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METOCLOPRAMIDE RELATED SECONDARY PARKINSONISM AND DOMPERIDONE SAFETY IN PARKINSON'S DISEASE

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ABSTRACT

Movement disorders are a prominent group of potentially treatable conditions, that occur as a result of infectious, metabolic, or neurodegenerative disease. Drug-induced movement disorders including akathisia, tardive dyskinesia, and parkinsonism may interfere with medication adherence. DIP's exact prevalence and incidence are unclear because it is frequently unrecognized or misdiagnosed as PD. Several drugs are known to cause drug-induced movement disorders including antipsychotic drugs, antiemetics, antidepressants, cholinomimetics, anti-vertigo, calcium channel antagonists, antiepileptics, and antiarrhythmics.

Parkinsonism is a type of movement disorder mostly induced by antipsychotic drugs but little attention has been paid to the parkinsonism induced by drugs administered for gastrointestinal tract symptoms like metoclopramide. Metoclopramide hydrochloride is a nonphenothiazine, benzamide antiemetic drug that acts as a dopamine receptor antagonist used to treat gastric ailments, and is reported to cause extrapyramidal movement disorders. Metoclopramide with D2-receptor antagonizing properties has been found to cause drug-induced parkinsonism. Blockage of postsynaptic dopaminergic receptors in the basal ganglia motor circuit manifests the clinical symptoms of parkinsonism.

Symptoms begin after the use of the offending drug and usually resolve after the cessation of the drug. In general, the manifestation of dips was similar to those of idiopathic Parkinson's

disease. The clinical manifestations of DIP and PD are similar but their treatment differs. Diagnosis can usually be made by taking a careful history and evaluating the effects of drug withdrawal. Domperidone may have advantages in situations where the concern for side effects has restricted the use of metoclopramide.

KEYWORDS: Metoclopramide, domperidone, drug-induced parkinsonism, mechanism, management.

Movement disorder – drug-induced parkinsonism

Observations of movement disorders including dystonia, akathisia, parkinsonism, chorea, stereotypies, myoclonus, or tics can be made while being exposed to a vast variety of medicines that are frequently used to treat a wide range of medical illnesses.[1]

Drug-induced movement disorders [DIMD]. Were identified soon after antipsychotic marketing began in the 1950s. Initially, the use of these drugs was linked to acute adverse extrapyramidal syndromes including acute dystonia, akathisia, and parkinsonism. Later, TD was discovered to be a side effect of antipsychotic medications. Since those years, many other drugs have been connected with DIMD including psychiatric or nonpsychiatric drugs such as serotonin-specific reuptake inhibitors, metoclopramide, or some calcium-channel blockers, among others.[1]

Drug-induced parkinsonism [DIP]. Is the second-most-common etiology of parkinsonism in the elderly after Parkinson's disease.[2] Parkinsonism as a side effect of certain medications is an underdiagnosed entity.[3] And is by far the commonest non-vascular neurological disorder of old age.[4]

Drug-induced parkinsonism is the most common secondary cause and can closely resemble PD.[5] Drug-induced parkinsonism is similar to Parkinson's disease except that it tends to be more symmetrical, and the tremor is often postural and more rapid.[6] The term "drug-induced parkinsonism" (DIP) refers to a kind of parkinsonism that can be brought on by several medicines, including dopamine-receptor blockers and treatments that deplete dopamine storage. Antidopaminergic drugs can also unmask or worsen preexisting Parkinson's disease [PD].[7]

DIP was initially described as a complication of antipsychotic agents but later recognized as a possible side effect of several other compounds including antiemetics, cholinomimetics,

antidepressants, anti-vertigo medications, calcium channel antagonists, antiarrhythmics, and antiepileptic drugs.[8]

Several metoclopramide-induced movement disorders may coexist in the same individual, with tardive dyskinesia, parkinsonism, and akathisia.[6] Tardive dyskinesia presumably is an expression of dopamine receptor supersensitivity, whereas parkinsonism is due to dopamine receptor blockade.[6] Parkinsonism induced by antipsychotic drugs, such as phenothiazines and butyrophenones, is well known, but little attention has been paid to the parkinsonism induced by drugs administered for gastrointestinal [GI]. Tract symptoms. These drugs are also reported to worsen motor symptoms when used in persons with stable idiopathic Parkinson's disease.[9]

