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Review Article

A REVIEW ON DUOPA–A NEW ANTIPARKINSONIAN COMBINATION AS ENTERAL SUSPENSION

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ABSTRACT

The present review article describes about the newly approved enteral suspension, "DUOPA" by US Food and Drug Administration (FDA) for the new treatment option for the advanced Parkinson 's disease with the people having motor fluctuations. This was approved in January 2015. Parkinson disease foundation's report state that about 10 million of the people suffering with this advance Parkinson's disease worldwide. With the several oral treatment options for this dieses the administered tablets may remain in the stomach too long due to slow and inconsistent emptying of its content which can delay in the absorption and delayed response to the treatment. But now DUOPA emerged a new trends for the treatment of parkinsonism with unique route of administration, which bypasses the stomach and enters directly in to small intestine by uses a portable infusion pump that delivers both the drugs of DUOPA directly in to intestine via a tube up to continuous 16 h. There was no such detailed review available in this area, so this present article helps the researches and readers to understand about the pathophysiology, and available treatment options for Parkinsonism in attractive manner and also perceive the significance of use of DUOPA a carbidopa and levodopa enteral suspension with an innovative administration technique.

Keywords: Parkinsonism, DUOPA, Enteral suspension, Small intestine.

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INTRODUCTION

Parkinson disease was first identified in 1817, scientist has persuaded the causes and treatment of disease [1]. In early 1960's the primary problem was identified. It was the loss of brain cells that produces a chemical called dopamine which helps in the control and coordination of muscle activity [2]. The history of Parkinson's disease (PD) expands from 1817 when British Apothecary James Parkinson published an essay on shaking palsy to modern times in western medical literature, As per the report established by Parkinson's disease foundation New York, an estimated 10 million people worldwide are suffering from PD and this incidence is increased with age, but surprisingly before the age of 50 y about 4% of patients diagnosed with PD. Parkison's disease is central nervous system disorder which affects approximately 1.5 million people in the united state alone.[3] In mid 1800's jean martin charcot was particularly influential in refining and expanding this early description and in disseminating information internationally about Parkinson disease. He separated Parkinson disease from multiple sclerosis and other disease characterized by tremor and he recognized cases that later would likely be classified among the parkinsonian plus syndromes. At early 19th century treatment of PD were based an empirical observation and the use of anticholinergic drugs [4]. In earlier days the treatment of PD is related to temporary symptomatic relief but in past few decades, it was begun to emerge a treatment by identifying the cause of the disease. Arvid Carlsson awarded the noble prize as he pointed about the fact of loss of dopamine (DA) as the principle deficit in PD and L-DOPA as a model of pharmacotherapy. The discovery of doponergic effects deficits in Parkinson disease and the synthetic pathway of dopamine led to the first human trial Of LEVODOPA. Further historically important anatomical, biochemical and pharmacological studies identified additional pharmacological and neurosurgical target for Parkinson disease. Parkinson disease is the progressive disease of the nervous system marked by tremor, muscular rigidity, and show impressive moment, chiefly affecting middle aged and elderly people. It is associated with degeneration of the basal ganglia of the brain and deficiency of the neurotransmitter dopamine [5]. If the disease advances can be difficult to control mortor fluctuation. Therefore, in this conditions treatment with proper dose and administration is required. In advance parkinsonism stage patients may start the experience "off time" of periods of poor mobility, slowness and stiffness additionally complete spontaneous emptying of stomach become delayed and unpredictable, it can affect the timing of orally administered levodopa-carbidopa, which leaves the stomach and absorbed in small intestine. In January 2015, the U. S food and drug administration (FDA) has approved Abbvie's DUOPA™, which is the carbidopa and levodopa enteral suspension for the treatment of advance Parkinsonism disease with motor fluctuations. DUOPA is administered with a portable small infusion pump which delivers the suspension directly in to small intestine for 16 continuous hours. FDA has approved DUOPA is an orphan drug.

Clinical sign and symptoms of Parkinson disease

Parkinson disease is a chronic, progressive neurologic disease which represents four cardinal motor manifestations. Motor manifestation, congestive, psychiatric and other manifestations [6]. The things which goes wrong during parkinsonism was illustrated in fig. 1.

