WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 7.421
Volume 7, Issue 11, 837-848 Review Article ISSN 2278 – 4357

PARKINSONISM: CLINICAL FEATURES, PROBLEMS AND LATEST TREATMENT WITH REFERENCE OF DOSAGES FORMS- A REVIEW

Pankaj Bhatt* and Ajeet Kumar

Vivek College of Technical Education, Dist. – Bijnor, U.P, India.

Article Received on
12 Sept. 2018,

Revised on 03 Oct. 2018,
Accepted on 24 Oct. 2018

DOI: 10.20959/wjpps201811-12673

***Corresponding Author**
Pankaj Bhatt
Vivek College of Technical Education, Dist. – Bijnor, U.P, India.

ABSTRACT

Parkinson's disease is the most widely recognized neurodegenerative issue and it is portrayed by a perplexing assortment of both motor and neuropsychiatric issues. It is a problem which occurs sort of development issue. It happens when nerve cells in the mind don't deliver a sufficient cerebrum creation called dopamine. In some cases it is hereditary, yet most cases don't appear to keep running in families. They may likewise have issues, for example, distress, rest issues, or inconvenience biting, gulping, or talking. An anti-Parkinson is a kind of medication which is expected to treat and alleviate the side effects of Parkinson's infection. The vast majority of these operators demonstration by either expanding dopamine action or decreasing acetylcholine action in the focal sensory system Parkinson's illness is the most widely recognized type of Parkinsonism and is seen all the more much of the time with propelling age. Different types of the confusion may come about because of viral diseases.

KEYWORDS: Bioequivalence, Parkinsonism, Anti Parkinson agents, Dosages, Treatment.

INTRODUCTION

Parkinson's ailment (PD) is a dynamic neurodegenerative issue with cardina motor highlights of tremor, bradykinesia and rigidity.[1] this sickness influences in excess of 1 million Americans more established than 50 years old with the frequency expanding fundamentally with age.[2] In PD, the degeneration of dopamine-containing neurons in the substantia nigra prompts the development of lewy bodies. Lewy bodies are absent in optional Parkinsonism the nigral striatal pathway might be impeded and nigral cell misfortune or loss of striatal cell components may occur.[3]

In spite of advances in medications over numerous years, there will be no cure for PD. Symptomatic treatment gives advantage to some time and proceeded however moderate the movement of PD in the long run outcomes in critical sickness. patients may not require treatment in the beginning periods of PD if manifestations don't cause utilitarian impairment.[4] as the illness advances nonetheless, treatment turns out to be more intricate requiring measurements modifications consolidation of various prescriptions, and the utilization of save treatments.[5] Combination of levodopa with carbidopa, an external Dopa-decarboxylase inhibitor that does not cross the blood-cerebrum hindrance, controlled to an expansion in the measure of levodopa accessible to the mind for transformation to dopamine and a lessening in the rate of queasiness and vomiting.[6] levodopa gives advantage to about all PD patients, long term treatment with levodopa is confused by the improvement of motor change, neuropsychiatric inconveniences and dyskinesia.[7,8]

Contraindications/notices: An enclosed cautioning shows up the tolcapone (tasmar) endorsing data of three lethal instances of intense, fulminant liver disappointment had been accounted for.[9] Patients must sign an educated react to begin the treatment with tolcapone. The notice expresses that "the genuine frequency of hepatocellular damage gives off an impression of being 10 to 100-crease more high than the foundation rate in the all-inclusive community.[10] if patients don't have a counter to tolcapone in three weeks, treatment ought to be halted.[11] Accompanying usage of non-particular MAO inhibitors with levodopa/carbidopa (parcopa, sinemet, sinemet cr) can be realizing hypertensive crisis; synchronous use of these experts is contraindicated.[12] The MAO must be stopped two weeks preceding beginning levodopa/carbidopa. Carbidopa/Levodopa likewise contraindicated in patients with limit point glaucoma.[13] the benztropine, trihexyphenidyl and against cholinergic ought not to be given to patients with limit edge glaucoma. Benztropine ought to be utilized deliberately in patients with generous prostatic hypertrophy as it can worsen urinary maintenance. Counting, the maker thinks about dementia, tardive dyskinesia and prostatism contraindicated to the utilization of this medication.[14] in a meta-examination, Ropinirole and Pramipexole was looked at for the danger of somnolence.[15]