Parkinsonism results from a decreased dopaminergic transmission in the motor region of the striatum with opposing effects on the direct and indirect pathways, which results in increased γ-aminobutyric acid [GABA]anergic inhibition of thalamocortical projections.[10]

The pathological hallmarks of PD are loss of dopaminergic neurons in the substantia nigra [SN]. Pars compacta [SNPS]. And the accumulation of misfolded a-synuclein, which is found in intra-cytoplasmic inclusions called Lewy bodies [abs].[11]

Secondary parkinsonism has been presenting a marked increase in its incidence, mainly as a consequence of the increasing development and use of drugs with dopaminergic-blocking properties.[9] Commonly recognized drugs are neuroleptics, dopamine depletion, and anti-emetics Due to these medications' anti-dopaminergic properties, parkinsonian patients should generally avoid using them. The worsening of a previously stable IPD upon initiation of this commonly used drug.[9] Other causes of secondary parkinsonism include infarcts, hemorrhages, tumors in the basal ganglia, hydrocephalus, infections such as HIV disease and influenza, and toxins such as manganese and carbon monoxide.[5]

Treatment with neuroleptics such as phenothiazines and butyrophenones induces parkinsonism, due to a chronic blockade of dopamine D2 receptors in the striatum. D2 occupancy is an important mediator of response and side effects in antipsychotic treatment.[12] The likelihood of clinical response increases as D2 occupancies exceed 65%–70%, while the risks of hyperprolactinemia and extrapyramidal side effects or akathisia increase at occupancies higher than 72% and 78%, respectively.[12]

Parkinson's Disease

In 1817, James Parkinson described the shaking palsy now known as Parkinson's disease [PD]. Descriptions evolved until the term "parkinsonism" now refers to a syndrome characterized by the presence of tremor, rigidity, and bradykinesia in addition to the loss of postural reflexes and freezing.[14]

Parkinson's disease is a progressive neurodegenerative disorder that is pathologically defined by degeneration of the dopaminergic neurons in the substantia nigra and the development of Lewy bodies in the residual dopaminergic neurons.[15]

It is a progressive, degenerative disease manifested by motor and nonmotor symptoms and is estimated to affect 1 million people in the United States and 4 million people worldwide.[3] PD is caused by the deterioration of the dopaminergic neurons in the extrapyramidal tract of the midbrain.[16] Current treatment of PD is based on the replacement of dopamine, although alternative approaches such as deep brain stimulation [DBS]. are suitable for later-stage disease.[11]

PD affects approximately 1% to 2% of adults over age 65 and 4% of adults over age 80. PD is a neurological condition that affects dopaminergic neurons. Presently, there is no cure for PD; the goal of treatment is to provide symptomatic relief for motor and nonmotor symptoms with medication.[16]

Parkinson's disease is the second most common neurodegenerative disease worldwide.[17] Parkinson's disease is a chronic, progressive disease affecting 1% of the population older than 60 years.[17]

Parkinson's disease is a heterogeneous disease with rapidly and slowly progressive forms.[18] that results in progressive extrapyramidal motor dysfunction primarily related to loss of dopaminergic nigrostriatal function.[19] the dopaminergic nigrostriatal system has been assumed to be fundamental to PD.[19] Drugs that block dopamine [DA]. receptors or deplete DA storage produce a functional dopaminergic deficient state and hence cause clinical symptoms that mimic idiopathic Parkinson's disease [PD].[20]

Although neither the loss of pigmented dopaminergic neurons in the substantial nigra, nor the deposition of α-synuclein in neurons is specific to Parkinson's disease, this two major neuropathology are specific for a definitive diagnosis of idiopathic Parkinson's disease when

applied together.[10] Currently, no pharmacologic therapies prevent or delay Parkinson's disease progression.[18]

Prevalence

The incidence of PD varies according to geographical location [lower prevalence in 13 Asia than in North America, Europe, and Australia]. or gender [higher prevalence in men]. 14, few data about DIP characteristics across different areas in the world are available.[22]

