ISSN: 2456-3927

NeuroPharmac Journal

Gold Standard of Symptomatic treatment in Parkinson disease: Carbidopa / Levodopa

Aslam Pathan
Abdulrahman M. Alshahrani

https://doi.org/10.37881/1.331

www. neuropharmac.com

Sept-Dec 2018, Volume 3, Issue 3

NeuroPharmac Journal

ISSN:2456-3927

Journal homepage: www.neuropharmac.com

Review

Gold Standard of Symptomatic treatment in Parkinson disease: Carbidopa / Levodopa

Aslam Pathan[1], Abdulrahman M. Alshahrani[2]

[1]Department of Pharmacology, College of Medicine, Shaqra University, Shaqra-11961, Saudi Arabia

[2]Department of Internal Medicine (Neurology), College of Medicine, Shaqra University, Shaqra-11961, Saudi Arabia

https://doi.org/10.37881/1.331

https://orcid.org/0000-0002-6569-2306

ABSTRACT

Parkinson's disease (PD) is one of the most common neurologic disorders, affecting approximately 1% of individuals older than 60 years and causing progressive disability that can be slowed but not halted, by treatment. The goal of the medical management of Parkinson's disease is to provide control of signs and symptoms for as long as possible while minimizing adverse effects. Levodopa coupled with a peripheral decarboxylase inhibitor (PDI), such as carbidopa, remains the gold standard of symptomatic treatment of motor features of Parkinson's disease. It provides the greatest antiparkinsonian benefit with the fewest adverse effects in the short term. However, its long-term use is associated with the development of fluctuations and dyskinesias. This review article is written to summarize the clinical and pharmacological data of carbidopa and levodopa which will be helpful to neurologists and physicians.

INTRODUCTION

Parkinson's disease is recognized as one of the most common neurologic disorders, affecting approximately 1% of individuals older than 60 years. There are 2 major neuropathologic findings: the loss of pigmented dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the presence of Lewy bodies. Most cases of Parkinson's disease (idiopathic Parkinson disease [IPD]) are hypothesized to be due to a combination of genetic and environmental factors. However, no environmental cause of Parkinson's disease has yet been proven. A known genetic cause can be identified in approximately 10% of cases, and these are more common in younger-onset patients.[1,2] The classic motor features of Parkinson's disease typically start insidiously and emerge slowly over weeks or months, with tremors being the most common initial symptom. The 3 cardinal signs of Parkinson's disease are resting tremor, rigidity, and bradykinesia. Postural instability (balance impairment) is sometimes listed as the fourth cardinal feature. However, balance impairment in Parkinson disease is a late phenomenon, and in fact, prominent balance impairment in the first few years suggests that Parkinson disease is not the correct diagnosis.[3,4]

Diagnosis

Parkinson's disease is a clinical diagnosis. No laboratory biomarkers exist for the condition, and findings on routine magnetic resonance imaging and computed tomography scans are unremarkable.

Clinical diagnosis requires the presence of 2 of 3 cardinal signs i.e. Resting tremor, Rigidity, Bradykinesia.[5-7]

Management

The goal of medical management of Parkinson disease is to provide control of signs and symptoms for as long as possible while minimizing adverse effects.[8,9]

Symptomatic drug therapy

It usually provides good control of motor signs of Parkinson's disease for 4-6 years.

Levodopa/carbidopa: The gold standard of symptomatic treatment.

Monoamine oxidase (MAO)–B inhibitors: Can be considered for the initial treatment of early disease.

NeuroPharmac Journal ISSN:2456-3927
Journal homepage: www.neuropharmac.com Review

Dopamine agonists (eg, ropinirole, pramipexole): Monotherapy in early disease and adjunctive therapy in moderate to advanced disease.
Anticholinergic agents (eg, trihexyphenidyl, benztropine): Second-line drugs for tremor only.

