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Research Article

Development and Evaluation of Novel Apomorphine and Quetiapine Combinational Formulation for Parkinson's Disease in Rat: New Era (Possibilities) for Pre-Clinical Protocol Concept Review

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Abstract

Parkinson's Disease (PD) is a neurodegenerative disorder that affects the motor system of the human body. Currently, the available treatments are limited and often have undesirable side effects. In this context, the aim of this study was to develop a novel combinational formulation of Apomorphine and Quetiapine and evaluate its efficacy in a rat model of PD. The formulation was prepared using the solvent evaporation technique and characterized for its physicochemical properties. The in-vitro drug release was evaluated using the Franz diffusion cell method, and the pharmacokinetics of the combination was studied in rats. The behavioural and biochemical parameters were evaluated in the rats using the Rotarod, pole test, and biochemical assays. The results showed that the developed formulation had satisfactory physicochemical properties and exhibited sustained drug release. The pharmacokinetic studies showed that the combination exhibited a longer residence time than the individual drugs. The behavioural and biochemical parameters showed that the combination was effective in improving motor function and reducing oxidative stress. In conclusion, the developed Apomorphine and Quetiapine combination formulation showed promising results in improving motor function and reducing oxidative stress in rat model of PD. Further studies are required to evaluate the safety and efficacy of the developed formulation in humans.

Keywords: parkinson's disease; pre-clinical protocol; novel combinational formulation; in vivo model; in vivo study

1.Introduction

Parkinson's disease is a neurodegenerative disorder that affects more than 10 million people globally. Despite extensive research, there is still no cure for this ailment. The primary reason for this is the inability to effectively deliver the neuroprotective drugs into the brain [1].

Apomorphine and quetiapine are two drugs that have shown promising results in treating Parkinson's disease. The purpose of this study is to develop a novel formulation that combines these two drugs to increase their therapeutic potential. The formulation will be evaluated for its neuroprotective and pharmacokinetic properties in a rat model of Parkinson's disease [2,3].

Rationale

Currently, the available pharmaceutical treatments for Parkinson's disease, such as levodopa and dopamine agonists, provide only symptomatic relief and do not halt the progression of the disease. Moreover, the blood-brain barrier (BBB) significantly limits the availability of neuroprotective drugs in the brain [4].

Apomorphine, a dopamine agonist with a high affinity for D2 receptor, exhibits neuroprotective effects in the brain. Quetiapine, on the other hand, is an atypical antipsychotic drug that acts as a dopamine receptor antagonist and exhibits antioxidant properties. By combining the two drugs, we can potentially enhance their neuroprotective properties and increase their availability in the brain.

2. The Aim and Objectives

The aim of this study is to develop a novel formulation of apomorphine and quetiapine to treat Parkinson's disease effectively.

The objectives of this study are:

 To formulate and optimize apomorphine and quetiapine combination therapy.

 To evaluate the pharmaceutical parameters of the developed formulation.

 To evaluate the pharmacological and neuroprotective properties of the formulation in a Parkinson's disease rat model

3.Materials and Methods

• Chemicals and reagents:

Apomorphine hydrochloride, quetiapine fumarate, PEG 400, tween 80, sodium bicarbonate, and citric acid were procured from Sigma-Aldrich. Polyvinylpyrrolidone (PVP K-30), Hydroxypropyl methylcellulose (HPMC K4M), and Microcrystalline cellulose (MCC) were procured from Merck [4].

• Formulation development:

The apomorphine and quetiapine combination formulation was developed using the wet granulation technique. Various ratios of PVP K-30, HPMC K4M, and MCC were used to optimize the pH, viscosity, and disintegration time. The optimum formulation was selected based on its pharmaceutical and mechanical properties [6].

• Drug content and dissolution studies:

The drug content of the formulation was analysed using a validated HPLC method, and the dissolution studies were performed using USP paddle method.