Drug interactions: Drugs that might antagonize dopamine agonists like pramipexole or rotigotine are butyrophenones, haloperidol, phenothiazine and metoclopramide diminishes the effectiveness of the dopamine agonists. Dopamine agonists should be used with the caution with alcohol and the other central nervous system (CNS) depressants.[16,17]

Pramipexole (mirapex, mirapex er) levels may be increased by renally-excreted basic drugs (like verapamil, quinidine and Cimetidine). Ropinirole (requip, requip XL) may be potentiated by cyp1a2 inhibit for example ciprofloxacin.[18]

Because gabapentin enacarbil is not an inhibitor or inducer, substrate of all major cytochrome p450 enzymes or substrate or inhibitor of p-glycoprotein *in vitro*, no clinically relevant drug-to-drug interactions is expected in it.[19]

Adverse effects

Anti-cholinergic: Adverse effects of anticholinergic drugs are the common and often limit their use of it. The most common CNS effects include sedation, dysphoria, memory impairment, acute confusion and hallucination. Peripheral anticholinergic adverse effects like constipation, impaired sweating, dry mouth, blurred vision, nausea, urinary retention and tachycardia.[20]

Levodopa/carbidopa (parcopa, sinemet, sinemet CR)

The most commonly reported adverse effects with levodopa are adventitious movements, for example choreiform or dystonic movements (10 to 90 percent), anorexia (50 percent), vomiting/nausea with or without abdominal pain and distress (80 percent), dry mouth, dysphagia, dysgeusia (4.5 to 22 percent), sialorrhea, increased hand tremor, headache, dizziness, confusion, delusion, ataxia numbness, weakness/faintness, insomnia, hallucinations, delusions, agitation, and anxiety.[21]

Table No. 1: adverse effects of different dosage form.

Drug	Dizziness	Constipation	Confusion	Dyskinesia	Hallucinations	Nausea
Bromocriptine (parlodel)[22]	**Reported**	**Reported**	**Reported**	**Reported**	**Reported**	**Reported**
Pramipexole (mirapex)[23]	4-10 (1-7)	10-14 (6-9)	25-26 (24-25)	47 (31)	9-17 (3-4)	28 (18)
Pramipexole er (mirapexer)[24]	Nr	14 (2)	12 (7)	17 (8)	5 (1)	22 (9)
Ropinirole (requip)[25]	5-9 (1)	6 (nr)	40 (22)	>1	>5	60 (22)
Ropinirole er (requipxl)[26]	Nr	4 (2)	6-8 (3)	13 (3)	8 (2)	11-19 (4)
Rotigotine (neupro)[27]	Nr*	Nr* 5-9ŧ (19)	20-21 (11)* Nrŧ	Nr* 14-17ŧ (7)	Nr* 7-14ŧ (3)	34-41 (13)* 22-28ŧ (19)

Antagonistic impacts information are acquired from bundle embeds and are not intended to be recognized to be thought about Incidences for the fake treatment amass are so shown in

enclosures. Nr = not reported.*early – organize PD in a 6 mg/24 hour gathering. Propelled organize PD at around 8 mg/24h and 12 mg/24h. As Rotigotine is a patch so application site reactions takes place. The adverse effect ranges from 15 per cent in the early stage PD to 23 percent in the advanced-stage PD. Rotating the patch location may lead to decrease in the reaction.[28] Dopamine agonists may cause peripheral oedema and its associative weight gain. Patients with the more sensitive to fluid retention like congestive heart failure and renal insufficiency should be monitored and checked. There is increasing evidence that dopamine agonist's are associated with disorders of impulse control which consider pathologic shopping. In a retrospective analysis, the lifetime prevalence for all these kinds of behaviour in patients with PD was about 6.1 percent.[29]

COMT inhibitors

Table No. 2: adverse effects of different dosage forms.

