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A REVIEW ON: PARKINSON'S DISEASE IN PHARMACOVIGILANCE

Shravani p.pawar, Priyanka P. Shinde, Madhura S. Chavan, Shreya N. Dhadme

Assistant professor, student

arvind gavali college of pharmacy satara

Abstract:

Background: Parkinson's disease is a common progressive neurodegenerative condition associated with significant disability and negative impact on quality of life .This overview of Parkinson's disease is designed to serve as a background to the discussion elsewhere in this supplement on the pharmacotherapy used in its management .Although the cause of Parkinson's disease is unknown the pathologic manifestation involves the loss or dysfunction of dopaminergic neurons in the substantia nigra pars compacta . **Methods:** Generally dopamine precursor are used. Dopamine does not readily pass the blood brain barrier. The most effective and commonly encountered treatment is levodopa. This is a dopamine precursor which undergoes conversion, peripherally and within the CNS, to dopamine by the enzyme dopa decarboxylase. **Result:** It is important to carefully monitor patients for these potential ADRs when combining Levodopa with other drugs .our project has provided a comprehensive overview of the treatment options available for Parkinson's disease. **Conclusion:** Some of the case studies has also been done which confirms that there are patients which are suffering from Parkinson's disease. Although there is no cure for Parkinson's disease a number of pharmacologic treatments are available for managing the motor and non-motor symptoms.

INTRODUCTION:

Classification of nervous system:

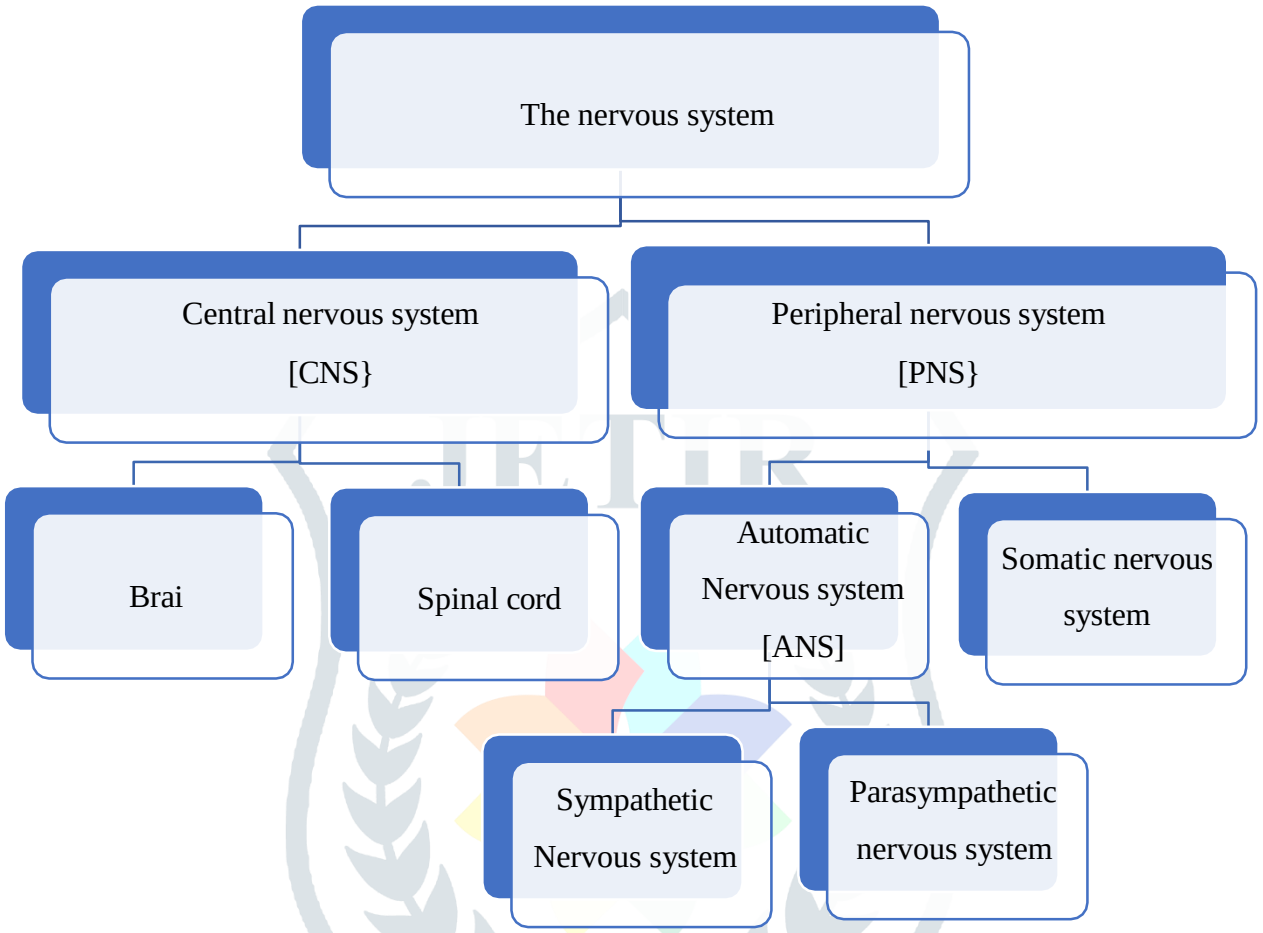


Fig.no. 1

Central Nervous System:

The central nervous system comprises of the spinal cord and the brain. The spinal cord is found in the vertebral column and the brain is located in the cranium/ skull. The spinal cord has 32 segments and the brain consist of the brain stem, diencephalon, cerebellum and cerebrum. The 12 cranial nerves attached to the brain form upper part of the peripheral nervous system and record general sensations of pain, temperature, touch and pressure in addition we find special senses of smell , vision, hearing , balance and taste.

Important part of CNS are:

1. Brain: It is the complex organ that control thought, memory and other body processes

2. Spinal cord: It lies within the spinal column and extends from the Brainstem to lower back through the vertebral foramen of vertebrae. It sends motor commands from the brain to body sends sensory information from the body to the brain, and coordinate reflexes. [1]

1. **What are neurons and which type of neurons are present in the brain?**

Neurons are nerve cells that send messages all over your body to allow you to do everything from breathing to talking, eating, walking, and thinking.

- **Due to loss of neurons neurodegenerative disorder can occur some of neurodegenerative diseases are as follows:**

  • A neurodegenerative disease is caused by the progressive loss of function of neurons, and this process is known as **neurodegeneration.**

1. Parkinson's disease :

It is a chronic degenerative disease of basal ganglia which causes tremor at rest, muscle rigidity and hypokinesia, often with dementia. PD is a disease with an unknown cause, but it may follow stroke, virus infection and can be drug- induced [antipsychotic drug].

2. Alzheimer's disease :

AD is also called as presenile dementia.AD is associated with brain shrinkage and localized loss of neurons, mainly in the hippocampus and basal forebrain. The main pathological features of AD comprises amyloid plaque, neurofibrillary tangles and loss of neurons.

3. Huntington's disease:

It is an incurable neurodegenerative disease that is mostly inherited .The earliest symptoms are often subtle problems with the mood or mental/ psychiatric abilities.

It is disorder resulting in progressive brain degeneration, starting in adulthood and causing rapid deterioration and death.

4. Amyotrophic lateral sclerosis:

Also known as motor neuron disease [MND], it is rare and terminal neurodegenerative disease that results in progressive loss of motor neurons that control voluntary muscles.

5. Neurodegenerative Prion diseases:

A group of human and animal diseases associated with a characteristic type of neurodegeneration known as

spongiform encephalopathy because of the vacuolated appearance of the affected brain, has recently been the focus of the intense research activity. [2]

History:

Parkinson's disease is a slowly progressive degenerative disease having three cardinal features that are tremors, rigidity, and hypokinesia

Parkinson's disease [PD] is a progressive degenerative disorder mostly affecting older people, first described by James Parkinson in 1817. Majority of cases are idiopathic, some are arteriosclerotic while post encephalitic are now rare. [3]

Essay on the shaking palsy:

James Parkinson's short monograph is the first clear medical document dealing with Parkinson disease . The first symptoms perceived are a slight sense of weakness, with a proneness to trembling in some particular part ; sometimes in the head , but most commonly in one of the hand and arms .[4]

- More than 10 million people worldwide are living with PD.
- Additional clinical trial results in 2023 :Data from laboratory trial using UDCA to treat models of Parkinson's , indicated that UDCA is neuroprotective – that it may rescue , recuperate or regenerate nerve cells or neurons.
- Nearly one million people in US are living with Parkinson's disease. This number is expected to rise to 1.2 million by 2030.
- As estimated 15% to 25% OF people with Parkinson's disease have a family history

Pathophysiology of Parkinsonism:

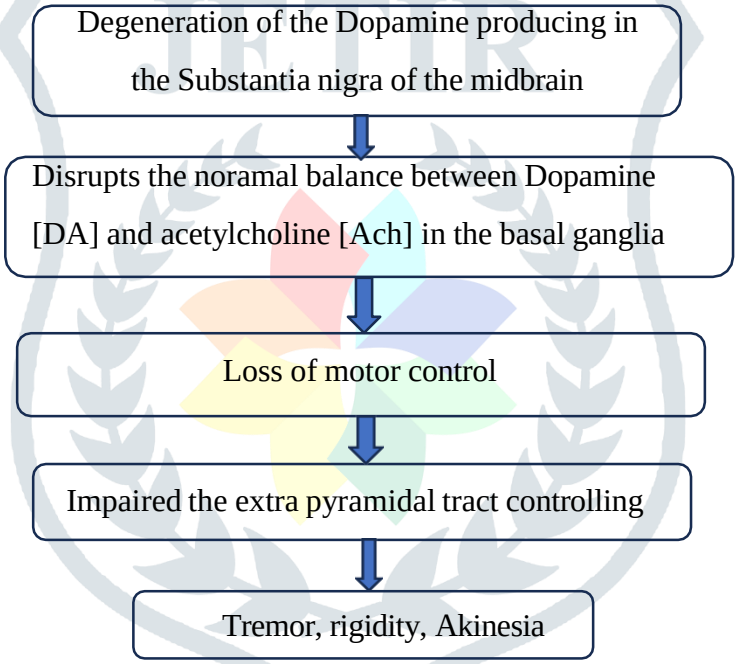
Degeneration of neurons in the nigrostriatal {dopaminergic} tract and Substantia nigra pars compacta [CNS - PC] is the most common lesion in Parkinson's disease (PD). This leads to a dopamine [DA] shortage in the striatum, which regulates coordination and muscular tone. The motor dysfunction is caused by an imbalance in the striatal dopaminergic [inhibitory] and cholinergic [excitatory] systems. Although the cholinergic system is not the main target, equilibrium is typically restored by suppressing it [with anticholinergics].Although the exact etiology of the selective degeneration of nigrostriatal neurones is unknown, it seems to have multiple contributing factors. Genetic susceptibility, oxidative degradation of free radicals, environmental toxins such as N-methyl-4phenyl tetrahydropyridine [MPTP] and excitotoxic neuronal death resulting from excitatory glutamate receptor (NMDA) driven Ca+2 excess have all been

linked to aging have been held accountable.[5] A neurodegenerative illness affecting both motor and nonmotor brain pathways is called Parkinson disease. It is typified by two main pathologic processes involving neurons: (a) early selective loss of dopamine neurons; (b) the build-up of Lewy bodies, which are made of misfolded α-synuclein and accumulate in several systems of Parkinson disease patients. It's uncertain which procedure takes place initially. In light of pathologic research.[6]

The neurodegeneration of dopaminergic neurons in the basal ganglia region is the generally acknowledged pathogenesis. It is a deep area of the brain that supports coordinated posture and fluid movement during a variety of tasks. Dopamine is the main neurotransmitter; additional ones include 5 HT, NA, and Ach.

Pathophysiology:

[Fig.no.2]



Etiology:

The etiology of PD is not clear, still majority of a patient show numerous symptoms with the administration of Dopamine antagonist. [example: neuroleptics , benzamide]. The sensitivity to above therapy increases with the increasing age. The reason probably is age related decline in dopaminergic neurons in basal ganglia

.PD is a multifactorial disease , with both genetic and environmental factors for parkinson's disease with the median age of onset being 60 years of age.

Sudden appearance of PD in young drug addicts consuming a a heroin substitute containing methyl phenyl tetrahydropyridine {MTPT} highlighted role of MTPT . This MTPT undergoes conversion to its toxic metabolite MPP^+ which is further selectively taken up by the dopaminergic neurons in nigro striatum ,causing its destruction. This particular PD ia also known as "Frozen addict syndrome ''. In addition useof herbicides having similarity to methyl-phenyl-tetrahydropyridine [MTPT]have also proposed role . [7]

Clinical Manifestation :