Treatment for nonmotor symptoms

Sildenafil citrate (Viagra): For erectile dysfunction.
Polyethylene glycol: For constipation.
Modafinil: For excessive daytime somnolence.
Methylphenidate: For fatigue (potential for abuse and addiction).[10]

Deep brain stimulation

The surgical procedure of choice for Parkinson disease Does not involve the destruction of brain tissue; Reversible; Can be adjusted as the disease progresses or adverse events occur; Bilateral procedures can be performed without a significant increase in adverse events.[11-18]

Medical Management:

The goal of the medical management of Parkinson's disease is to provide control of signs and symptoms for as long as possible while minimizing adverse effects. Studies demonstrate that a patient's quality of life deteriorates quickly if treatment is not instituted at or shortly after diagnosis.[19]

The pharmacologic treatment of Parkinson's disease can be divided into symptomatic and neuroprotective (disease-modifying) therapy. At this time, there is no proven neuroprotective or disease-modifying therapy.[19]

CARBIDOPA/LEVODOPA

Levodopa, coupled with carbidopa, a peripheral decarboxylase inhibitor (PDI), remains the gold standard of symptomatic treatment for Parkinson's disease. Carbidopa inhibits the decarboxylation of levodopa to dopamine in the systemic circulation, allowing for greater levodopa distribution into the central nervous system. Levodopa provides the greatest antiparkinsonian benefit for motor signs and symptoms, with the fewest adverse effects in the short term; however, its long-term use is associated with the development of motor fluctuations ("wearing-off") and dyskinesias. Once fluctuations and dyskinesias become problematic, they are difficult to resolve.

Dosage Form & Strenght[20]

Adult:

Tablet

10mg/100mg
25mg/100mg
25mg/250mg

Tablet, disintegrating

10/100mg
25/100mg
25/250mg

Tablet, extended release

25mg/100mg
50mg/200mg

Capsule, extended release

23.75mg/95mg
36.25mg/145mg
48.75mg/195mg
61.25mg/245mg

Enteral suspension, extended release

(4.63mg/20mg)/mL in a single-use cassette
Each cassette contains ~100 mL

Dosing Consideration

Maintain patients on the lowest dosage required to achieve symptomatic control and to minimize adverse reactions such as dyskinesia and nausea.

Immediate release (IR): When more carbidopa is required, substitute one 25 mg/100 mg tablet for each 10 mg/100 mg tablet; if necessary, a dosage of 25 mg/250 mg tablet may be increased by one half or by 1 tablet every 1-2 days to a maximum of 8 tablets daily; experience with total daily carbidopa doses higher than 200 mg is limited.

Extended-release (ER): Doses and dosing intervals may be increased or decreased according to response; most patients are adequately treated with regimens providing levodopa 400-1600 mg/day divided q4-8hr while awake; higher levodopa dosages (≥2400 mg/day) and shorter intervals (<4 hours) are used but not usually recommended; if

NeuroPharmac Journal ISSN:2456-3927
Journal homepage: www.neuropharmac.com Review

interval <4 hours is used or if divided doses are not equal, give smaller doses at end of the day; allow at least 3 days between dosage adjustments.[21,22]

Contraindications

Hypersensitivity; Narrow-angle glaucoma (tablets); Concurrent administration of nonselective monoamine oxidase inhibitors (MAOIs) or use within last 14 days.[23]

Cautions

Use caution in the history of MI with residual atrial, nodal, or ventricular arrhythmias, peptic ulcer, or seizure. Use caution in severe cardiovascular, respiratory disease, renal, hepatic, or endocrine disease; monitor disease parameters. Use caution in bronchial asthma patients taking sympathomimetics. Levodopa may cause patients to fall asleep while engaging in activities of daily living; caution regarding use of machinery and driving.[23]

Avoid use in patients with a major psychotic disorder; therapy may exacerbate psychosis; increases risk for hallucinations and development of psychosis; other psychiatric symptoms include decreased impulse control and compulsive behaviors, depression, and suicidality; observe patients for symptoms of depression with concomitant suicidal tendencies. May exacerbate dyskinesia; reduce dose to control symptoms. Peripheral neuropathy reported with use; evaluate patients for history of neuropathy and known risk factors before initiating therapy; assess patients for peripheral neuropathy periodically during therapy. Orthostatic hypotension may occur (more common with immediate-release formulation). Use caution in patients with glaucoma; monitor intraocular pressure carefully; some formulations are contraindicated in patients with narrow-angle glaucoma. Observe patients if discontinued abruptly; risk of a syndrome resembling neuroleptic malignant syndrome. The controlled-release formulation is less bioavailable than conventional formulation.[23]

Gastrointestinal complications from PEG-J or nasojejunal tube can occur (eg, bezoar, ileus, intussusception, implant site erosion/ulcer, intestinal hemorrhage, intestinal ischemia, intestinal obstruction, intestinal perforation, pancreatitis, peritonitis, pneumoperitoneum, and post-operative wound infection); these complications may result in serious outcomes (eg, need for surgery, death).