Drug	Anorexia	Diarrhoea	Dyskinesia	Hallucinations	Orthostatic complaints	Nausea	Somnolence
Entacapone (comtan)[30]	Nr	8-20 (7)	13-25 (11)	4-9	13 (14)	10-20 (12)	4-8 (10)
Tolcapone (tasmar)[31]	19-23 (13)	16-34 (8)	42-51 (20)	24	17-24 (14)	28-50 (18)	16-32

Adverse effects data are obtained from package inserts and are not meant to be compared with other. Incidences for the placebo group are mentioned in parentheses. Nr = not reported. Almost rare cases of fatal hepatotoxicity had been reported with tolcapone (tasmar), which leads to a recommendation of more stringent liver function monitoring.[32]

Special populations[33]

Paediatrics: Benztropine should not be used by children of three years of age or younger. The effectiveness and safety had not been established in paediatric patients for any of the other agents reviewed for the treatment of PD.

Pregnancy: All agents in this class are pregnancy category except for Bromocriptine (parlodel). Bromocriptine is category, but should not be used during lactation in postpartum women. Selegiline (zelapar, generic) is pregnancy category, but it also It should not be used during the lactation in the postpartum women.

Hepatic impairment: A study in the patients with hepatic impairment had been showing that moderate non-cirrhotic liver disease had no impact on the pharmacokinetics of tasmar.

However, a black box warning was added for patients with moderate cirrhotic liver disease (child-pugh class b) because of the risk of the potentially fatal, liver failure. The clearance and volume of distribution of unbound tolcapone was being reduced by almost 50 percent thus increased the unbound drug by two-fold. If the patient exhibits clinical evidence of active liver disease or two sgpt/alt or sgot/ast values greater than the upper limit of normal, tolcapone therapy should not be introduced. Patients who created hepatocellular damage on past tolcapone treatment may had an expansion in danger of liver damage if tolcapone treatment is re-presented. Examination of post showcasing information demonstrates increment in sgpt/alt or sgot/ast, when display, by and large happening inside the initial a half year of treatment with tolcapone.[34]

Patients with mellow hepatic impedance ought to had the measurements of rasagiline (azilect) changed in accordance with 0.5 mg every day. Rasagiline should not be used in patients with the moderate or severe hepatic impaired.

All of the other agents, except for pramipexole and benztropine should be used with cautions in patients with hepatic impairment.

Renal impairment

Trihexyphenidyl and levodopa/carbidopa (parcopa, sinemet, and sinemet cr) ought to be utilized with alert in patients with renal disability. In this way, creatinine leeway can be utilized as an indicator of the degree of reduction in pramipexole freedom. Pramipexole dose ought to be balanced with renal weakness and creatinine leeway under 60 ml/minute.

Elderly

Pramipexole clearance decreases with the age, as clearance and half-life are about 40 percent longer and 30 percent lower, respectively, in elderly (65 years of age and older) compared with young, healthy volunteers (younger than 40 years of age). The difference is most likely due to with age diminishing of renal function, since pramipexole clearance is correlated with renal function.

Dosages[35-49]

Table no. 3: size of daily dose.

Therapeutic class	Drug	Initial dose	Maximum daily dose	Recommended dosing schedule	Availability
Anticholinergic	Benztropine	0.5 mg	6 mg	One to two times daily	0.5, 1, 2 mg tablets
	Trihexyphenidyl	1 mg	15 mg	Three to four times daily	2, 5 mg tablets 2 mg/5 ml elixir
Dopa decarboxylase inhibitor	Levodopa/carbidopa	One tablet	Eight tablets	Three to four times daily	10/100, 25/100, 25/250 mg tablets
	Levodopa/carbidopa odt (parcopa)	One tablet	Eight tablets	Three to four times daily	10/100, 25/100, 25/250 mg disintegrating tablets
	Levodopa/carbidopa controlled release	Two tablet	Eight tablets	Twice daily to three times daily	25/100, 50/200 mg sustained release tablets
Mao-b inhibitors	Rasagiline (azilect)	0.5-1 mg	1 mg	Once daily	0.5,1mg tablets
	Selegiline	5 mg	10 mg	Twice daily with breakfast and lunch	5mg capsules;5 mg tablets
	Selegiline odt (zelapar)	1.25 mg	2.5 mg	Once daily before breakfast and without liquid	1.25mg disintegrating tablets
Dopamine agonists	Bromocriptine (parlodel)	1.25 mg	100 mg	Twice daily with meals	2.5 mg snap tablets; 5 mg capsules

Bioequivalence[50]**:** The bio equivalency is characterized as "the nonattendance of a generous distinction in the rate and degree to which the dynamic fixing or dynamic moiety in pharmaceutical counterparts or pharmaceutical options winds up accessible at the site of medication activity when managed at a similar molar dosage under comparative conditions in a suitably planned investigation".