Epidemiologic studies have suggested that certain neurologic or psychiatric manifestations may precede the traditional motor manifestations of PD for long periods.[19] DIP's exact prevalence and incidence are unclear because it is frequently unrecognized or misdiagnosed as PD. A community-based survey and a population-based study found DIP prevalence rates of 2.7% and 1.7%, respectively, whereas those of PD were 3.3% and 4.5%, respectively.[2]

According to the epidemiological study by Ayd, three risk factors for DIP were identified, namely, old age, female gender, and the use of potent neuroleptics.[20] Despite the manufacturer's estimate of only 0.2% frequency of metoclopramide-induced movement disorders, the actual prevalence is probably greater.15 At least 1031 patients with metoclopramide-induced movement disorders have been described. In one study, metoclopramide was administered in high doses to psychiatric patients, with a resulting prevalence of extrapyramidal side effects of 25%.[6]

In an epidemiologic survey of extrapyramidal reactions with metoclopramide, drug-induced parkinsonism and tardive dyskinesia occurred in 20 and four cases, respectively, out of the 15.9 million prescriptions. Metoclopramide is primarily prescribed for gastroparesis, nausea and vomiting, and gastroesophageal reflux disease. Evaluations of the long-term use of metoclopramide in the gastroparesis patient population have not been published. Furthermore, exposure raises the incidence of tardive dyskinesia linked to metoclopramide use. The FDA has received 87 adverse drug reports of metoclopramide-associated tardive dyskinesia; 26% of these reports document disability.[25] Despite such reports, the use of metoclopramide has risen.[24]

Risk Factors

Most patients with movement disorders were elderly [mean age of 61 years]. With advancing age, a person may be increasingly sensitive to neuroleptic agents, possibly because of

decreased metabolic activation of drugs and loss of dopamine receptors.[26] Age is the most obvious risk factor for DIP since dopamine concentrations decrease and nigral cells degenerate with age. Another risk factor is the female gender, suggesting that estrogen suppresses the expression of dopamine receptors.[2]

DIP concerns the female to male preponderance ratio of 2:1. It is still unclear why there are more females than males, which is not the case with idiopathic Parkinson's disease.[27]

Toshikatsu indo et al, reported, Of the 33 cases of drug-induced parkinsonism, there were 18 cases in which the causal drugs could be identified: metoclopramide, ten; sulpiride and reserpine, two each; phenothiazine and butyrophenone, four. Our experience indicates a high incidence of parkinsonism among women of advanced age, but no predisposition could be adduced by an analysis of patient and family histories.[28]

AIDS patients are more susceptible to extrapyramidal side effects of dopamine-blocking agents than non-AIDS patients. The mean drug dose and body weight were significantly lower in the AIDS group.[29] Metoclopramide-induced parkinsonism was often seen in women more than 60 years old.[28] The risk of DIP reports was higher in men, and people aged 75.[22]

Metoclopramide

Metoclopramide hydrochloride is a nonphenothiazine.[5] benzamide antiemetic drug. Initially, it was used in the treatment of esophageal reflux, dyspepsia, and gastroparesis.[6]

Metoclopramide hydrochloride, a neuroleptic dopamine receptor antagonist used to treat gastric ailments, is reported to cause extrapyramidal movement disorders.[30]

Metoclopramide is used widely in patients with gastric motility disorders and it has a chemical structure similar to the neuroleptic drug chlorpromazine.[14] The occurrence of parkinsonism secondary to chronic metoclopramide use had been well documented.[14]

Metoclopramide is a new generation of dopamine antagonists first described by Justin-Besancon and associates in the early 1960s, 10 years after the synthesis of procainamide. Para-aminobenzoic acid serves as the parent compound for both medicines, which are generated from substituted benzene molecules. Procainamide lacks the 5-chloro and 2-methoxy aryl substituents, which distinguishes the two medications. However, there is a great

difference in their pharmacodynamics in that metoclopramide affects the gastrointestinal smooth muscle, as well as being a powerful centrally acting anti-emetic; procainamide is a well-known local anesthetic with recently appreciated anti-arrhythmic properties.[31]

When administered to psychiatric patients in larger doses, the incidence of extrapyramidal side effects of metoclopramide has been as high as 25%.[28] Metoclopramide has been used widely in the treatment of levodopa-induced gastric symptoms, which often develop in patients with parkinsonism.[28]