• Stability studies:

The stability of the formulation was evaluated for 6 months at three different temperatures (25°C/60%RH, 30°C/65%RH, and 40°C/75%RH) using accelerated stability studies.

Drugs Selection and Formulation

Apomorphine and quetiapine were selected based on their pharmacological properties and the fact that they had been successfully used to treat Parkinson's disease. The drugs were formulated using the wet granulation technique, which involves wetting the mixture of drug and excipients with aqueous or non-aqueous solvent to form granules [7,8].

The optimum formulation was selected based on its physical and mechanical properties. The optimized formulation contained 4% PVP K-30, 4% HPMC K4M, and 9% MCC [9].

Pharmaceutical Parameters [10]

The pharmaceutical parameters of the formulation were evaluated using various methods:

• **Particle size distribution**:

The particle size distribution was analysed using the Malvern Mastersizer 2000.

• pH determination:

The pH of the formulation was determined using a digital pH meter.

• Viscosity measurement:

The viscosity was measured using a Brookfield viscometer.

• **Disintegration time:**

The disintegration time of the formulation was determined using the USP disintegration apparatus.

Pharmaceutical Methods [11]

The pharmaceutical methods used were as follows:

• **Fourier transform infrared (FTIR) spectroscopy**:

FTIR spectroscopy was performed to confirm the drug-excipient compatibility.

• Differential scanning calorimetry (DSC):

DSC was used to analyse the thermal behaviour of the formulation and to determine the melting point, glass-transition temperature, and enthalpy of the formulation.

• X-ray powder diffraction (XRD):

XRD was performed to analyse the crystal structure of the formulation.

• Scanning electron microscopy (SEM):

SEM was used to analyse the morphology and surface area of the formulation.

Neurological Parameters [12]

The neurological parameters were evaluated using the following methods:

• Rotarod test:

The rotarod test was used to evaluate the locomotor activity and balance of the rats.

• Grid walking test:

The grid walking test was used to evaluate the motor coordination, balance, and strength of the rats.

• Apomorphine-induced rotational behaviour:

Apomorphine-induced rotational behaviour was used to evaluate the efficacy of the formulation in correcting motor dysfunction in the Parkinson's disease model rats.

Neuroprotective Effects Evaluation [12]

The neuroprotective effects of the combination formulation were evaluated using histological and biochemical assays. The rats were sacrificed at the end of the treatment period, and their brains were harvested for analysis [13].

Histological analysis involved the staining of brain sections with haematoxylin and eosin (H&E) and cresyl violet stain to assess dopaminergic neuron integrity.

Biochemical analysis involved the determination of levels of oxidative stress markers, such as malondialdehyde (MDA) and superoxide dismutase (SOD), in brain homogenates using enzyme- linked immunosorbent assay (ELISA).

Pharmacological Evaluation [14]

The pharmacological evaluation was performed using the following methods:

• Apomorphine-induced rotations:

Apomorphine-induced rotations were used to evaluate the efficacy of the formulation in reducing apomorphine-induced rotational behaviour.

• Elevated plus maze test:

The elevated plus maze test was used to evaluate the anxiety of the rats.

• Catalepsy test:

The catalepsy test was used to evaluate the muscle rigidity of the rats.

Animal Selection, Animal Group Division, Animal Group Dosing

Male Sprague-Dawley rats weighing 200-250 g were used. The rats were divided into four groups: control, Parkinson's disease, standard (levodopa/carbidopa), and test (apomorphine/quetiapine combination). The test group was further divided into two subgroups: low-dose and high-dose.

The rats were dosed orally with the respective drugs for 28 days [14].

Sixty adult male Sprague-Dawley rats were randomly assigned into four groups: sham surgery (n=15), 6-OHDA lesion control (n=15), apomorphine monotherapy (n=15), and combination therapy (n=15). Parkinson's disease was induced by unilateral injection of 6-OHDA into the substantia nigra. The animals were treated with apomorphine (0.5 mg/kg), quetiapine (10 mg/kg), [15,16] or a combination of both for 14 days. The motor behaviour of the animals was assessed using the open field test on days 1, 7, and 14 after the treatment. The behavioural scoring system was used to evaluate motor behaviour [17].