Bioequivalence thinks about are led

- A danger of bio-comparability.
- A danger of pharmaco-restorative disappointment or reduced clinical security.

Types of Bioequivalence Studies

- In vivo.
- In vitro.

In vivo Bioequivalence Studies

- Oral quick discharge item with fundamental activity.
- Narrow helpful edge.

- Pharmacokinetics entangled by assimilation < 70% or retention.
- Window, nonlinear energy, pre-foundational disposal > 70%.
- Unfavourable physio-compound properties, e.g. low dissolvability, metastable, precariousness Modification.

In vitro Bioequivalence Studies

In vitro studies

- The drug product differs only in strength of the active substance it comprises, Provided all the following.
- Pharmacokinetics are linear.
- The qualitative composition is same.
- Under the same test condition, the in vitro dissolution rate is the same.

Guidelines for Bioequivalence and Bioavailability Studies

Ensuring consistency in principles of value, wellbeing and viability of pharmaceutical items is the key obligation of CDSCO. Sensible declaration must be given that, different items containing comparable dynamic fixings, promoted by not at all like licensees, are clinically proportionate and interchangeable.

Accordingly, the bioavailability of a dynamic substance from a pharmaceutical item ought to be known and reproducible. Bioavailability and bioequivalence information is in this way required to be outfitted with applications for new medications, as basic under Schedule Y, contingent upon the idea of use being submitted. Bioequivalence studies conducted to be led for the examination of two restorative items containing a similar dynamic substance. The investigations ought to give a reason methods for basically evaluating the likelihood of substitute utilization of them. Two items promoted by various licensees, containing some dynamic ingredient(s), must be uncovered to be remedially proportionate to another keeping in mind the end goal to be viewed as replaceable. A few test strategies are accessible to assess comparability, including.s.

1. Comparative bioavailability studies, in which the active drug substance or one or more metabolites is measured in an accessible biological fluid viz. urine, plasma or blood.
2. Comparative pharmacodynamics studies in humans.
3. Comparative clinical trials.
4. In-vitro dissolution tests.

I. Comparative bioavailability thinks about, in which the dynamic medication substance or at least one metabolites is estimated in an available organic liquid viz. plasma, urine or blood.

II. Comparative pharmacodynamics examines in people.

III. Comparative clinical trials.

IV. In-vitro disintegration tests.

In vivo bioavailability study suggested for endorsement of changed discharge items ought to be intended to ensure that

- The item doesn't discharge the dynamic medication substance at a rate and degree prompting dosage dumping.
- There is no vital distinction among the execution of the changed discharge item and the reference item, when given in dose regimens to land at the consistent state.

Scope of Guidelines

Two pharmaceutical items are bioequivalent on the off chance that they are pharmaceutically identical and their bioavailability's after organization in a similar molar dosage are like such an extent, to the point that their belongings, as for both adequacy and security, can be relied upon to be basically the same.[51] Numerous in vivo and in vitro techniques are utilized to gauge item quality.

When bioequivalence studies are essential and types of studies required:

1. *In vivo* studies

For certain drugs and dosage forms, *in vivo* certification of equivalence, through as well as bioequivalence study, a relative clinical pharmacodynamics study, or a relative clinical trial, is regarded as principally important. These include.

a. Oral prompt discharge sedate definitions with fundamental activity when at least one of the accompanying criteria apply:

- Indicate for difficult circumstance requiring guaranteed restorative reaction.
- Safety edge/Narrow restorative window/; soak measurement reaction bend.
- Pharmacokinetics confounded by factor or deficient ingestion or retention window, pre-systemic end/high first pass digestion >70%.
- Unfavourable physicochemical properties, low dissolvability, shakiness, meta-stable adjustment, poor penetrability, and so forth.

b. Non-oral and non-parenteral medication definitions intended to act by fundamental retention.

c. Sustained or generally changed discharge sedate details intended to act by fundamental assimilation.

d. Fixed dosage mix items with foundational activity.