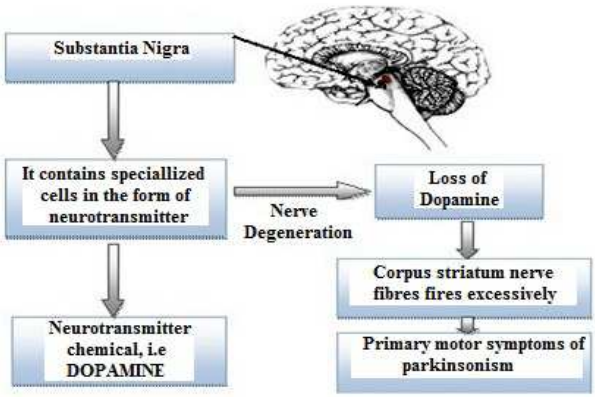

Fig. 1: Facts which goes wrong in Parkinsonism disease

Motor manifestation

Tremors at rest

About 70% of patients experience this kind of manifestation with other neurological conditions including multiple system atropies,

progressive supranuclear palsy and cortico basal ganglion degeneration [7].

Rigidity

It is detected as resistance to passive movement of the limbs. It is often uniform in directions of flexion and extension (lead pipe rigidity) but may be superimposed ratcheting (cogwheel rigidity).

Bradykinesia

Slowness and paucity of movement include facial expression, moments associated with arms swinging when walking, limb rigidity, difficulty in swallowing intern cause "aspiration pneumonia."[8]

Postural instability

It is most potentially dangerous, and will respond less well to L-DOPA.

Cognitive and psychiatric manifestation

Psychiatric dysfunctions mainly lead to dementia (28%), which causes irritability, depression (48%) which causes apathy, hallucinations which further causes anxiety [9].

Other manifestation

It includes disturbing symptoms and pain in affected limbs which further leads to autonomic failure, orthostatic hypertension, constipation, urinary hesitancy, impotency in men [10].

Pathophysiology of Parkinsonism

The compound 1-methyl-4 phenyl, 1-2-3-6 tetrahydro, pyridine is generally considered for the destruction of nigrostriatal dopaminergic neuron and produce a PD. The toxic metabolite MPP^+ comes from the conversion of MPTP by the action of MAO-B, which produces oxidative stress by inhibiting mitochondrial oxidation reaction [11]. Including pathological factors with various other factors like etiological, environmental, and genetic factors also involved for the development of PD. The detailed scheme how these factors involved in PD development has shown in fig. 2.

Possible treatments

The possible treatments for Parkinson disease has been explained by in two ways as follows.