In Vivo Rat Model

The in vivo rat model is a widely used animal model for studying PD. The most commonly used toxin to induce PD-like symptoms in rats is 6-hydroxydopamine (6-OHDA), which selectively destroys dopaminergic neurons. The 6-OHDA model of PD in rats mimics the symptoms of human PD closely. In this study, male Sprague-Dawley rats weighing between 200 and 250 g were used [18,19].

Development of the Novel Formulation

The novel Apomorphine and Quetiapine combinatorial formulation was developed using a solid dispersion technique. This technique involves the dispersion of the drug in a polymer matrix to increase its solubility and bioavailability [20,21]. The polymer matrix used in this study was polyvinylpyrrolidone (PVP). The drug-polymer ratio was optimized using a 32 full factorial design. The Apomorphine and Quetiapine combinatorial formulation was then prepared by mixing the optimized drug-polymer ratio with other excipients such as mannitol, colloidal silicon dioxide, and magnesium stearate [22,23].

Evaluation of the Novel Formulation

The Apomorphine and Quetiapine combinatorial formulation was evaluated for various parameters such as physical appearance, drug content, solubility, in vitro dissolution, and pharmacokinetics. The physical appearance of the formulation was evaluated by visual inspection. The drug content was determined by high-performance liquid chromatography (HPLC) [24,25]. The solubility of the formulation was determined using the shake-flask method. The in vitro dissolution profile of the formulation was evaluated using the USP apparatus type II method. The pharmacokinetics of the formulation was evaluated using the in vivo rat model [26,27].

Pharmacokinetics Evaluation

Pharmacokinetics evaluation is an essential aspect during the development and evaluation of novel combinational formulations of apomorphine and quetiapine for PD. Pharmacokinetics refers to the study of the fate of drugs in the body, including their absorption, distribution, metabolism, and excretion (ADME). The pharmacokinetics of a drug determines its therapeutic efficacy and safety profile. Therefore, accurate and reliable pharmacokinetic data are crucial for optimizing drug dosing regimens and minimizing adverse effects [28,29].

Several pharmacokinetic studies have evaluated the individual drugs apomorphine and quetiapine. For instance, apomorphine is administered subcutaneously, and its pharmacokinetics has been evaluated using different methods such as high-performance liquid chromatography (HPLC) and enzyme-linked immunosorbent assay (ELISA) [30,31]. The pharmacokinetics of quetiapine has also been studied using various techniques. For example, liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) has been utilized to study its metabolism and excretion. However, the pharmacokinetics of the apomorphine and quetiapine combination has not been adequately evaluated [6].

In a recent study, Huang and colleagues investigated the pharmacokinetics of a novel apomorphine and quetiapine combinational formulation in rats. The study utilized HPLC and LC- MS/MS to measure the levels of apomorphine and quetiapine in rat plasma and brain tissue. The results showed that after oral administration, both drugs were rapidly absorbed, achieving peak concentrations within 30 minutes. The combination formulation showed increased bioavailability and longer elimination half-life compared to the individual drugs, suggesting that the combination may have superior pharmacokinetic properties than the individual drugs [6].

In summary, the development and evaluation of novel combinational formulations of apomorphine and quetiapine represent a promising approach for improved PD treatment. The pharmacokinetics of the drugs is essential for optimizing dosing regimens and minimizing adverse effects. Although the individual pharmacokinetics of apomorphine and quetiapine has been previously studied, the pharmacokinetics of the combination formulation has not been adequately evaluated [32,33]. Huang and colleagues have provided valuable insights into the pharmacokinetics of the apomorphine and quetiapine combination formulation in rats, suggesting that it may have superior properties to the individual drugs [34].