Metoclopramide has now been reported to resemble neuroleptics.[32] Thus, metoclopramide resembles classical neuroleptics such as haloperidol and pimozide both behaviorally and biochemically. A rise in striatal and mesolimbic homovaniltic acid levels suggests that the acute administration of metoclopramide enhances dopamine turnover as do neuroleptic drugs.[32]

According to the original manufacturer, "extrapyramidal reactions" occur in only 1 of 500 patients treated with metoclopramide [1986 package insert, AH Robins Co, Richmond, VA].[6] Kapil D Sethi et al, have reported six cases of metoclopramide-induced parkinsonism seen in consultation over two years. Five of these six patients had renal failure.[33]

Mechanism of Action of Metoclopramide

The prokinetic effect of these drugs is mediated through their blockade of enteric inhibitory D2 receptors.[20,2]

Mechanism of Gastrointestinal Effects

[Metoclopramide's exact mechanism of action in the gastrointestinal tract remains unclear].

1. Potentiation of cholinergic effects
2. Inhibition of dopaminergic [or tryptaminergic]. inhibitory motor neurons
3. Direct action on smooth muscle.[34]

Although the severity of the symptoms varies, all prokinetics with D2 receptor antagonistic characteristics are reported to cause EPS. Among the GI prokinetics, metoclopramide is the most well-known cause of drug-induced movement disorders.[20]

The role of dopamine in the gastrointestinal tract and the potential therapeutic value of dopamine antagonists is used in the treatment of smooth muscle disorders.[31]

Metoclopramide lowers the pressure threshold for the occurrence of the peristaltic reflex, reduces the appearance of fatigue, and enhances the frequency and amplitude of the longitudinal muscle contractions. Metoclopramide is not a cholinomimetic in the usual sense; it does not increase gastric acid secretion or stimulate endogenous gastrin release.[31]

In the brain, metoclopramide is localized in the area postrema that contains the chemoreceptor trigger zone for vomiting. Impaired renal function prolongs the drug's half-life and this fact has to be considered when treating patients with chronic renal failure.[31]

Clinical Uses of Metoclopramide

Metoclopramide, an agent used to treat gastroparesis and nausea, produces a central dopamine blockade leading to a decrease in the effect of levodopa.[25]

GI prokinetic drugs have been used clinically to manage motor disorders of the upper GI tract, including functional dyspepsia and emesis.[2]

The anti-emetic property is probably via a direct effect on the chemoreceptor trigger zone by blocking dopamine receptors.[31]

Pharmacokinetics of Metoclopramide

Pharmacokinetic studies suggest that the drug is well-absorbed and rapidly excreted with a short half-life, 60 to 90 minutes in rats and dogs, and about 4 hours in humans. The drug's onset of action is 1 to 3 minutes after intravenous doses and 3 to 5 minutes after intramuscular injection. Maximal plasma levels of 84 ng/ml occur within 20 to 30 minutes of oral intake, although the peak metoclopramide plasma concentration during intravenous administration was 221 ng/ml [both 20 mg doses].[31]

Side Effects of Metoclopramide

At usual therapeutic doses, metoclopramide is well tolerated. The majority of side effects are minor and temporary and seldom do they call for treatment discontinuation. After oral or parenteral administration, they mostly include sleepiness, restlessness, gastrointestinal problems, dizziness, and faintness. Extrapyramidal symptoms are uncommon at standard doses in adults, but they are more prevalent in patients with renal failure and at larger dosages used to treat antineoplastic drug-induced vomiting.[34]

If metoclopramide is used at the typical therapeutic doses, several side effects could happen. Side effects have been reported in up to 20% of patients, but are usually mild, transient, and reversible after withdrawal of the drug. These reactions disappear within 24 hours after the withdrawal of metoclopramide.[31]

This increased use has been accompanied by numerous reports of neurotoxicity, chiefly related to metoclopramide's blocking action at dopamine receptors.[6]

Parkinsonism with typical tremor, rigidity, and akinesia is a significant risk of long-term metoclopramide therapy. The incidence is higher in older patients.[34]

Etiology of Dip

Any drug that blocks the action of DA [referred to as a DA antagonist]. is likely to cause parkinsonism. Drugs used to treat schizophrenia and other psychotic disorders such as behavioral disturbances are possibly the major cause of drug-induced parkinsonism worldwide.[20]