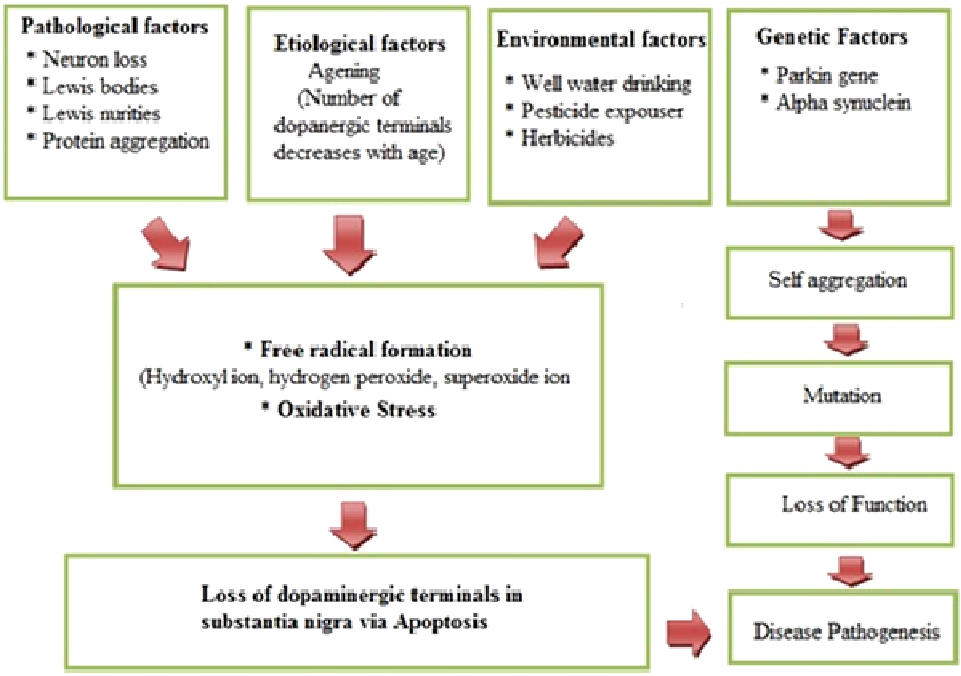

Fig. 2: Pathophysiology of Parkinsonism disease

Drug treatment

Treatment with the drugs was categorized in different ways, In the first category, drugs can administrate directly or indirectly to increase the level of dopamine in the brain. Dopamine cannot be taken directly hence it is always given as precursor like levodopa, in order to cross BBB (Blood-brain barrier). In the second category, the drug effects other neurotransmitters in the body in order to ease some of the symptoms of the disease.[12] In the third category, the drug prescribed for PD includes medication that help to control non-motor symptoms (depression related problems). e. g. antidepressants.

Brain surgery

It can be done through pallidotomy, by removing or destroying the parts of the brain that are misfiring, especially destroyed part of Globus pallidus is known as the pallidotomy and thalamotomy is the removal of destroyed part of the thalamus. The surgical treatment can also done by deep membrane stimulation, which is a reversible process in which electrode are implanted in the brain this kind of brain surgery is much safer than pallidatomy and thalamotomy. DBS reduces the need of levodopa hence results in a decrease in the involuntary movements called dyskinesias.

Drugs used in the treatment of Parkinson disease

The available drugs for the treatment of PD were available either combined or single dosage form, most of the cases levodopa was combined with either benserazide or carbidopa. Treatment can also do with several dopamine agonist, MAO-B inhibitors, and COMT inhibitors. The details of available drugs [13] with brands along with side effects were demonstrated in table 1.

Description of duopa

DUOPA is a combination of carbidopa, and levodopa [14]. Carbidopa is an inhibitor of aromatic amino acid crystalline compound, slightly soluble in water, with a molecular weight of 244.3. It is designed chemically as (-)-L- (α-hydrazine-(α-methyl-β- (3, 4-dihydroxy-benzene) propanoic acid monohydrate. Its empirical formula is $C_{10}H_{14}N_2O_4.H_2O$, and its structural formula shown in fig. 3.

Table 1: List of drugs available for the treatment of parkinsonian disease

Levodopa (given combinley with benserazide or carbidopa)			
Unbranded (generic)name	Dosage form available	Branded names	Side effects
Cocareldopa (carbidopa+ levodopa)	CR tablets*, intestinal gel, PR tablets**	Duopa Sinemet plus CR, Half sinamet CR, Lecado	sleeplessness, hypotension, hallucinations, nausea, vomiting.
Cobeneldopa (Benserazide+ levodopa)	Capsules, dispersible tablets, CR tablets	Mad par, Mad par CR	Dyskinesia, nausea, vomiting, loss of appetite, hypotension.
Dopamine agonists			
Carbergoline	Tablets	Cabaser	Nausea, vomiting, constipation
Bromocriptine	Tablets and Capsules	Parlodel	a headache, drowsiness, sudden
Pergolide	Tablets	-	attacks of dizziness of fainting,
Ropinirole	Tablets	Adartrel	low blood pressure, hallucinations,
Pramipexole	Tablets+PR	Mirapexin	
Rotagotine	Skin patch	Neupro	
Apomorphine	Pre-filled pen for injection	Apo-go-PEN	
MAO-B INHIBITORS			
Salegiline	Tablets that dissolve on tongue	Eldepryl, Zelepar	Headache, aching nausea, joints, indigestion, flue like
Rasagiline	Tablets	azilect	symptoms, depression.
Comt inhibitors			
Tolcopone	Tablets	Tasmar	Sickness, sleeping problems,
Entacopone	Tablets	Comtess	diarrhoea,dizziness