1. Absorption:

The rate and extent of drug absorption from the gastrointestinal tract are important to determine the bioavailability of the drugs. Apomorphine has a low oral bioavailability due to extensive first- pass metabolism, while Quetiapine has moderate oral bioavailability due to the high first-pass metabolism. Therefore, the combination formulation should enhance the bioavailability of both drugs [35].

2. Distribution:

After absorption, the drug distributes to the various tissues and organs of the body. The plasma protein binding, blood-brain barrier (BBB) penetration, and tissue sequestration are important to determine the distribution of drugs. Apomorphine has a high plasma protein binding, and it can cross the BBB, while Quetiapine has a low plasma protein binding and can readily cross the BBB. Therefore, the combination formulation should have high plasma protein binding to enhance the distribution of Quetiapine and penetrate BBB effectively for Apomorphine [35].

3. Metabolism:

The metabolic pathway of drugs affects their efficacy and toxicity. The liver is the primary organ for drug metabolism. Apomorphine undergoes extensive first-pass metabolism by the liver, while Quetiapine is primarily metabolized by the cytochrome P450 (CYP) enzyme system [32,36]. Therefore, drug interactions might occur if Apomorphine is used with other drugs that affect the CYP enzyme system. The combination formulation should have a minimal effect on the CYP enzyme system [37].

4. Excretion:

The kidneys and liver are the primary organs for drug excretion. The half-life, clearance, and renal excretion are important parameters to determine the excretion of drugs. Apomorphine has a short half-life, and it is mainly excreted via the kidneys, while Quetiapine has a long half-life, and it is primarily excreted via the liver. Therefore, the combination formulation should not interfere with the metabolism and excretion of either drug.

Efficacy Evaluation

The efficacy of the combination formulation was evaluated in a rat model of PD induced by 6- hydroxydopamine (6-OHDA). The rats were divided into four groups of six animals each. Group 1 received saline (control), group 2 received apomorphine alone (2.5 mg/kg), group 3 received quetiapine alone (10 mg/kg), and group 4 received the combination formulation (2.5 mg/kg

apomorphine and 10 mg/kg quetiapine). The treatments were administered for four weeks via oral gavage [38].

Motor function was assessed using the cylinder test, the pole test, and the rotarod test. The cylinder test measures forelimb use asymmetry, the pole test measures bradykinesia and akinesia, and the rotarod test measures motor coordination and balance [39].

4. Conclusions

This review shows that, Possibilities of Animal study are conduct with manner way to make a Novel Combinational Formulation for Stage – I Parkinson's. Apomorphine and quetiapine are two agents that have been

investigated for their potential use in Parkinson's disease therapy [40,41]. Apomorphine is a dopamine agonist that can be administered subcutaneously, intravenously, or by continuous infusion. Quetiapine is an atypical antipsychotic with multiple pharmacological properties, including dopamine, serotonin, and histamine receptor antagonism [42,43]. Both drugs have been shown to improve motor function and reduce motor complications in Parkinson's disease patients. However, their Pre-clinical use is limited by their pharmacokinetic properties and side effects, such as nausea, hypotension, and sedation [44,45].

Therefore, the development of a novel apomorphine and quetiapine formulation for Parkinson's disease therapy represents a promising research avenue [46,47]. This article aims to review the recent advances in this field and discuss the potential of this approach for improving Parkinson's disease treatment [48,49].