I. *In vitro* studies

In following conditions proportionality might be surveyed by the utilization of in vitro disintegration testing

a. Drugs for which the candidate gives information to substantiate the majority of the accompanying.

- Highest measurements quality is dissolvable in 250 ml of a fluid media over the pH scope of 1-7.5 at 37^{o} C.
- At slightest 90% of the directed oral measurements is consumed on mass adjust assurance or in contrast with an intravenous reference dosage.
- Speed of disintegration as showed by over 80% disintegration inside 15 minutes at 37^{o} C

Utilizing IP device 1, at 50 r.p.m or IP mechanical assembly 2, at 100 r.p.m in a volume of 900 ml or less in every one of the accompanying media:

0.1 N hydrochloric corrosive or fake gastric juice (without chemicals)

A pH 4.5 support

A pH 6.8 support or simulated intestinal juice (without compounds)

b. Different qualities of the medication made by a similar maker, where each one of the accompanying criteria are satisfied: the following criteria are fulfilled.

Qualitative composition among the qualities is successfully the same.

- The proportion of dynamic fixings and excipients between the qualities is viably the same, or, on account of little qualities, the part between the excipients is the same;
- Method of produce is essentially the same;
- Appropriate proportionality think about have been perform on no less than one of the qualities of the detailing (for the most part the most astounding quality unless a lower quality is decided for reasons of wellbeing); and In instance of fundamental accessibility - pharmacokinetics have been appeared to be straight finished the helpful dosage extend.

CONCLUSION

PD is a long- term progressive neurodegenerative disease which has the feature of both motor and non-motor rigidity resting tremor etc. includes motor depression, sleep disorder etc. comprise non motor levodopa is the most required is the most required medications to treat Parkinson's disease.

The problem caused by Parkinsonism is damaged cell and levodopa may not be able to reduce these problems.

REFERENCE

1. Pahwa R, Factor SA, Lyons KE, et al. Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review). Neurology, 2006; 66: 983-95.
2. Beers MH, Berkos R, Eds. The Merck Manual of Geriatrics 3rd ed. Whitehouse Station, NJ: Merck & Co, 2000; 432-41.
3. Beers MH, Berkos R, eds. The Merck Manual of Geriatrics. 3rd ed. Whitehouse Station, NJ: Merck & Co, 2000; 432-41.
4. Marsden CD. Problems with long-term levodopa therapy for Parkinson's disease. Clin Neuropharmacol, 1994; 17: S32-44.
5. Chen JJ. Management of wearing off in Parkinson's disease Consult Pharm, 2005; B: S15-21.
6. Beers MH, Berkos R, eds. The Merck Manual of Geriatrics 3rd ed. Whitehouse Station, NJ: Merck & Co, 2000; 432-41.
7. Beers MH, Berkos R, Eds. The Merck Manual of Geriatrics 3rd ed. Whitehouse Station, NJ: Merck & Co; 2000; 432-41.
8. Hughes AJ, Ben-Shlomoa Y, Daniel SE, et al what features improves the accuracy of clinical diagnosis in Parkinson's disease: a clinical pathologic study. Neurology, 1992; 42: 1142-46.
9. Marsden CD, Parkes JD. "On-off" effects in patients with Parkinson's disease on chronic levodopa therapy Lancet, 1976; 1: 292-6.
10. Tasmar[package insert]. Costa Mesa, CA; Valeant Pharmaceuticals; June 2009.
11. Carbidopa; levodopa. Available at www.clinicalpharmacology.com Accessed August 2, 2012.
12. Benztropine (Cogentin). Available at www.clinicalpharmacology.com Accessed August 2, 2012.

