Considerations about PD Treatment

Subjects: Psychology, Biological
Contributor: Sara Silva

The treatment of PD starts when motor signs are developed. Current treatments include pharmacologic therapy, physical therapy, rehabilitating therapy and surgery. Physical therapy and exercise are beneficial in PD patients for both motor and non-motor symptoms. The activities include speech therapy, nutrition, physiotherapy, and support groups.

Keywords: Parkinson's disease ; nanoparticles ; drug ; treatment ; delivery systems ; administration routes ; nanotheranostics

1. Levodopa and Carbidopa

Levodopa is a prodrug of dopamine that was discovered in 1961 and is considered a replacement treatment of dopamine [1]. Levodopa facilitates central nervous system (CNS) penetration and brain dopamine delivery. Levodopa is still the most potent pharmacologic compound for treating PD [1]. Although dopamine is a great potent compound, it presents a low oral bioavailability, and only 1% of levodopa reaches the brain. In addition, the peripheral release of dopamine negatively affects different peripheral body functions such as decrease intestinal motility, insulin production, and vasodilation. So, co-administration with carbidopa is crucial to decrease the peripheral breakdown of levodopa and avoid side-effects. Carbidopa is an inhibitor of aromatic L-amino acid decarboxylase [2]. These compounds do not pass blood–brain barrier (BBB) which contributes to a higher therapeutic efficacy of levodopa in the brain and decrease peripheral side-effects [3][4][5]. Still, chronic long-term treatment cause motor complications such as dyskinesia.

2. Dopamine Agonists

2.1. Apomorphine

Apomorphine is used in PD due the capacity to activate D1 like and D2 like receptors and its lipophilicity proprieties enables crossing the BBB. Unfortunately, apomorphine presents a short half-life (33 min), which necessitates administration through subcutaneous injections several times a day. The administration of this therapy is usually applied in the advance stage of PD to reduce off-time and dimmish motor fluctuations from levodopa treatment [6][7][8].

2.2. Pramipexole

In 1997, pramipexole—a novel non-ergolinic dopamine agonist—was approved to treat PD. Pramipexole is an aminobenzothiazole with the full stimulation of the D2 subfamily dopamine receptor. After oral administration, it can reach 90% bioavailability and have protein binding of less than 15%, and an increase half-life (8–12 h) however can cause severe side-effects such as nausea, vomiting, hypotension, impulsive control disorder, and hallucinations [9][10][11].

2.3. Ropinirole

Ropinirole is a non-ergoline selective dopamine D2 agonist, and it can be administered through all stages of PD. The beneficial outcomes of this therapy in the early stages of PD include a delay of the development of dyskinesias and a great efficacy to decrease motor symptoms and improve non-motor symptoms (sleep disturbances). In addition, this compound is administered through a silicone-based transdermal patch for a period of 24 h, at which point the systemic circulation results in a low protein binding and good half-life. Still, some adverse effects such as nausea, dizziness, somnolence, headache, vomiting, fatigue, and pain can occur [12][13].

2.4. Rotigotine

Another option for PD treatment is the use of rotigotine, which is a non-ergolinic dopamine agonist of dopamine receptor families D3, D2, and D1 that uses a transdermal system. This compound can be used as monotherapy in early stage of PD and adjunctive therapy with levodopa in advanced PD. Some adverse effects are consistent with the over-stimulation

of peripheral dopamine receptors, and they include nausea, somnolence, and application site reactions [12][14][15].

3. MAO-B Inhibitors

Another current strategy chosen to treat PD is the use of MAO-B inhibitors. MAO-B is an enzyme responsible for dopamine degradation. Thus, by inhibiting dopamine degradation, the levels of dopamine increase. Some examples of MAO-B inhibitors are rasagiline and selegiline. Even though MAO-B inhibitors present less effects, they also have less side-effects compared to treatments. Furthermore, several studies have demonstrated that another possible key feature of these compounds is their ability to act as neuroprotectants from oxidative stress [16][17].