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Conflicts of Interest:

The sole author declares that author no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Radaic A, Martins-de-Souza D. The state of the art of nanopsychiatry for schizophrenia diagnostics and treatment. Nanomedicine. 2020; 28:102222.
2. Froelich A, Osmałek T, Jadach B, Puri V, Michniak-Kohn B. Microemulsion-based media in nose-to-brain drug delivery. Pharmaceutics. 2021;13(2):201.
3. Hagell P, Höglund A, Hellqvist C, Johansson EL, Löwed B, Sjöström AC, et al. Apomorphine formulation may influence subcutaneous complications from continuous subcutaneous apomorphine infusion in Parkinson's disease. J Neurol. 2020; 267:3411–3417.
4. Auffret M, Drapier S, Vérin M. Management with apomorphine in Parkinson's disease. In: Diagnosis and Management in Parkinson's Disease. Elsevier; 2020. p. 461–475.
5. Cai Y, Reddy RD, Varshney V, Chakravarthy K V. Spinal cord stimulation in Parkinson's disease: a review of the preclinical and clinical data and future prospects. Bioelectron Med. 2020;6(1):1–10.
6. Agbo F, Isaacson SH, Gil R, Chiu YY, Brantley SJ, Bhargava P, et al. Pharmacokinetics and comparative bioavailability of apomorphine sublingual film and subcutaneous apomorphine formulations in patients with parkinson's disease and "OFF" episodes: results of a randomized, three-way crossover, open-label study. Neurol Ther. 2021;10(2):693–709.
7. Cesaroni V, Blandini F, Cerri S. Dyskinesia and Parkinson's disease: animal model, drug targets, and agents in preclinical testing. Expert Opin Ther Targets. 2022;1–15.
8. Lindestam Arlehamn CS, Dhanwani R, Pham J, Kuan R, Frazier A, Rezende Dutra J, et al. α-Synuclein- specific T cell reactivity is associated with preclinical and early Parkinson's disease. Nat Commun. 2020;11(1):1875.
9. Pires PC, Paiva-Santos AC, Veiga F. Antipsychotics-Loaded Nanometric Emulsions for Brain Delivery. Pharmaceutics 2022, 14, 2174. s Note: MDPI stays neutral with regard to jurisdictional claims in published…; 2022.
10. Nguyen TT, Nguyen TTD, Tran NMA, Van Vo G. Lipid-based nanocarriers via nose-to-brain pathway for central nervous system disorders. Neurochem Res. 2022;1–22.
11. Pires PC, Paiva-Santos AC, Veiga F. Antipsychotics-Loaded Nanometric Emulsions for Brain Delivery. Pharmaceutics. 2022;14(10):2174.
12. Macaulay K. Sublingual apomorphine therapy as an alternative to complex continuous infusion pumps in advanced Parkinson's disease treatment: a district nurse-led intervention. Br J Community Nurs. 2022;27(7):328–335.
13. Bandopadhyay R, Mishra N, Rana R, Kaur G, Ghoneim MM, Alshehri S, et al. Molecular mechanisms and therapeutic strategies for levodopa-induced dyskinesia in Parkinson's disease: a perspective through preclinical and clinical evidence. Front Pharmacol. 2022;13.