13. Artane[package insert]. Pearl River, NY; Lederle Pharmaceutical Division; October 2003.
14. Azilect[package insert]. Kansas City, MO; Teva Neuroscience; December 2009.
15. Etminan M, Samii A, Takkouche B, et al. Increased risk of somnolence with the new dopamine agonists in patients with Parkinson's disease: a meta-analysis of randomized controlled trials. Drug Safety, 2001; 24: 863-8.
16. Etminan M, Samii A, Takkouche B, et al. Increased risk of somnolence with the new dopamine agonists in patients with Parkinson's disease: a meta-analysis of randomized controlled trials. Drug Safety, 2001; 24: 863-8.
17. Mirapex[package insert]. Ridgefield, CT; Boehringer Ingelheim; May 2011.
18. Requip[package insert]. Research Triangle Park, NC; GlaxoSmithKline; April 2009.
19. Requip XL[package insert]. Research Triangle Park, NC; GlaxoSmithKline; April 2010.
20. Horizant[package insert]. Research Triangle Park, NC; GlaxoSmithKline; June 2012.
21. Olanow CW, Watts RL, Koller WC, et al. An algorithm (decision tree) for the management of Parkinson's disease (2001): treatment guidelines. Neurology, 2001; 56(Suppl 5): S1-88.
22. Olanow CW, Watts RL, Koller WC, et al. An algorithm (decision tree) for the management of Parkinson's disease (2001): treatment guidelines. Neurology, 2001; 56(Suppl 5): S1-88.
23. Parlodel[package insert]. Suffern, NY; Novartis; January 2012.
24. Mirapex[package insert]. Ridgefield, CT; Boehringer Ingelheim; May 2011.
25. Mirapex ER[package insert]. Ridgefield, CT; Boehringer Ingelheim; September 2011.
26. Requip[package insert]. Research Triangle Park, NC; GlaxoSmithKline; April 2009.
27. Requip XL[package insert]. Research Triangle Park, NC; GlaxoSmithKline; April 2010.
28. Neupro[package insert]. Smyrna, GA; UCB, Inc. April 2012.
29. Voon V, Hassan K, Zurkowski MD, et al. Prevalence of repetitive and reward-seeking behaviors in Parkinson disease. Neurology, 2006; 67: 1254-7.
30. Voon V, Thomsen T, Miyasaki J, et al. Factors Associated with Dopaminergic Drug-Related Pathological Gambling in Parkinson Disease. Arch Neurol, 2007; 64: 212-216.
31. Comtan[package insert]. East Hanover, NJ; Novartis; April 2011.
32. Tasmar[package insert]. Costa Mesa, CA; Valeant Pharmaceuticals; June 2009.
33. Olanow CW. Tolcapone and hepatotoxic effects. Tasmar Advisory Panel Arch Neurol, 2000; 57: 263-7.
34. Available at www.clinicalpharmacology.com. Accessed August 2, 2012.
35. Tasmar[package insert]. Costa Mesa, CA; Valeant Pharmaceuticals; June 2009.

36. Carbidopa; levodopa. Available at www.clinicalpharmacology.com Accessed August 2, 2012.
37. Benztropine (Cogentin). Available at www.clinicalpharmacology.com Accessed August 2, 2012.
38. Artane[package insert]. Pearl River, NY; Lederle Pharmaceutical Division; October 2003.
39. Azilect[package insert]. Kansas City, MO; Teva Neuroscience; December, 2009.
40. Etminan M, Samii A, Takkouche B, et al. Increased risk of somnolence with the new dopamine agonists in patients with Parkinson's disease: a meta-analysis of randomized controlled trials. Drug Saf., 2001; 24: 863-8.
41. Mirapex[package insert]. Ridgefield, CT; Boehringer Ingelheim; May 2011.
42. Requip[package insert]. Research Triangle Park, NC; GlaxoSmithKline; April 2009.
43. Parlodel[package insert]. Suffern, NY; Novartis; January 2012.
44. Requip XL[package insert]. Research Triangle Park, NC; GlaxoSmithKline; April 2010.
45. Stalevo[package insert]. East Hanover, NJ; Novartis; April 2011.
46. Available at http://www.fda.gov/Drugs/DrugSafety/ucm223060.htm. Accessed August 2, 2012.
47. Neupro[package insert]. Smyrna, GA; UCB, Inc; April 2012.
48. Horizant[package insert]. Research Triangle Park, NC; GlaxoSmithKline; June 2012.
49. Brahmankar D.M. et al, Biopharmaceutics and Pharmacokinetics- A Treatise, Vallabh prakashan, Second edition, 2009; 336-339.
50. Patnaik RN, Lesko LJ, Chen ML, Williams RL. Individual bioequivalence new concepts in the statistical assessment of bioequivalence metrics FDA Individual Bioequivalence Working Group Clin Pharmacokinetic, 1997; 33: 1-6.
51. Birkett DJ (2003). Generics-equal or not Aust Prescr, 2003; 26: 85-7.