**Prolonged Released. *Control Released.

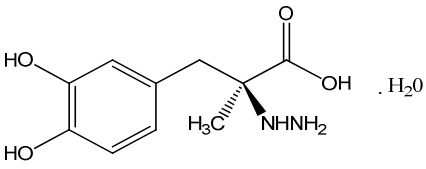

Fig. 3: Chemical structure of levodopa

The content of carbidopa in DUOPA is expressed in terms of anhydrous carbidopa with a molecular weight 226.3. Anhydrous carbidopa 4.63 mg/ml is equivalent to 5.0 mg/ml of carbidopa. Levodopa is a white, crystalline compound, slightly soluble in water, with a molecular weight 197.2. It is designated chemically (-)-L-α-amino-β-(3,4-dihydroxybenzene) propanoic acid having empirical formula $C_9H_{11}NO_4$ and its structural formula shown in fig. 4.

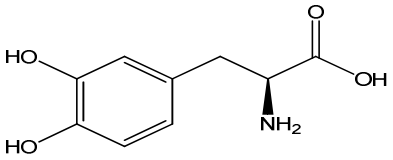

Fig. 4: Chemical structure of carbidopa

Mechanism of action of duopa

DUOPA which is an enteral suspension of carbidopa and levodopa. When levodopa converted to dopamine was formed in extracerebral tissues after rapidly decarboxylation, so that only a small amount of a given dose is transported unchanged to the central nervous system. Carbidopa inhibits the decarboxylation of peripheral levodopa, making levodopa more available for delivery to the brain. Levodopa which is the precursor of dopamine metabolically does cross the blood-brain barrier, and probably is converted to dopamine in the brain. This is thought to be the mechanism of DUOPA [14] outlined in fig. 3.

Clinical trial

It was performed to check the efficacy of DUOPA in a randomized double-blind, active controlled, double dummy 12 w parallel study with the patients of advanced Parkinson disease who had persistent motor fluctuations and levodopa responsive while treatment with oral immediate release carbidopa-levodopa and other Parkinson disease medications. Patients (n=71) were randomized to either DUOPA+placebo capsules or placebo suspension+immediate release carbidopa/levodopa, 25 mg/100 mg capsules. All patients had a PEG J device placement. The clinical outcome measures were the mean changes from the baseline to 12 w for DUOPA non-significantly greater (P=0.0015) than oral immediate release carbidopa-levodopa. There is also the increase in mean scale in "on "time without dykinesia from baseline to 12th week was significantly greater (4.1 vs 2.22 hour, P=0.0059) for DUOPA than oral immediate release carbidopa-levodopa.

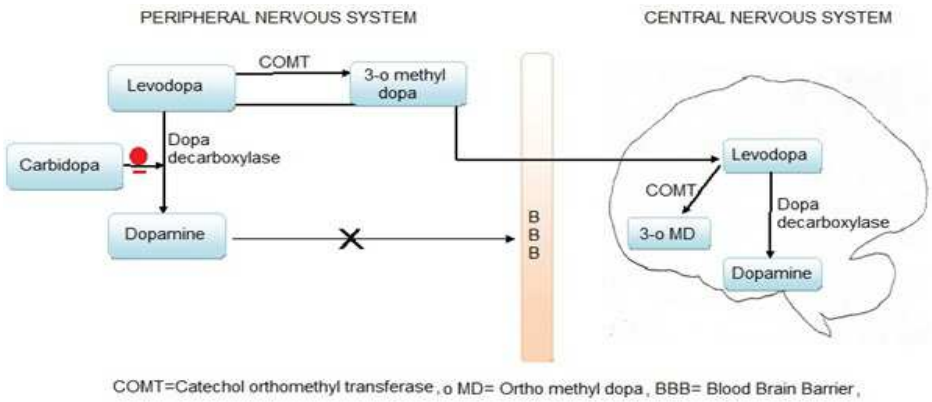

Fig. 5: Mechanism of action of DUOPA

Pharmacokinetics

The pharmacokinetics of carbidopa and levodopa with 16hour intrajejunal infusion of DUOPA evaluated in18 patients with advanced PD has been on DUOPA therapy for 30 d or longer. Carbidopa is approximately 36% bound to plasma proteins. Levodopa is approximately 10-30% bound to plasma proteins. Levodopa with DUOPA 16 h intra jejunal infusion, plasma concentration (mean± standard deviation) vs. time profile is shown in fig. 6.