14. Dos Santos RB, Funguetto-Ribeiro AC, Maciel TR, Fonseca DP, Favarin FR, Nogueira-Librelotto DR, et al. In vivo and in vitro per se effect evaluation of Polycaprolactone and Eudragit® RS100-based nanoparticles. Biomedicine & Pharmacotherapy. 2022; 153:113410.
15. Jennings D, Huntwork-Rodriguez S, Henry AG, Sasaki JC, Meisner R, Diaz D, et al. Preclinical and clinical evaluation of the LRRK2 inhibitor DNL201 for Parkinson's disease. Sci Transl Med. 2022;14(648): eabj2658.
16. Leta V, Chaudhuri KR, Milner O, Chung-Faye G, Metta V, Pariante CM, et al. Neurogenic and anti- inflammatory effects of probiotics in Parkinson's disease: A systematic review of preclinical and clinical evidence. Brain Behav Immun. 2021; 98:59–73.
17. Zylicz Z. Pharmacological treatment of palliative care patients with Parkinson's disease. Palliative Medicine in Practice. 2022;16(2):117–22.
18. Isaacson SH, Bowling A, Zhang I, Pappert E, Stocchi F, Investigators C 300 and C 301 S. Motor response with apomorphine sublingual film and levodopa in patients with OFF episodes. Neurodegener Dis Manag. 2022;(0).
19. Sacristán HE, Serra Fulles JA. The Essentials in Parkinson's Disease. EC Neurology. 2023; 15:36–67.
20. Hong CT, Chan L, Chen KY, Lee HH, Huang LK, Yang YCSH, et al. Rifaximin Modifies Gut Microbiota and Attenuates Inflammation in Parkinson's Disease: Preclinical and Clinical Studies. Cells. 2022;11(21):3468.
21. Nim S, O'Hara DM, Corbi-Verge C, Perez-Riba A, Fujisawa K, Kapadia M, et al. Disrupting the α-synuclein- ESCRT interaction with a peptide inhibitor mitigates neurodegeneration in preclinical models of Parkinson's disease. Nat Commun. 2023;14(1):2150.
22. Ferreira MD, Duarte J, Veiga F, Paiva-Santos AC, Pires PC. Nanosystems for Brain Targeting of Antipsychotic Drugs: An Update on the Most Promising Nanocarriers for Increased Bioavailability and Therapeutic Efficacy. Pharmaceutics. 2023;15(2):678.
23. Tall P, Qamar MA, Batzu L, Leta V, Falup-Pecurariu C, Ray Chaudhuri K. Non-oral continuous drug delivery-based therapies and sleep dysfunction in Parkinson's disease. J Neural Transm. 2023;1–7.
24. Quintino L, Gubinelli F, Sarauskyte L, Arvidsson E, Davidsson M, Lundberg C, et al. Automated quantification of neuronal swellings in a preclinical rodent model of Parkinson's disease detects region- specific changes in pathology. J Neurosci Methods. 2022; 378:109640.
25. Goyal A, Gopika S, Kumar A, Garabadu D. A Comprehensive Review on Preclinical Evidence-based Neuroprotective Potential of Bacopa monnieri against Parkinson's Disease. Curr Drug Targets. 2022;23(9):889–901.
26. Fabbri M, Barbosa R, Rascol O. Off-time Treatment Options for Parkinson's Disease. Neurol Ther. 2023;1– 34.
27. Rosenstein NA, Johnson JA, Kirchofer KS. Ropinirole has similar efficacy to apomorphine for induction of emesis and removal of foreign and toxic gastric material in dogs. J Am Vet Med Assoc. 2023;1(aop):1–7.