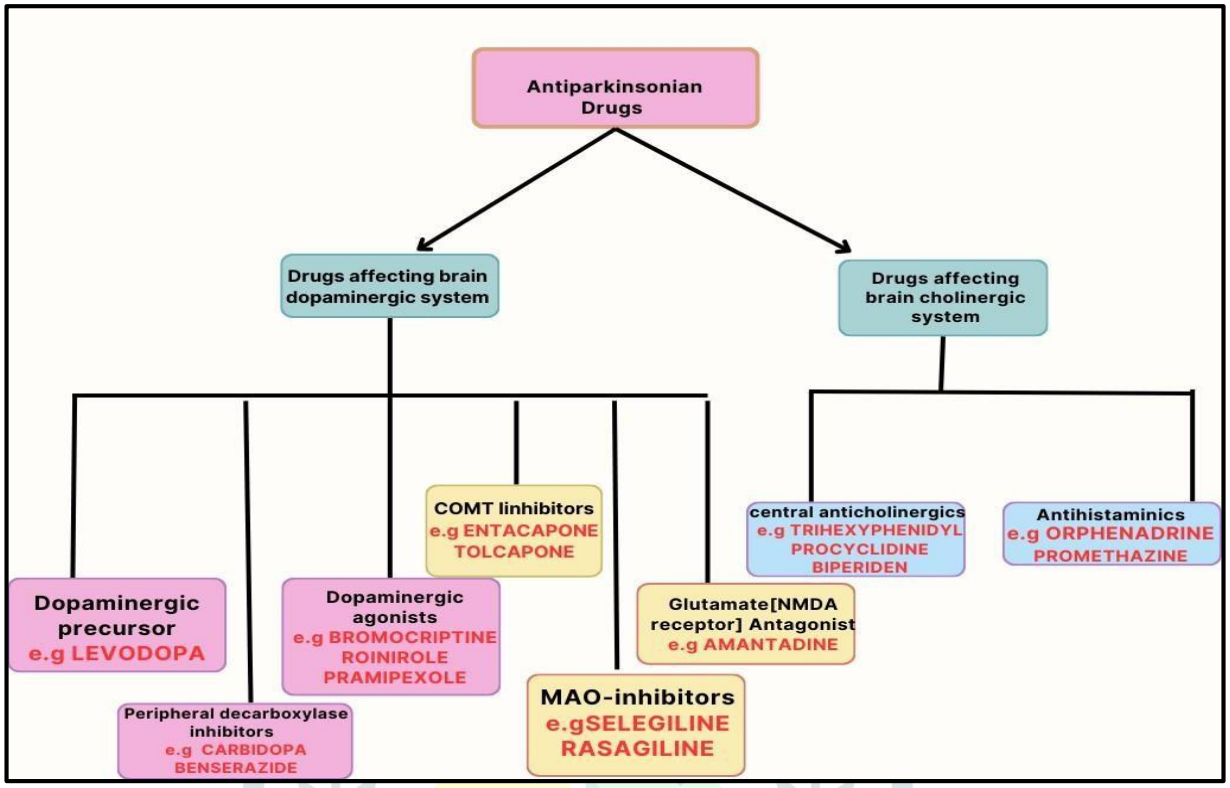
- Tremors
- Rigidity
- Slowness of the movement
- Suppression of voluntary movements [hypokinesia] caused partially by muscle rigidity partially by motor system.
- Shaking of hands
- Tumbling of head
- Twitching of facial muscle
- Dyskinesia.[8]

Diagnosis :

There are no specific tests for PD however, patient's history is important to differentiate between Parkinson's disease from Parkinsonian syndrome. In some patient , certain serological tests and CT scanning of brain are done to detect other disorders like thyrotoxicosis , Huntington's chorea etc. Where quite similar manifestation .[9] Now a days diagnosis of Parkinson disease is based on clinical features from history and examination and it is also based on response to dopamine agents and development of motor fluctuations .[10] Motor manifestation of the disorder begin asymmetrically , and commonly include a resting tremor , a soft voice [hypophonia] , masked facies [initially presenting as reduced blink rate] , small handwriting , stiffness [rigidity] , slowness of movements [bradykinesia] , shuffling steps and difficulties with balance . A classic symptom is resting tremor , usually affecting one upper limb , although 20% of patients do not have it.[11].

Treatment :

Classification of antiparkinsonian drugs:



A] sDrugs affecting brain dopaminergic system :

Dopamine is neurotransmitter that works to control bodily movement. Drug induced parkinsonism is caused by medication that reduced dopamine level in the brain.

1. Dopamine precursor:

Example: Levodopa:

• Compared to other medications taken alone, levodopa has a unique beneficial effect in Parkinson's disease (PD). Although it is the direct predecessor of the transmitter DA, it is inactive on its own. The first-line treatment for Parkinson's disease (PD) is levodopa; it is almost always taken in conjunction with a peripheral dopa decarboxylase inhibitor, such as benserazide or carbamazepam, which decreases the peripheral adverse effects and almost tenfold lowers the dosage required.

2. Peripheral decarboxylase inhibitors:

Carbidopa and benserazide are extracerebral dopa decarboxylase inhibitors; they do not cross the blood-brain barrier and do not prevent the conversion of levodopa to DA in the brain. When administered with levodopa, they raise its t1/2 in the periphery, allowing more of it to penetrate the blood-brain barrier and reach its target location.