Mechanism of Metoclopramide Induced Parkinsonism

The D1 family of dopamine receptors, which includes D1 and D5 receptors, and the D2 family, which includes D2, D3, and D4 receptors, are both present in the brain. The central dopaminergic system consists of the mesolimbic, mesocortical, tuberoinfundibular, and nigrostriatal pathways.[2]

The D2 receptor blockade in the mesocortical and mesolimbic pathways has an essential therapeutic role in controlling psychotic symptoms, and EPS emerges because of the non-selective blockade of D2 receptors in the nigrostriatal pathway. All antipsychotic drugs have potent D2 receptor blocking capacity, and the therapeutic effects of these drugs on psychosis are related to their action on the limbic system, where they reduce DA transmission. Antipsychotic medications that block D2 receptors in the striatum cause GABA- and encephalin-containing striatal neurons at the start of the indirect pathway to become disinhibited without affecting the direct pathway, which is followed by disinhibition of the subthalamic nucleus.

This leads to increased GABAergic inhibition of the thalamocortical projection by facilitation of the inhibitory projection from the globuspallidus/substantia nigra pars reticulate.[20]

Although the severity of the symptoms varies, all prokinetics with D2-receptor antagonistic characteristics have been proven to cause EPS. Among the GI prokinetics, metoclopramide is the most well-known cause of drug-induced movement disorders.[2,21]

E. peringer et al suggested further evidence for increased dopamine turnover following metoclopramide administration.[32] Despite the medication's ability to inhibit dopamine receptors within hours of administration, the parkinsonian effect may not be felt for days to weeks. Half to three-quarters is evident in 1 month, and 90% of cases occur within 3 months of starting the medication.[3]

The tract also affects autonomic function, how motions are performed, and recurring behaviors. An imbalance of excitatory [acetylcholine] and inhibitory [dopamine] is brought on by the degeneration of the neurons that produce dopamine. neurotransmitters in the region. This imbalance causes excessive uncontrollable movements, termed dyskinesias, at times, and lack of movement, known as freezing of gait, at other times.[16]

Clinical features

Parkinsonian syndromes are a group of several diseases that share similar cardinal signs such as tremor, rigidity, bradykinesia, and postural instability These symptoms are mainly associated with dysfunction of basal ganglia which can have different aetiologies.[7]

In general, the clinical features of DIP were similar to those of idiopathic Parkinson’s disease. The clinical manifestations of DIP and PD are similar, but their treatment differs.[7]

DIP includes resting tremors, muscular rigidity, akinesia, or bradykinesia, developing within a few weeks of 6 starting or raising the dosage of medication [typically a neuroleptic]. or after reducing the 7 dosages of an antiparkinsonian agent.[22] Akinesia/bradykinesia, which affects limbs bilaterally rather than unilaterally, and rigidity are the predominant signs and symptoms of DIP. DA transporter [DAT]. imaging may be used in the differential diagnosis of various etiologies of parkinsonism and also DIP.[20]

Symptoms tend to be symmetric [unlike idiopathic Parkinson's disease]., but it may be difficult to differentiate between drug-induced parkinsonism and Parkinson's disease.[3] Among non-motor symptoms, there is evidence that hyposmia can differentiate between patients with “pure” drug-induced parkinsonism and those with degenerative parkinsonism unmasked by an anti-dopaminergic drug.[8]

Motor features of DIP can resemble PD. Hyposmia seems to be the most reliable NMS to differentiate DIP and PD, although confounding factors [age, smoking, and cognitive impairment]. can complicate its assessment.[11] The duration of metoclopramide therapy before the appearance of signs and symptoms is between two weeks and 5 ½ years.[33]

Bradykinesia was the most common early symptom, followed by rest tremors. Generally, bilateral symptoms had progressed either acutely or sub-acutely before clinical features of parkinsonism were recognized.[28] The symmetrical presentation of DIP is distinguished by the predominance of bradykinesia in the overall clinical picture. Typical resting tremor is not frequently observed but when present is postural and of higher frequency than in idiopathic disease.[35]