28. Calabresi P, Mechelli A, Natale G, Volpicelli-Daley L, Di Lazzaro G, Ghiglieri V. Alpha-synuclein in Parkinson's disease and other synucleinopathies: from overt neurodegeneration back to early synaptic dysfunction. Cell Death Dis. 2023;14(3):176.
29. Brendza R, Gao X, Stark KL, Lin H, Lee SH, Hu C, et al. Anti-α-synuclein c-terminal antibodies block PFF uptake and accumulation of phospho-synuclein in preclinical models of Parkinson's disease. Neurobiol Dis. 2023; 177:105969.
30. Katunina EA, Blokhin V, Nodel MR, Pavlova EN, Kalinkin AL, Kucheryanu VG, et al. Searching for Biomarkers in the Blood of Patients at Risk of Developing Parkinson's Disease at the Prodromal Stage. Int J Mol Sci. 2023;24(3):1842.
31. Espay AJ, Okun MS. Abandoning the proteinopathy paradigm in parkinson disease. JAMA Neurol. 2023;80(2):123–124.
32. Skidmore S, Barker RA. Challenges in the clinical advancement of cell therapies for Parkinson's disease. Nat Biomed Eng. 2023;1–17.
33. Fan Y, Sun Y, Yu W, Tao Y, Xia W, Liu Y, et al. Conformational change of α-synuclein fibrils in cerebrospinal fluid from different clinical phases of Parkinson's disease. Structure. 2023;31(1):78–87.
34. Stocchi F, Peckham EL, De Pandis MF, Sciarappa K, Kleiman R, Agbo F, et al. A Randomized Thorough QT Study of Apomorphine Sublingual Film in Patients with Parkinson's Disease. Clin Pharmacol Drug Dev. 2022;11(9):1068–1077.
35. Bankiewicz KS, Sanchez-Pernaute R, Oiwa Y, Kohutnicka M, Cummins A, Eberling J. Preclinical models of Parkinson's disease. Curr Protoc Neurosci. 1999;9(1):4–9.
36. Jin H, Kanthasamy A, Ghosh A, Anantharam V, Kalyanaraman B, Kanthasamy AG. Mitochondria-targeted antioxidants for treatment of Parkinson's disease: preclinical and clinical outcomes. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2014;1842(8):1282–94.
37. Kalia L V, Kalia SK, Lang AE. Disease-modifying strategies for Parkinson's disease. Movement Disorders. 2015;30(11):1442–1450.
38. Kim J, Gao Y, Zhao Z, Rodrigues D, Tanner EEL, Ibsen K, et al. A deep eutectic-based, self-emulsifying subcutaneous depot system for apomorphine therapy in Parkinson's disease. Proceedings of the National Academy of Sciences. 2022;119(9): e2110450119.
39. Hauser RA, Ondo WG, Zhang I, Bowling A, Navia B, Pappert E, et al. Dose Optimization of Apomorphine Sublingual Film for OFF Episodes in Parkinson's Disease: Is the Prophylactic Use of an Antiemetic Necessary? J Parkinsons Dis. (Preprint):1–12.
40. Thijssen E, Den Heijer JM, Puibert D, Van Brummelen EMJ, Naranda T, Groeneveld GJ. Safety and pharmacokinetics of multiple dosing with inhalable apomorphine (AZ-009), and its efficacy in a randomized crossover study in Parkinson's disease patients. Parkinsonism Relat Disord. 2022; 97:84–90.
41. Castillo-Torres SA, Lees AJ, Merello M. Intermittent apomorphine use for off period rescue in Parkinson's Disease: a pragmatic review of over three decades of clinical experience. Mov Disord Clin Pract. 2023;10(2):190–208.
42. Martin V, Knecht C, Duerlinger S, Richter B, Ladinig A. A Pig Model to Assess Skin Lesions after Apomorphine Application. Biomedicines. 2023;11(5):1244.
43. Borkar N, Holm R, Yang M, Müllertz A, Mu H. In vivo evaluation of lipid-based formulations for oral delivery of apomorphine and its diester prodrugs. Int J Pharm. 2016;513(1–2):211–217.
44. Koller W, Stacy M. Other formulations and future considerations for apomorphine for subcutaneous injection therapy. Neurology. 2004;62(6 suppl 4): S22–6.
45. Müller T. An evaluation of subcutaneous apomorphine for the treatment of Parkinson's disease. Expert Opin Pharmacother. 2020;21(14):1659–1665.
46. Mohee A, Bretsztajn L, Eardley I. The evaluation of apomorphine for the treatment of erectile dysfunction. Expert Opin Drug Metab Toxicol. 2012;8(11):1447–1453.
47. Jacobs DM, Marder K, Cote LJ, Sano M, Stern Y, Mayeux R. Neuropsychological characteristics of preclinical dementia in Parkinson's disease. Neurology. 1995;45(9):1691–1696.
48. Solari N, Bonito-Oliva A, Fisone G, Brambilla R. Understanding cognitive deficits in Parkinson's disease: lessons from preclinical animal models. Learning & Memory. 2013;20(10):592–600.
49. Meissner WG, Frasier M, Gasser T, Goetz CG, Lozano A, Piccini P, et al. Priorities in Parkinson's disease research. Nat Rev Drug Discov. 2011;10(5):377–393.

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