4. Catechol O-Methyltransferase Inhibitors

Catechol *o*-methyltransferase (COMT) is responsible for the conversion of different catechols (like dopamine and epinephrine) and is another PD target therapy with the inhibition of this dopamine metabolization. Levodopa can be metabolized by decarboxylase in the peripheral system, and the co-administration of carbidopa will inhibit this process; however, once the system is occupied, levodopa is also metabolized by COMT in the periphery. Thus, the use of COMT inhibitors can prevent peripheral metabolization and allow for more levodopa to reach the brain. For instance, COMT inhibitors can extend the half-life of levodopa by 85% and increase absolute bioavailability. Some examples of these compounds include entacapone and tolcapone (oral formulation). Both of these compounds have been used as adjunctive therapy to control motor fluctuations acquired by patients from chronic levodopa treatment [18][19][20].

5. Anticholinergic

5.1. Trihexyphenidyl

Trihexyphenidyl is an oral anticholinergic agent used to treat motor symptoms of PD and movement disorders. Trihexyphenidyl blocks central cholinergic receptors allowing maintenance of cholinergic transmission in the basal ganglia inhibiting the reuptake and storage of dopamine. This compound is usually used as adjunctive therapy with levodopa in early stage of PD. Trihexyphenidyl is available in tablets form (2 mg and 5 mg) and elixir form. The side-effects are nervousness, confusion, drowsiness, tachycardia, constipation and nausea [21].

5.2. Benztropine

Another anticholinergic agent used in PD treatment as adjunctive therapy is benztropine. Benztropine belongs to muscarinic receptor antagonists' class. Mechanisms of action includes reduction of the central cholinergic effect with the inhibition of muscarinic receptors (that inhibit the reuptake and storage of dopamine). This compound is not chosen often due to its several contraindications [22].

6. Amantadine

Amantadine is a non-competitive NMDA-receptor antagonist and was first used in 1960 as antiviral drug but soon showed a reduction of dyskinesias in PD patients. Thus, researchers found that an imbalance of dopamine levels is associated with an increased concentration of extracellular glutamate, which increase the expression and activity of NMDA-type glutamate receptors. By acting on this mechanism, amantadine is able to control glutamate concentrations and reduce the motor fluctuations present in PD. Still, this compound response is different between patients, and even though it has a half-life of 17 h, a two- or three-times daily dose is required [23][24].

7. Neurosurgical Treatments

The surgical approach is used when pharmaceutical therapy is no more beneficial to the patient, as in cases of severe motor fluctuations, dyskinesia, hallucinations, and intractable tremors. Deep brain stimulation is usually conducted at an advanced stage of PD and is characterized by the insertion of electrodes into the target area of the brain. After levodopa treatment, surgical intervention is the second most effective therapeutic showing benefits for up to five years. Although some disadvantages have to be taken in account when performing this type of treatment. Neurosurgical treatment do not improve speech or swallow issues, can have complications (infection, stroke, and seizures) and some patients reported cognitive decline [25][26].