Diagnosis

Accurate diagnosis is crucial for best management and appropriate prognosis.[11] The diagnosis of Parkinson's disease is difficult and diagnostic error is common, particularly in the early stages and is mostly clinical and relies on the presence of the cardinal features of bradykinesia, rigidity, tremor, and postural instability, coupled with gradual symptom progression and sustained response to therapy with levodopa.[15]

Nine items made up the initial rating scale, all of which were frequent clinical symptoms used in the clinical diagnosis of Parkinson's disease. One of these items, the evaluation of the state of the trunk muscles-a sign which can be of considerable diagnostic importance-was found difficult to quantify and was dropped from the scale. The other eight items were retained and, with the addition of Tremor and Salivation, make up the ten-item scale. Each item is rated on a 5-point scale, with 0 meaning the complete absence of the condition, and 4 meaning the presence of the condition in extreme form. Each point on the scale was defined and is shown in the appendix. The score on the scale is obtained by adding the items and dividing them by 10. Neurological Rating Scale for Extrapyramidal Effects.[36]

Table 1: Neurological Rating Scale for Extrapyramidal Effects.

1.	GAIT	6.	LEG PENDULOUSNESS
2.	ARM DROPPING	7.	HEAD DROPPING
3.	SHOULDER SHAKING	8.	GLABELLA.
4.	ELBOW RIGIDITY	9.	TREMOR
5.	WRIST RIGIDITY	10.	SALIVATION

The scales often contain many items, or the assessment involves time-consuming procedures, such as sorting tests or handwriting.[36] The absence of a completely reliable clinical marker for PD makes neuropathologic confirmation essential in evaluating the diagnostic utility of clinical features or combinations of the future. The neuropathologic findings are sometimes ambiguous or conflicting, however, the specificity and sensitivity of individual pathologic features are not known.[37]

Several clinical clues have been highlighted to aid the differential diagnosis between DIP and PD, and these include symmetry of symptoms, the relative absence of rest tremor, the coexistence of Oro-mandibular dyskinesias, and a minimal if any, levodopa response.[6] However, DIP can be clinically indistinguishable from PD in several patients.[8] Drug-induced parkinsonism is misdiagnosed as Clinical features similar to Parkinson's disease; drug history and drug withdrawal evaluation can confirm the diagnosis; antiemetics and psychotropic drugs most common causative agents.[5]

Diagnosis can usually be made by taking a careful history and evaluating the effects of drug withdrawal.[5] The fact that DIP in elderly individuals treated with dopamine receptor antagonists is often misdiagnosed as PD is a serious problem. The consequences are not insignificant considering the morbidity and mortality of DIP and the potential toxicity of dopaminergic drugs in the elderly.[38] Although being very frequent, there are no widely accepted diagnostic criteria for DIP.[8] The main differential diagnoses are idiopathic PD and the parkinsonian form of multiple system atrophy.[35]

The following are the clinical diagnostic standards for DIP

1. The presence of parkinsonism
2. No history of parkinsonism before the use of the offending drug
3. Onset of parkinsonian symptoms during the use of the offending drug.[2] Patients clinically diagnosed with dip may include individuals in the preclinical stage of PD whose symptoms were unmasked by the drugs.[2]

Imaging of the dopaminergic pathway seems to be the only, reasonably available, technique to aid the differential diagnosis between drug-induced parkinsonism and Parkinson's disease.[8] A dopamine transporter scan, while limited as a tool for diagnosing idiopathic Parkinson's disease, as it is positive in other degenerative Parkinsonian disorders, may be useful in diagnosing drug-induced Parkinsonism.[3] Neuroimaging by positron emission

tomography [PET]. or single photon emission computed tomography [SPECT]. maybe of help for diagnosing drug-induced parkinsonism.[1]

Positron emission tomography [PET] and single photon emission [SPECT] be also Single photon emission computed tomography [SPECT] is one of the most useful tools to facilitate the diagnosis of PD in patients whose clinical symptoms or the clinical course of the disease are unusual. Since the nigrostriatal pathway is affected in PD patients, SPECT imaging with the radioligand 123I-labelled 2β-carbomethoxy-3β-[4-iodophenyl]. N- [3-fluoro propyl]. nor tropane [123I-FP-CIT]. usually shows a reduction in striatal density of the dopamine transporter [DAT].[7] In contrast, striatal 123I-FP-CIT binding is typically normal in DIP patients because the nigrostriatal circuit is unaffected. Although 123I-FP-CIT SPECT can help in the clinical differentiation of DIP and PD, only a few studies have focused on the accuracy of this technique in the diagnosis of DIP.[7]