Example: 1.carbidopa. 2.Benserazide

3. Dopaminergic Agonists: Dopamine agonists can function on striatal dopamine agonist receptors even in advanced patients who have lost the ability to generate, store, and release DA from given levodopa. Furthermore, they have a longer half-life, can activate subtypes of DA receptors relevant in Parkinson's disease, and do not share the concern that levodopa contributes to dopaminergic neuronal damage caused by oxidative metabolism.

Examples: 1) Bromocroptine 2. Ropinirol. 3.Pramipexole

4. MAO-B inhibitor :

- Selegiline [Deprenyl]:

It inhibits MAO-B selectively and irreversibly. MAO has two isoenzyme forms, MAO-A and MAO-B, which are both found in peripheral adrenergic tissues and intestinal mucosa, but the latter is more prevalent in the brain and blood platelets. In the early stages, selegiline alone produces weak antiparkinsonian effects.When selegiline is combined with levodopa, it prolongs its activity, reduces motor fluctuations, and reduces the "wearing off" effect. In advanced cases, the "on off" effect does not improve.

- Rasagiline: [Dose : 1mg OD in the morning]

It is selective MAO-B inhibitor with selegiline like therapeutic effect in parkinsonism disease . However , it is five times more potent , longer acting and not metabolized to Amphetamine . Therefore it is given once a day in the morning . It does not produce excitatory side effect .

5.COMT inhibitor:

Entacapone and Tolcapone are specific, strong, and reversible COMT inhibitors. It extends the treatment efficacy of levodopa-carbidopa in advanced and fluctuating Parkinson's disease. It has been introduced as an adjuvant to levodopa-carbidopa for advanced Parkinson's disease (PD). Carbidopa/Bensrazide inhibits peripheral decarboxylation of levodopa. It is mostly metabolized by COMT into 3-O-methyl dopa. COMT plays a crucial function in dopamine breakdown in the brain. COMT inhibitors may protect dopamine, which is produced in the striatum and supplements the peripheral impact. They are not used in early Parkinson's disease instances.

Examples: 1.Entacape , 2. Tolcapone

6.Glutamate [NMDA receptor] antagonist [Dopamine facilitator] :

- Amantadine:

It was created as an antiviral medication for the treatment of influenza A2.It has been shown to help with Parkinson's disease. It operates quickly but has less efficacy than levodopa. It was discovered that approximately two-thirds of patients benefit with amantadine, although tolerance developed over time, and amantadine's usefulness eventually faded.

It stimulates presynaptic synthesis and dopamine release in the brain. It also possesses anticholinergic properties. These were thought to account for all of its positive effects in Parkinsonian patients. The striatal dopaminergic system is currently regarded as more important due to its influence. A single dose of 100 mg BD lasts 8 to 12 hours.

B.Drugs affecting brain cholinergic system :

1.Central Anticholinergic : These drugs have a stronger central-peripheral anticholinergic activity ratio than atropine. The pharmacological profile is identical to atropine. They work by reducing the unbalanced cholinergic activity in the striatum of a Parkinsonian patient. After a single dose of anticholinergics, parkinsonian symptoms improve by 10 to 25% and last for 4 to 8 hours. Central anticholinergics have significantly poorer efficacy than levodopa. However, they are not pricey and generate fewer negative effects than the levodopa. They may be used alone in some moderate situations where levodopa is contraindicated. They can also be used in conjunction with levodopa to reduce the effect of the levodopa dose. example :Trihexyphenidyl Dose [2 to 10 mg per day]

2.Antihistaminic :

These medicines totally inhibit the function of histamine at H1 receptors.Older antihistamines cause varying degrees of CNS depression. It has the ability to cross the blood-brain barrier and has a stronger affinity for the central than peripheral H1 receptors.

- Promethazine :

Promethazine, an antihistaminic, reduces tremors, rigidity, and excessive saliva production in Parkinson's disease.It collects in brain mitochondria. In vivo, it inhibits Ca2+-induced mitochondrial permeability transition pore (PTP) in rat liver mitochondria. It may have a protective effect in the mitochondrial toxin Parkinson disease model. It functions as an antagonist at the dopamine D2 receptor.

- Orphenadrine :

Orphenadrine produces muscular relaxant actions via acting on the central nervous system [CNS]. It relieves the stiffness, soreness, and discomfort caused by muscle strains, sprains, or other injuries, as well as the tremors induced by Parkinson's disease. [12]

Adverse drug reaction:

WHO's definition of an adverse drug reaction, which has been in use for about 30 years, is "a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function[13] However, in its use of the word "noxious" this definition is vague; does it, for example, include all adverse reactions, no matter how minor? Such inclusiveness would defeat surveillance systems as they currently operate. [14]

1. **Adverse event (or Adverse Experience)**

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

2. **Adverse Drug Reaction (ADR):** all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.The phrase "responses to a medicinal products" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

3. **Unexpected Adverse Drug Reaction:**

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product).