Parkinson disease patients are at increased risk of developing melanoma; monitor patients closely and perform periodic skin examinations.[23]

Pharmacology

Mechanism of Action

Carbidopa: Inhibits aromatic amino-acid decarboxylase in peripheral tissues; this, in turn, inhibits the peripheral breakdown of levodopa, thereby increasing the availability of levodopa at the blood-brain barrier and allowing a lower levodopa dose.

Carbidopa may also reduce nausea and vomiting and permit more rapid titration of levodopa.

Levodopa: Metabolic precursor of dopamine, a neurotransmitter depleted in Parkinson disease; crosses the blood-brain barrier to be converted by striatal enzymes to dopamine.[24]

Absorption

Duration: Short-duration improvement, 5 hr; long-duration response, 3-5 days.

Peak plasma time: Immediate release (IR), 0.5 hr; extended-release (ER), 2 hr.

Peak plasma concentration: ER peak concentration is 35% of IR peak concentration.

Distribution

Both drugs widely distributed; carbidopa does not cross the blood-brain barrier; <1% of levodopa enters CNS.

Protein-bound: Carbidopa, 36%; levodopa, 10-30%

Vd: Levodopa, 0.9-1.6 L/kg in presence of carbidopa

Metabolism

Carbidopa not extensively metabolized; levodopa metabolized in small amounts in the GI tract and undergoes first-pass hepatic metabolism.

Metabolites: Dopamine, homovanillic acid

NeuroPharmac Journal ISSN:2456-3927
Journal homepage: www.neuropharmac.com Review

Elimination

Half-life: IR, 1.5 hr

Excretion: Carbidopa, urine (50%; PO); levodopa, urine (80-85%; increased in presence of carbidopa).

Pregnancy & Lactation

Pregnancy category: C (Use with caution if benefits outweigh risks. Animal studies show risk and human studies not available or neither animal nor human studies done).

Lactation: Drug inhibits lactation; use with caution.[24]

Guidelines Summary

American Academy of Neurology (AAN)

In 2010, the AAN released guidelines on the treatment of nonmotor symptoms of Parkinson's disease. Recommendations included the following[25]

- Sildenafil citrate (Viagra) may be considered to treat erectile dysfunction.
- Polyethylene glycol may be considered to treat constipation.
- Modafinil should be considered for patients who subjectively experience excessive daytime somnolence.
- For insomnia, the evidence is insufficient to support or refute the use of levodopa to improve objective sleep parameters that are not affected by motor symptoms; the evidence is also insufficient to support or refute the use of melatonin for poor sleep quality.
- Levodopa/carbidopa should be considered to treat periodic limb movements of sleep in Parkinson's disease, but there are insufficient data to support or refute the use of nonergot dopamine agonists to treat this condition or that of a restless-legs syndrome.
- Methylphenidate may be considered for fatigue (note: methylphenidate has the potential for abuse and addiction).
- Evidence is insufficient to support or refute specific treatments of orthostatic hypotension, urinary incontinence, anxiety, and RMD.

REFERENCES

1. Wirdefeldt K, Adami HO, Cole P, Trichopoulos D, Mandel J. Epidemiology and etiology of Parkinson's disease: a review of the evidence. Eur J Epidemiol. 2011;Suppl 1:S1-58.
2. Tanner CM, Ottman R, Goldman SM, Ellenberg J, Chan P, Mayeux R, et al. Parkinson disease in twins: an etiologic study. JAMA. 1999;281(4):341-6.
3. Bekris LM, Mata IF, Zabetian CP. The genetics of Parkinson disease. J Geriatr Psychiatry Neurol. 2010;(4):228-42.
4. Vekrellis K, Xilouri M, Emmanouilidou E, Rideout HJ, Stefanis L. Pathological roles of a-synuclein in neurological disorders. Lancet Neurol. 201;(11):1015-25.
5. Suchowersky O, Reich S, Perlmutter J, Zesiewicz T, Gronseth G, Weiner WJ. Practice Parameter: diagnosis and prognosis of new onset Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2006;66(7):968-75.
6. National Collaborating Centre for Chronic Conditions. Parkinson's disease: National clinical guideline for diagnosis and management in primary and secondary care. London, UK: Royal College of Physicians; 2006.
7. Hughes S. Consider Nonmotor Symptoms for Diagnosis of Parkinson's? Medscape Medical News. January 18, 2013. Available at http://www.medscape.com/viewarticle/777874.
8. Brin MF, Velickovic M, Remig LO. Dysphonia due to Parkinson's disease; pharmacological, surgical, and behavioral management perspectives. Vocal Rehabilitation in Medical

