive metabolism of levodopa by enzymes (L-aromatic amino-acid decarboxylase and catechol-O-methyl transferase respectively) has brought about the co-administration of levodopa with the inhibitors of these enzymes resulting in extension of the duration of levodopa pharmacological effect and its half-life in the blood (60 minutes to 90 minutes).

Levodopa as sine qua non therapeutic agent

Levodopa is regarded as the gold standard for the treatment of Parkinsonism and the first line drug of choice for clinicians despite its questionable value in long-term therapy due to its poor bioavailability, reduced efficacy and adverse effects [22-24].

It remains the primary and most potent symptomatic agent against Parkinson's disease and has increased the quality of life and longevity for patients with the disease [25].

Due to its consistent and dramatic beneficial effects, levodopa has not been investigated against placebo in therapeutic randomized controlled trials [26].

Its dose-dependent beneficial effect on mood and anxiety in disease patients increases with the duration of therapy [27]. The duration of benefit following administration of a single dose of levodopa is long lasting and far exceeds the plasma half-life of the drug in the early stages of the disease [28].

Three decades after its introduction, no more efficacious drug has yet been developed [29]. Even the dopaminergic agonists, which provide invaluable therapeutic support to levodopa are less effective.

Inhibitors of peripheral metabolism of levodopa (such as carbidopa or benserazide) have substantiated the importance of levodopa in the treatment of Parkinson's disease by allowing more levodopa to reach the brain [30].

As the mainstay agent against the disease, further enhancement of its concentration in the brain was achieved by adding another enzyme (catechol-O-methyl transferase or monoamine oxidase-B) inhibitor to a mixture of levodopa-carbidopa [23].

Motor fluctuation [between periods of good motor function(''on'' responses) and periods of poor motor function (''off'' responses)] which appear to be one of the early major adverse effects following long-term use of levodopa [31,32] is being effectively managed by the co- administration of levodopa with COMT inhibitor or amantadine.

Furthermore, motor fluctuation can also be controlled by providing more physiologic continuous dopaminergic stimulation to striatal dopamine receptors by long-acting dopaminergic agents rather than pulsatile stimulation of striatal dopamine receptors [33].

Other newer agents against Parkinson's disease (dopamine agonists, monoamine oxidase and catechol-O-methyltransferase inhibitors, anticholinergic agents, amantadine etc.) are less effective than levodopa in monotherapy, hence mostly administered as adjunct with levodopa and their adverse effects are similar to levodopa [34].

Adverse effects associated with levodopa therapy

The adverse effects of levodopa are subdivided into peripheral and central nervous system respectively [35]:

- Peripheral:
    - Anorexia, nausea and vomiting.
    - Orthostatic hypotension (probably arising from decarboxylation of the drug and release of dopamine into the circulation).

- Cardiac arrhythmias (stimulation of cardiac α- and β-adrenoreceptors by dopamine).
- Hypertensive crisis and hyperpyrexia (co-administration of levodopa with non-selective MAO inhibitors such as phenelzine, tranylcypromine) and could be life-threatening.
- Severe mydriasis in narrow-angle glaucoma patients.

- Central nervous system:
  - On-off effect (unpredictable changes between mobility and immobility).
  - Dyskinesias (abnormal and excessive choreiform movements of hands, limbs, tongue, trunk).
  - Confusion, delirium, hallucinations, insomnia.

Conclusion

Studies have shown that levodopa is the most effective therapeutic agent for Parkinson's disease symptoms, especially bradykinesia and rigidity.

Dopamine agonists are very effective therapeutic agents to treat early Parkinson's disease.

In case of motor complications in patients with advanced Parkinson's disease, co-administration of levodopa with dopamine agonist, catechol O-methyltransferase inhibitor or monoamine oxidase-B inhibitor has been found to be very beneficial not only by improving the motor activities, but also enhances the biological activity of levodopa as well as reducing the risk of the drug inducing pulsatile stimulation of the dopamine receptor.

Finally, despite some its troublesome adverse effects; levodopa not only continues to be a key component of the therapeutic armamentarium for Parkinsonism but it also provides life expectancy for disease patients on current treatment regimens close to that of the normal population, hence justifiable to consider levodopa as sine qua non therapeutic agent for Parkinson's disease.

Bibliography

1. Olanow CW and Koller WC. "An algorithm (decision tree) for the management of Parkinson's disease: treatment guidelines". *American Academy of Neurology* 50.3 (1998): S1-S57.
2. Palmer AM. "The role of the blood-CNS barrier in CNS disorders and their treatment". *Neurobiology of Disease* 37.1 (2010): 3-12.
3. Nutt JG and Wooten GF. "Clinical practice. Diagnosis and initial management of Parkinson's disease". *New England Journal of Medicine* 353 (2005): 1021-1027.
4. Gibb WR. "Neuropathology of Parkinson's disease and related syndromes". *Neurologic Clinics* 10.2 (1992): 361-376.
5. Langston JW., *et al.* "Etiology of Parkinson's disease". In: Olanow CW, Lieberman AN, editions. The scientific basis for the treatment of Parkinson's disease. Park Ridge, New Jersey: Parthenon (1992): 33-58.
6. Sanchez-Ramos JR. "A markerof oxyradical-mediated DNA damage. (8-hydroxy- 2′deoxyguanosine) is increased in nigro striatum of Parkinson's disease brain". *Neurodegeneration* 3 (1994): 197-204.
7. Tanner CM. "Epidemiology of Parkinson's disease". *Neurologic Clinics* 10 (1992): 317-329.