Serious Adverse Event or Adverse Drug Reaction:

- Results in death
- is life-threatening,
- hospitalization
- persistent or significant disability/incapacity, or
- Congenital anomaly/birth defect.

1**.Expectedness of an Adverse Drug Reaction**

In countries where a pharmaceutical product is not yet licensed for marketing, a company's Investigator's Brochure will be the source document. (For the investigator's brochure, see section III.F. and the ICH Guideline.)

2. Unexpected events include reports that provide new information on the severity or specificity of a previously documented major ADR. A more specific or severe incident than indicated in the Investigator's Brochure, for example, would be labeled "unexpected". Examples include (a) acute renal failure as a labeled ADR followed by a new report of interstitial nephritis, and (b) hepatitis with a first report of fulminant hepatitis.

Minimum Criteria for Reporting ADR:

- an identifiable reporter

- an identifiable patient
- an adverse reaction
- a suspect product.

Reporting Time Frames

1.Fatal or Life-Threatening Unexpected ADRs:

7 calendar days after first knowledge by the sponsor that a case qualifies, followed by as complete a report as possible within 8 additional calendar days.

All Other Serious, Unexpected ADRs:

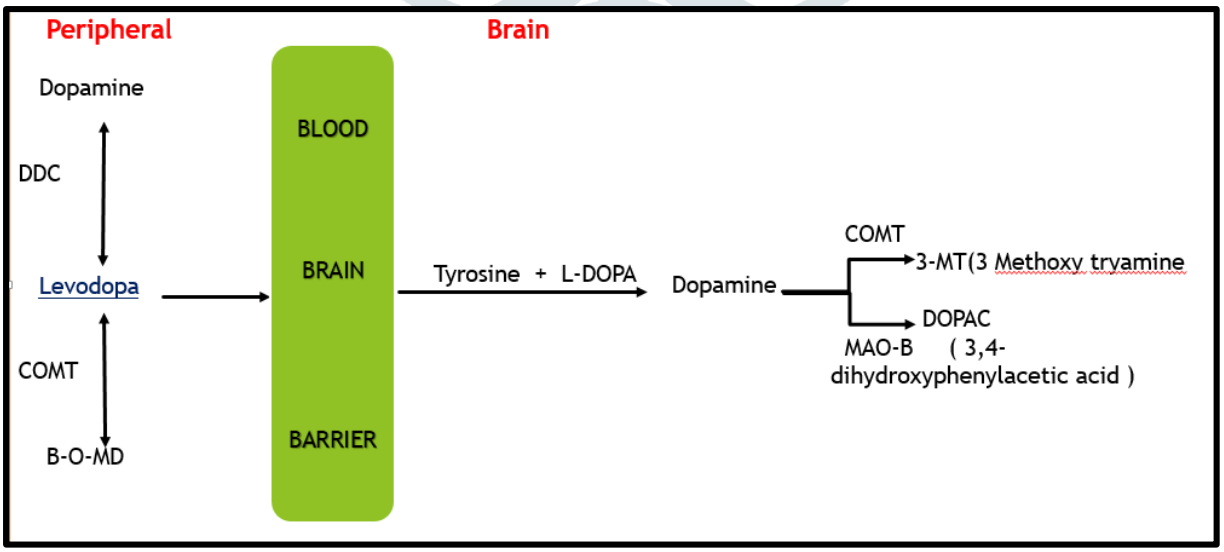
15 calendar days after first knowledge by the sponsor that the case meets the minimum criteria for expedited reporting.

How to Report :

The CIOMS I form is a generally established standard for rapid adverse event reporting. However, regardless of the form or style employed, it is critical that some essential information/data pieces, if available, be included in any accelerated report, whether in tabular or narrative format. [15] [16]

DOPAMINE PRECURSOR:

E.g.Levodopa:



Pathways systemically administered levodopa [fig.3]

Mechanism of action :

Dopamine does not readily cross the blood-brain barrier. The most effective and often used therapy is levodopa. The enzyme dopa decarboxylase converts this dopamine precursor to dopamine, both peripherally

and within the CNS (Fig. 1). Levodopa is taken in conjunction with a peripherally acting dopa decarboxylase inhibitor (DDI), such as benserazide. This allows for a lower levodopa dose while reducing peripheral dopaminergic side effects (tachycardia, dysrhythmias, nausea, and vomiting). [17]To boost levodopa's absorption and reduce side effects, it is frequently used with peripheral decarboxylase inhibitors. Dopamine decarboxylase inhibitors block the peripheral conversion of levodopa to dopamine, allowing more levodopa to cross the BBB. Once converted to dopamine, it activates postsynaptic dopaminergic receptors and compensates for the decrease in endogenous dopamine[18].