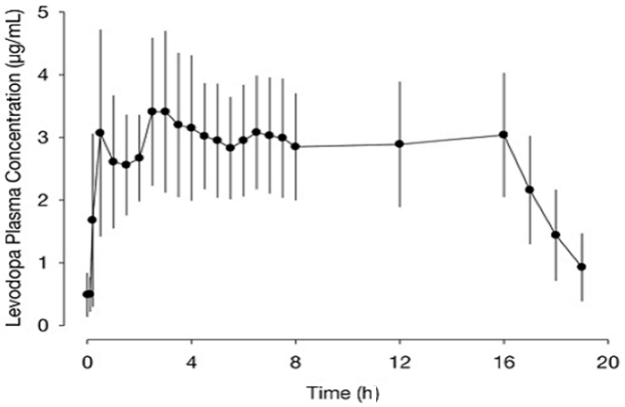

Fig. 6: Plasma concentration vs. time profile of Levodopa with DUOPA 16 hour infusion [15]

Metabolism and elimination

Carbidopa is metabolized to two main metabolites (α-methyl-3-methoxy-4-hydroxyphenyl propionic acid and α-methyl-3, 4-dihydroxyphenylproinoic acid). Unchanged carbidopa accounts for 30% of the total urinary excretion. The elimination half-life is about 2 h. Levodopa mainly eliminated via metabolism by the aromatic amino acid decarboxylase (AAAD) and the catechol-o-methyl-transferase (COMT) enzyme. Other routes of metabolism are transamination and oxidation. When administered with carbidopa, the elimination half-life of levodopa is approximately 1.5 h.

Pharmacodynamics

Because its decarboxylase inhibiting activity is limited to extracerebral tissue, administration of carbidopa with levodopa makes levodopa more available to the brain. The addition of carbidopa to levodopa reduces the peripheral effects (nausea, vomiting) due to decarboxylation of levodopa. However, carbidopa does not decrease the adverse reactions due to the central effects of levodopa.

Dosage and administration

Enteral suspension with 4.63 mg carbidopa and 20 mg levodopa per ml in a single-use cassette. Each cassette contains approximately 100 ml of suspension. DUOPA is administered over a 16-hr infusion period. The daily dose is determined by individualized patient titration and composed of three doses as follows

- A morning dose
- A continuous dose
- Extra dose

The maximum recommended a daily dose of DUOPA is 2000 mg of levodopa component (i.e. one cassette per day) administered over 16hours. At the end of the16-hour infusion, the patient should disconnect the pump from PEG-J and take their night-time dose of oral immediate-release carbidopa-levodopa tablets.[15,16]

Administration information

PEG-J tubing sets are used for the administration of DUOPA [17], listed in table 2. Following instructions should be maintained during administration

- DUOPA should be used at room temperature. And out of the carton 20 min prior to use; failure to this DUOPA in the absence of room temperature may cause the improper amount of medication.
- DUOPA is delivered as 16-hr infusion by nasojejunal tube for short-term use, and PEG-J for long-term administration.
- The cassettes are for single-use only and should not be used for longer than 16 h, even it remains.
- The open cassette should not be re-used.
- The PEG-J should be disconnected after 16 hr use of administration and flushed with room temperature potable water with a syringe.

Table 2: Tubing sets for Peg-J DUOPA administration

Product name	Manufacturer
Long-Term	
AbbVie™ PEG 15 and 20 Fr	AbbVie, Inc.
AbbVie™J, it is 9 Fr internal (J) tube,120 cm in length	AbbVie,Inc.
Endo Vive™ Standard PEG Kit-pull Method	Boston Scientific Crop.
Endo Vive Two-port PEG Jejunal feeding tube Kit	Boston Scientific Crop.
Short-Term	
NJFT-10**,**24 cm feeding tube length,50 cm Naso transverse tube length with minimum accuracy channel 3.2 mm	AbbVie,Inc.
NJFT-8™,24 cm feeding tube length,50 cm naso transverse tube length with minimum accuracy channel 3,7 mm	Wilson-Cook Medical, Inc, blomington USA.
NJFT-10**,**24 cm feeding tube length,50 cm naso transverse tube length with minimum accuracy channel 3.2 mm	Covidien
Kangaroo™Naso-jejunal feeding Tube	Covidine

Nonclinical toxicology

The nonclinical toxicology of DUOPA [17] has been described under carcinogenesis, mutagenesis and impairment of fertility.