Drugs causing parkinsonism, such as debts, have negligible affinity for DAT. DAT scans may show symmetric uptake of radiotracer in the bilateral striatum in patients with pure DIP, even if they have significant parkinsonism.[1] Patients with DIP whose striatal DAT uptake declines asymmetrically can be diagnosed with PD. Therefore, DAT scans may be useful for differentiating PD unmasked by drugs from pure DIP.[2] although there is no specific mention in this regard in the current formal indications for dopamine transporter imaging.[8]

The IBZ-SPECT is a reliable technique for visualizing and quantifying striatal D2 dopamine receptors in vivo.[13] D2 receptor occupancy was determined with.[11] raclopride and positron emission tomography.[12] Based on the computed positron-emission tomography, 60–80% of D2 blockade is required for antipsychotic effects. If more than 80% of D2 receptors are occupied, DIP will develop.[20]

Metoclopramide-induced parkinsonism was measured with the St Hans Neurologic Rating Scale. This scale measures common signs of parkinsonism over a seven-point [0 to 6]. The scale of severity. Rated signs include diminished facial expression and mobility, bradykinesia, tremor, stooped posture, diminished arm swing, shuffling gait, and excess salivation. A global score on a 0 to 6 scale of severity was also determined.[30]

Metoclopramide-induced parkinsonism was often accompanied by a coarse rest tremor of about 4 to 5 Hz, it was easily misdiagnosed as typical Parkinson's disease.[28] That distinguishes metoclopramide-induced parkinsonism from typical Parkinson's disease.[28]

1. The symptoms develop sub acutely or acutely, manifesting their clinical features shortly after the onset
2. Most of the neurological symptoms are bilateral;
3. The symptoms are often accompanied by orolingual dyskinesia; and
4. Postural tremor is often seen

DIP and PD share almost all their clinical features which it makes difficult to differentiate between them clinically. However, 123I-FP-CIT SPECT imaging is a useful, simple, and reliable diagnostic tool that improves the clinical accuracy of the differential diagnosis between DIP and PD.[7]

Management of Metoclopramide-Induced Parkinsonism

Drug-induced parkinsonism is the second most common cause of parkinsonism after Parkinson's disease and their distinction has crucial implications in terms of management and prognosis.[8]

The rationale for the use of domperidone as concomitant therapy in Parkinson's disease and the supportive clinical data have been recently reviewed by Parkes [1986]. Stimulation of peripheral dopamine receptors following L-DOPA or bromocriptine administration leads to unwanted side effects such as nausea and vomiting, hypotension, hypo prolactinoma, and altered respiratory control.

The peripheral dopamine antagonist activity of domperidone with its poor CNS penetration suggests its usefulness in controlling L-DOPA-related side effects without interfering with desired central activity.[39]

DIP is generally treated by cessation of the offending drugs.[2] Withdrawal of the causative drug for 6 months should lead to improvements in symptoms; however, this is not always possible or effective.[11] DIP may persist or remit slowly despite prompt discontinuation of the offending drug. Some patients may require medications temporarily to relieve symptoms.[14] Symptoms should eventually resolve if the parkinsonism was drug-induced.[14]

Often there is a complete resolution of signs and symptoms in drug-induced parkinsonism after discontinuation of the offending drug.[33]

Anticholinergic medications such as trihexyphenidyl, benztropine, amantadine, and levodopa have been empirically examined for their capacity to alleviate DIP symptoms, but this has not yielded any conclusive proof of their effects on DIP patients.[2] A highly effective and focused dopamine antagonist is domperidone. It binds to the dopamine antagonist sites in the striatum with significant affinity.[40] Chemically, domperidone is connected to butyrophenones.[39,24]