Action on :

1.CNS :Hypokinesia and rigidity resolved first, followed by tremor. Secondary symptoms of posture, gait, handwriting, speech, facial expression, mood, self-care, and interest in life eventually subside. Therapeutic benefit is nearly total in early disease, but diminishes as the disease progresses. Levodopa's effect on behavior has been defined as a 'general alerting response'. An embarrassingly disproportionate increase in sexual activity has been seen. Levodopa is utilized to create a nonspecific 'awakening' effect in hepatic coma .

2.CVS: The peripherally formed DA can cause tachycardia by acting on β adrenergic receptors. Excess DA and NA formed in the brain decrease sympathetic outflow; also DA formed in autonomic ganglia can impede ganglionic transmission. Gradual tolerance develops to both cardiac stimulant and hypotensive actions.

3. CTZ: Dopaminergic receptors are present in this area and DA acts as an excitatory transmitter.

4.Endocrine: DA acts on pituitary mammotopes to inhibit prolactin release and on somatotrophs to increase GH release.

Pharmacokinetics:

Bioavailability of levodopa is affected by:

(i) Slow gastric emptying exposes levodopa to gut and liver enzymes, reducing its ability to cross the blood-brain barrier.

(ii) Food contains amino acids that compete for the same absorption carrier, resulting in decreased blood levels when taken with meals.

Levodopa undergoes extensive first-pass metabolism in the gastrointestinal mucosa and liver. Levodopa metabolism occurs both peripherally and centrally.

The same change occurs in around 1% of levodopa delivered to the brain via amino acid carrier-mediated active transport across brain capillaries. Levodopa has a plasma half-life of 1–2 hours.

Adverse effects

At the initiation of therapy

These side effects can be minimized by starting with a low dose.

1. Nausea and vomiting :

2. Postural hypotension It occurs in about 1/3 of patients, but is mostly asymptomatic; some patients experience dizziness, few have fainting attacks.

3. Cardiac arrhythmias

4. Exacerbation of angina

5. Alteration in taste sensation

After prolonged therapy

1. Abnormal movements (dyskinesias)

2. Behavioural effects [19]

Rationale for a combination product.{Levodopa/carbidopa/entacapone}

Stalevo has the same clinical advantages as entacapone when used with levodopa/carbidopa. Furthermore, Stalevo provides the convenience of taking one pill instead of two (or more), and the available dose combinations allow for more delicate levodopa titration without the need to divide tablets. Stalevo comes in three strengths: 50/12.5/200 mg levodopa/carbidopa/entacapone (Stalevo 50), 100/25/200 mg (Stalevo 100), and 150/37.5/200 mg (Stalevo 150). These benefits are especially appealing for individuals who take multiple pills per day or who may mistakenly mix medications or have difficulties sticking to complex treatment regimens. The combo tablet simplifies therapy and promotes entacapone use by ensuring simultaneous administration of levodopa/carbidopa and entacapone. Furthermore, Stalevo 50 and 100tablets are smaller than entacapone tablets. [20],[21]

CASE STUDY 1

1. A 70-year-old man has been under treatment for Parkinson's disease for the last 5 years. He is currently receiving Tab. levodopa 100 mg + carbidopa 25 mg two tablets in the morning, afternoon and night. He now suffers stiffness, shaking and difficulty in getting up from bed in the morning. These symptoms decrease about ½ hour after taking the medicine, but again start worsening by noon. He notices one-sided twitching of facial muscles which is more frequent 1–2 hour after each dose of levodopa-carbidopa.

(a) Should his levodopa-carbidopa medication be stopped/replaced by another drug or the dose be increased further? Alternatively, can another drug be added to his ongoing medication? If so, should levodopa-carbidopa dose be changed or left unaltered?

SOLUTION

a. The patient's Parkinson's disease appears to have progressed during the last 5 years, and he is now experiencing the 'wearing off effect' of levodopa-carbidopa. He is also getting dyskinesia, a late-stage side effect of the medication. At this point, antiparkinsonian medication cannot be discontinued since he would develop considerable rigidity, immobility, and tremor, interfering with daily tasks. He is already having a side effect from his medicine, thus the amount should not be increased further. Because levodopa-carbidopa is the most effective and least expensive medicine for Parkinson's disease, it may be sensible to continue it at a lower dose and augment with another longer-acting agent to smooth the therapeutic impact. There are several alternatives for additional medication:

   • To lessen the dose of levodopa carbidopa, gradually add ropinirole/pramipexole, which is a direct dopamine agonist. Both medications can be taken three times each day. The longer-acting nature of ropinirole/pramipexole will improve symptom management. They also cause reduced dyskinesia.