8. Rao G., *et al.* "Does this patient have Parkinson disease". *Journal of American Medical Association* 289 (2003): 347-353.

9. Italian Neurological Society, Italian Society of Clinical Neurophysiology. Guidelines for the treatment of Parkinson's disease 2002. "The diagnosis of Parkinson's disease". *Neurological Sciences* 24.3 (2003): S157-164.

10. Kebabian JW and Calne DB. "Multiple receptors for dopamine". *Nature* 277 (1979): 93-96.

11. Smith Y and Kieval JZ. "Anatomy of the dopamine system in the basal ganglia". *Trends Neurosciences* 23 (2000): S28-S33.

12. Martindale: The Complete Drug Reference, 39th edition., Pharmaceutical Press, London (2017).

13. Hauser RA. "Levodopa: past, present, and future". *European Journal of Neurology* 62.1 (2009): 1-8.

14. Nagatsua T and Sawadab M. "L-dopa therapy for Parkinson's disease: past, present, and future". *Parkinsonism Related Disorder* 15.1 (2009): S3-S8.

15. Hoehn MM and Yahr MD. "Parkinsonism: onset, progression, and mortality". *Neurology* 17 (1967): 427-442.

16. Abbott A. "Levodopa: the story so far". *Nature* 466 (2010): S6-S9.

17. Poewe WH and Wenning GK. "The natural history of Parkinson's disease". *Neurology* 47.6. 3 (1996): S146-S152.

18. Olanow CW., *et al.* "The scientific and clinical basis for the treatment of Parkinson disease". *Neurology* 72.21-4 (2009): S1-S136.

19. Standaert DG and Young AB. "Treatment of central nervous system disorders". In: Hardman JG, Limbird LE, eds. Goodman and Gilman's the pharmacological basis of therapeutics, ninth edition. New York: Macmillan (1995): 503-519.

20. Hornykiewicz O. "L-DOPA: from a biologically inactive amino acid to a successful therapeutic agent". *Amino Acids* 23.1-3 (2002): 65-70.

21. Ehringer H and Hornykiewicz O. "Distribution of noradrenaline and dopamine (3-hydroxytyramine) in the human brain and Neuropsychopharmacology: The Fifth Generation of Progress1810 their behavior in diseases of the extrapyramidal system (German)". *Klin Wochenschr* 38 (1960): 1236-1239.

22. Lewitt PA. "Levodopa for the treatment of Parkinson's disease". *New England Journal of Medicine* 359 (2008): 2468-2471.

23. Nutt JG and Fellman JH. "Pharmacokinetics of levodopa" *Clinical Neuropharmacology* 7 (1984): 35-49.

24. Hagan JJ., *et al.* "Parkinson's disease: prospects for improved drug therapy". *Trends Pharmacological Sciences* 18 (1997): 156-163.

25. Goetz CG., *et al.* "Evidence-based medical review update: pharmacological and surgical treatments of Parkinson's disease :2001 to 2004". *Movement Disorder* 20 (2005): 523-539.

26. Miyasaki JM., *et al.* "Practice parameter: initiation of treatment for Parkinson's disease": an evidence based review: report of the Quality Standards Subcommittee of the American Academy of Neurology". *Neurology* 58 (2002): 11-17.

27. Maricle RA., *et al.* "Mood response to levodopa infusion in early Parkinson's disease". *Neurology* 50.6 (1998): 1890-1892.

28. Nutt JG and Holford NHG. "The response to levodopa in Parkinson's disease: imposing pharmacologic law and order". *Annals of Neurology* 39 (1996): 561-573.

29. Rascol O., *et al.* "A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa". *New England Journal of Medicine* 342 (2000): 1484-1491.

30. Nutt JG and Woodward WR. "Levodopa pharmacokinetics and pharmacodynamics in fluctuating parkinsonian patients". *Neurology* 36 (1986): 739-744.

31. Wright BA and Waters CH. "Continuous dopaminergic delivery to minimize motor complications in Parkinson's disease". *Expert Review Neurotherapy* 13 (2013): 719-729.

32. Obeso JA., *et al.* "Levodopa motor complications in Parkinson's disease". *Trends Neuroscience* 23 (2000): S2-S7.

33. Papa SM and Chase TN. "Levodopa-induced dyskinesias improved by a glutamate antagonist in Parkinsonian monkeys". *Annals of Neurology* 39 (1996): 574-578.

34. Oertel WH., *et al.* "Pergolide versus levodopa monotherapy in early Parkinson's disease patients": the PELMOPET study". *Movement Disorder* 21 (2006): 343-353.

35. Fahn S. "Adverse effects of levodopa". In: Olanow CW, Lieberman AN, eds. The scientific basis for the treatment of Parkinson's disease. United Kingdom: Parthenon (1992): 89-112.

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