Mutagenesis

In vitro Ames test of carbidopa was positive in the presence and absence of metabolic activation. *Invitro* mouse lymphoma *tk* assay of carbidopa also found positive in the absence of metabolic activation, but *invivo* mouse micronucleus assay was found negative. In published articles it was reported that hydrazine is found positive in *invitro* genotoxicity assays and *invivo* mouse micronucleus assay.

Carcinogenesis

In vitro carcinogenetic study of oral administration of carbidopa-levodopa in rat model for the period of two years demonstrated no evidence of carcinogenicity. DUOPA, which contains hydrazine, is a degradation product of carbidopa. Literature review revels about the positive carcinogenetic effect of hydrazine in multiple animal species e. g mouse, rat, and hamster.

Impairment of fertility

There was no effect on fertility was observed during reproduction studies of carbidopa-levodopa in rats.

Specific population use

DUOPA has been tested in specific populations e. g pregnancy, nursing mother and geriatric populations, reports of all study results has been explained as follows.

Pregnancy

In category c pregnancy, the effect is reported from the individual case study that levodopa enters the fetus and cross the human placental barrier and metabolized. The study of carbidopa-levodopa in animal model showed developmentally toxic at usual clinical dose. So the use of DUOPA during pregnancy only if the potential benefit justified the potential risk. No teratogenic effect was found during carbidopa-levodopa study in pregnant mice.

Nursing mothers

It was reported that levodopa is excreted in human milk, in a study of one nursing mother, so caution should be taken if DUOPA administered to a nursing women.

Geriatric use

About 49% patients of 65years and 8% patients of 75 y has been included during the controlled clinical trial of DUOPA, demonstrated the increased risk of BUN and CPK elevation in the patients with 65 y and older.

Contraindication

DUOPA is contraindicated in the patients who are currently taking the nonselective monoamine oxidase (MAO) inhibitor (eg, phenelzine and tranylcypromine) or have recently (within 2 w) taken a non-selective MAO inhibitor. Hypertension can occur if these drugs are used concurrently [18].

Warning and precautions

Since DUOPA is administrated through PEG-J or naso-jejunal tube, gastrointestinal complications may occur [17]. These complications include bezoar, ileus, implant site erosion/ulcer, intestinal hemorrhage. Intestinal ischemia, intestinal obstruction, intestinal perforation, pancreatitis, peritonitis, etc. these complications may result in serious outcomes, such as the need for surgery or death.

Adverse reactions

Following adverse reactions are generally found in the use of DUOPA [19]

- Gastrointestinal related problems
- Falling asleep during activities of Daily Living somnolence.
- Orthostatic hypotension
- Hallucinations/psychosis/confusion
- Impulse control/compulsive behaviors
- Depression and suicidality
- Dyskinesia
- Cardiovascular ischemic Events

Storage and handling of DUOPA

Should be Stored in freezer at-20 °C (-4 °F). Thaw in refrigerator at 2 °C to 8 °C (36 °F to 46 °F) prior to dispensing. Cassettes should be protected from sunlight and kept in the carton prior to use [20, 21].

CONCLUSION

The detailed literature data on DUOPA as enteral suspension for the treatment of advanced Parkinsonism, which was recently approved by US-FDA will help the research scientist to develop something new on this area with minimum side effect and other complications. This thorough information about the Parkinsonism will help to understand its pathophysiology, available drugs, mechanism action of DUOPA, dose calculation and its administration system along with contraindications and other information. This review article will must benefit to the scientists who wants to begin work in this area for future endeavours.

CONFLICT OF INTERESTS

The authors clarifies about their no conflict of interest for this review

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