   • Taking an MAO-B inhibitor, such as selegiline 5 mg twice a day or rasagiline 1 mg in the morning, helps limit dopamine breakdown in the brain, allowing levodopa-carbidopa to work longer and smoother.

   • \tEntacapone 200 mg with each dosage of levodopa-carbidopa inhibits COMT, which can enhance and prolong levodopa action. It can also be used as a third medicine in conjunction with levodopa-carbidopa and selegiline to provide more symptomatic relief. [22]

Case 2

A 70-year-old female with a 15-year history of Parkinson's disease that began with resting tremor of the left arm was referred to a movement disorder clinic. During the first years, the patient had a good and maintained response to levodopa treatment. At age 64, the patient began having leg dyskinesias, followed 1 year later by the onset of wearing-off. At age 67, the patient reported falls and gait disturbance. The referral to a movement disorders outpatient clinic was made due to falls and worsening of motor

fluctuations, namely wearing-off (~5 h of daily off) and on–off fluctuations. No cognitive or behavioural

complaints were recorded. The patient was medicated with levodopa/carbidopa, 100/25 mg one and a

half pill t.i.d. plus one pill t.i.d., ropinirole 5 mg t.i.d., amantadine 100 mg b.i.d. and domperidone 10 mg, two pills t.i.d. The clinical observation documented a severe off and on freezing as the major cause for falls. The patient did not present postural instability as documented by a good performance in the pull test. Gait disturbance and the risk of falls was her major complaint.

Clinical questions

- **Which therapeutic goals would you want to treat?**

Clinical questions

The current case shows an advanced-stage Parkinson's disease with an increasing load of motor problems, including dopaminergic non-responsive characteristics such as freezing. Despite being treated with a combination of multiple antiparkinsonian medications at medium to high therapeutic doses, motor fluctuations, such as unpredictable on-off occurrences, problematic dyskinesias, and severe freezing, imposed severe functional limitations.

• What therapeutic goals are you looking to achieve?

The current case shows an advanced-stage Parkinson's disease with an increasing load of motor problems, including dopaminergic non-responsive characteristics such as freezing. Despite being treated with a combination of multiple antiparkinsonian medications at medium to high therapeutic doses, motor fluctuations, such as unpredictable on-off occurrences, problematic dyskinesias, and severe freezing, imposed severe functional limitations.

After listing the detected clinical concerns (wearing-off, on-off fluctuations, freezing, postural instability, and dyskinesias), freezing was determined as the primary cause of disability and treated as such. Clinical observations were made during both on and off periods, allowing for the characterisation of freezing, its severity, and the assessment of the risk of falls, which was deemed identical for both periods.

- **If the patient presented freezing during off-time what should be the best pharmacological intervention to improve freezing of gait?**

As with other clinical problems present in the advanced stage, freezing and postural instability do not respond significantly to dopaminergic treatments. Very limited evidence suggests that low-frequency stimulation of the subthalamic nucleus in advanced PD patients may have a beneficial effect on freezing episodes[31]

The most logical treatment option for gait freezing that happens primarily during off time is to diminish off time. However, patients commonly exhibit additional motor difficulties such as biphasic dyskinesias and unpredictable on-off swings, which necessitate specific techniques and are challenging to manage. At this point, different options for dealing with a more advanced illness stage may be considered, taking into account the broad spectrum of motor problems. These are:

1. Increase daily dose of IR levodopa; 2. Switch to CR levodopa; 3. Increase dose of dopamine agonist; 4. Begin MAO-I therapy with rasagiline or selegiline; 5. Begin entacapone alone or in combination with levodopa/carbidopa [23]

Conclusion:

The findings of this study emphasize the significance of a comprehensive Pharmacovigilance program that focuses on monitoring adverse drug reactions associated with Parkinson's disease. Dopamine agonists, MAO-B inhibitors, and levodopa can all be combined and COMT inhibitors to increase its therapeutic efficacy. When combining Levodopa with other medications, patients should be cautiously monitored for these potential ADRs. Some of the case studies has also been done which confirms that there are patients which are suffering from Parkinson’s disease. Although there is no cure for Parkinson’s disease a number of pharmacologic treatments are available for managing the motor and non-motor symptoms.

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