References

1. Reich, S.G.; Savitt, J.M. Parkinson’s Disease. Med. Clin. North Am. 2019, 103, 337–350.
2. Markham, C.H.; Diamond, S.G.; Treciokas, L.J. Carbidopa in Parkinson Disease and in Nausea and Vomiting of Levodopa. Arch. Neurol. 1974, 31, 128–133.
3. Haddad, F.; Sawalha, M.; Khawaja, Y.; Najjar, A.; Karaman, R. Dopamine and levodopa prodrugs for the treatment of Parkinson’s disease. Molecules 2018, 23, 40.
4. Whitfield, A.C.; Moore, B.T.; Daniels, R.N. Classics in chemical neuroscience: Levodopa. ACS Chem. Neurosci. 2014, 5, 1192–1197.
5. Fahn, S. Levodopa in the treatment of Parkinson’s disease. J. Neural Transm. Suppl. 2006, 1–15.
6. Jenner, P.; Katzenschlager, R. Apomorphine-pharmacological properties and clinical trials in Parkinson’s disease. Park. Relat. Disord. 2016, 33, S13–S21.
7. Auffret, M.; Drapier, S.; Vérin, M. Pharmacological Insights into the Use of Apomorphine in Parkinson’s Disease: Clinical Relevance. Clin. Drug Investig. 2018, 38, 287–312.
8. Subramony, J.A. Apomorphine in dopaminergic therapy. Mol. Pharm. 2006, 3, 380–385.
9. Antonini, A.; Barone, P.; Ceravolo, R.; Fabbrini, G.; Tinazzi, M.; Abbruzzese, G. Role of pramipexole in the management of Parkinsons disease. CNS Drugs 2010, 24, 829–841.
10. Hametner, E.M.; Seppi, K.; Poewe, W. Pramipexole extended release in Parkinson’s disease. Expert Rev. Neurother. 2011, 11, 1229–1234.
11. Lloret, S.P.; Rey, M.V.; Ratti, L.; Rascol, O. Pramipexole for the treatment of early Parkinsons disease. Expert Rev. Neurother. 2011, 11, 925–935.
12. Frampton, J.E. Rotigotine Transdermal Patch: A Review in Parkinson’s Disease. CNS Drugs 2019, 33, 707–718.
13. Pahwa, R.; Lyons, K.E.; Hauser, R.A. Ropinirole therapy for Parkinson’s disease. Expert Rev. Neurother. 2004, 4, 581–588.
14. Reynolds, N.A.; Wellington, K.; Easthope, S.E. Rotigotine. CNS Drugs 2005, 19, 973–981.
15. Morgan, J.C.; Sethi, K.D. Rotigotine for the treatment of Parkinson’s disease. Expert Rev. Neurother. 2006, 6, 1275–1282.
16. Ebadi, M.; Sharma, S.; Shavali, S.; El Refaey, H. Neuroprotective actions of selegiline. J. Neurosci. Res. 2002, 67, 285–289.
17. Siddiqui, M.A.A.; Plosker, G.L.M. Rasagiline. Drugs Aging 2005, 22, 83–91.
18. Schrag, A. Entacapone in the treatment of Parkinson’s disease. Lancet Neurol. 2005, 4, 366–370.
19. Chong, B.S.; Mersfelder, T.L. Entacapone. Ann. Pharmacother. 2000, 34, 1056–1065.
20. Keating, G.M.; Lyseng-Williamson, K.A. Tolcapone. CNS Drugs 2005, 19, 165–184.
21. Shear, N. TRIHEXYPHENIDYL. In Litt’s Drug Eruptions & Reactions Manual; CRC Press: Boca Raton, FL, USA, 2010; pp. 603–610.
22. Katzenschlager, R.; Sampaio, C.; Costa, J.; Lees, A. Anticholinergics for symptomatic management of Parkinson´s disease. Cochrane Database Syst. Rev. 2002.
23. Rascol, O.; Lozano, A.; Stern, M.; Poewe, W. Milestones in Parkinson’s disease therapeutics. Mov. Disord. 2011, 26, 1072–1082.
24. Chang, C.; Ramphul, K. Amantadine; Pfeiffer, R.F., Wszolek, Z.K., Ebadi, M., Eds.; CRC Press: Boca Raton, FL, USA, 2020; ISBN 9780429149344.
25. Groiss, S.J.; Wojtecki, L.; Südmeyer, M.; Schnitzler, A. Review: Deep brain stimulation in Parkinson’s disease. Ther. Adv. Neurol. Disord. 2009, 2, 379–391.
26. Okun, M.S. Deep-Brain Stimulation for Parkinson’s Disease. N. Engl. J. Med. 2012, 367, 1529–1538.