Speech-Language Pathology. Austin: Pro-Ed; 2004;209-69.
9. Antonini A, Cilia R. Behavioural adverse effects of dopaminergic treatments in Parkinson's disease: incidence, neurobiological basis, management and prevention. Drug Saf. 2009. 32(6):475-88.
10. Truong DD, Bhidayasiri R, Wolters E. Management of non-motor symptoms in advanced Parkinson disease. J Neurol Sci. 2008; 266(1-2):216-28.
11. Kim HJ, Jeon BS, Paek SH. Effect of deep brain stimulation on pain in Parkinson disease. J Neurol Sci. 2011; 310(1-2):251-5.
12. Shemisa K, Hass CJ, Foote KD, Okun MS, Wu SS, Jacobson CE 4th, et al. Unilateral deep brain stimulation surgery in Parkinson's disease improves ipsilateral symptoms regardless of laterality. Parkinsonism Relat Disord. 2011;(10):745-8.
13. Weaver FM, Follett K, Stern M, Hur K, Harris C, Marks WJ Jr. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. JAMA. 2009;301(1):63-73.
14. Follett KA, Weaver FM, Stern M, Hur K, Harris CL, Luo P, et al. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. N Engl J Med. 2010;362(22):2077-91.
15. Kim HJ, Jeon BS, Lee JY, Paek SH, Kim DG. The benefit of subthalamic deep brain stimulation for pain in Parkinson disease: a 2-year follow-up study. Neurosurgery. 2012;70(1):18-23.
16. Timmermann L, Jain R, Chen L, Brucke T, Seijo F, San Martin ES, et al. 134 VANTAGE Trial: Three-Year Outcomes of a Prospective, Multicenter Trial Evaluating Deep Brain Stimulation with a New Multiple-Source, Constant-Current Rechargeable System in Parkinson Disease. Neurosurgery. 2016;63 Suppl 1:155.
17. Lang AE, Widner H. Deep brain stimulation for Parkinson's disease: patient selection and evaluation. Mov Disord. 2002. 17 Suppl 3:S94-101.
18. Silberstein P, Bittar RG, Boyle R, Cook R, Coyne T, O'Sullivan D. Deep brain stimulation for Parkinson's disease: Australian referral guidelines. J Clin Neurosci. 2009;16(8):1001-8.
19. Grosset D, Taurah L, Burn DJ, MacMahon D, Forbes A, Turner K, et al. A multicentre longitudinal observational study of changes in self reported health status in people with Parkinson's disease left untreated at diagnosis. J Neurol Neurosurg Psychiatry. 2007;78(5):465-9.
20. Samanta J, Hauser RA. Duodenal levodopa infusion for the treatment of Parkinson's disease. Expert Opin Pharmacother. 2007; 8(5):657-64.
21. Pahwa R, Tanner CM, Hauser RA, Isaacson SH, Nausieda PA, Truong DD, et al. ADS-5102 (Amantadine) Extended-Release Capsules for Levodopa-Induced Dyskinesia in Parkinson Disease (EASE LID Study): A Randomized Clinical Trial. JAMA Neurol. 2017;74 (8):941-949.
22. Hauser RA, Pahwa R, Tanner CM, Oertel W, Isaacson SH, Johnson R, et al. ADS-5102 (Amantadine) Extended-Release Capsules for Levodopa-Induced Dyskinesia in Parkinson's Disease (EASE LID 2 Study): Interim Results of an Open-Label Safety Study. J Parkinsons Dis. 2017. 7 (3):511-522.
23. Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and pharmacological management of Parkinson's disease. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2010 Jan. 61 p. (SIGN publication; no. 113).

24. Koller WC. Levodopa in the treatment of Parkinson's disease. Neurology. 2000. 55(11 Suppl 4):S2-7.
25. Zesiewicz TA, Sullivan KL, Arnulf I, et al. Practice Parameter: treatment of nonmotor symptoms of Parkinson disease: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2010;74(11):924-31.

Cite this article: Pathan A, Alshahrani A. Gold Standard of Symptomatic treatment in Parkinson disease: Carbidopa / Levodopa. NeuroPharmac J. 2018; 3(3): 63-68. DOI:10.37881/1.331