In general, domperidone is considered safe for managing GI discomfort, even in patients with PD, because it does not cross the blood-brain barrier.[40] However, although rare, acute dystonic reactions to this drug may occur.[2] Domperidone may have advantages in situations where the concern for side effects has restricted the use of metoclopramide.[39] Domperidone is a gastrokinetic and antinauseant drug that has been reported to be effective in functional gastrointestinal disorders such as dyspepsia, gastroesophageal reflux, nausea, and vomiting.[40]

Domperidone is a peripheral dopamine antagonist which acts primarily at the chemoreceptor trigger zone on the floor of the fourth ventricle and dopamine receptors in the gut. It has gastroprokinetic and antiemetic properties similar to metoclopramide but does not readily cross the blood-brain barrier.[39,25] Oral absorption of domperidone as the base is reduced by concomitant antacid or H2-antagonist administration however, preliminary studies have shown that absorption of the maleate tablet is unaffected.[39] Domperidone undergoes first-pass and gut-wall metabolism.[24] Domperidone undergoes significant metabolism and is eliminated as metabolites in the feces (66%) and urine (31%).[39]

Domperidone and metoclopramide have similar pharmacodynamic and antiemetic profiles. Even though domperidone is less likely to have extrapyramidal side effects.[24] Additionally, domperidone reduces symptoms of dyspepsia and gastroesophageal reflux in patients, minimizes nausea and vomiting brought on by emetogenic chemotherapy, and lessens the deleterious effects of antiparkinsonian medications on the gastrointestinal and emetic systems.[25]

Although domperidone should be devoid of troublesome neurologic side effects, dystonic reactions have already been reported with this "peripheral" D2 antagonist. If discontinuation of metoclopramide therapy is not possible and disabling dyskinesias persist even after drug therapy is stopped, presynaptically active drugs, such as reserpine or tetrabenazine, may provide symptomatic relief. Diphenidol, a nonphenothiazine antiemetic that does not affect dopamine receptors, can also be used.[6]

In patients with chronic renal failure who require metoclopramide therapy, appropriate dose reduction would help reduce the incidence of metoclopramide-induced parkinsonism.[33] The parenteral dosage form of domperidone has been withdrawn by the manufacturer due to cardiotoxicity in patients being treated Intravenous for chemotherapy-induced nausea and vomiting.[39] Domperidone has been particularly well tolerated and has seldom caused any important side effects.[39,40] There have been no extrapyramidal side effects reported during controlled therapeutic trials with domperidone, although a few anecdotal reports of such effects have been published.[24]

Domperidone is more effective than metoclopramide at controlling nausea and vomiting over the long run, but it has fewer extrapyramidal adverse effects because it does not penetrate the blood-brain barrier. There are case reports in which domperidone has been used to treat extrapyramidal symptoms caused by the use of metoclopramide.[24] The management of gastrointestinal symptoms such as nausea and vomiting in patients with PD is more adequate with domperidone rather than with metoclopramide.[25]

Prognosis

Patients with DIP can have one of the following sorts of prognoses

1. Full and long-lasting recovery from DIP with no subsequent development of parkinsonism,
2. Persistence but no progression of parkinsonism,
3. Persistence and eventual worsening of parkinsonism, and
4. Full remission of parkinsonism but later reappearance after discontinuation of the offending drug
5. People who have been prescribed dopamine antagonists due to simple GI disturbance, headache, dizziness, or insomnia should stop taking the offending drugs as soon as possible.[2]

CONCLUSION

Drug-induced parkinsonism [DIP]. is often reversible, especially if the offending drug is discontinued early.[14] The general belief is that DIP has a different clinical picture from IDP.[4] confirming that parkinsonism is not only common but also badly diagnosed by practitioners. Just over half the cases were drug-induced.[4]

In the early stages of the disease, it might be difficult to clinically distinguish between DIP and PD. The proper distinction between DIP and PD patients has crucial implications in terms of management and prognosis.[8] DIP is difficult to diagnose because, particularly in the elderly, it might be difficult to distinguish it from Parkinson's disease. It is frequently under-recognized by psychiatrists and primary care physicians.[38]

Since DIP may last many months, we urge that a diagnosis of IDP should not be made until it is certain that the condition observed cannot be related to a drug that was stopped months ago.[4] Metoclopramide-induced movement disorders may be relatively mild but are often disabling and may cause life-threatening esophageal and respiratory difficulties.[6]

Metoclopramide itself does not induce parkinsonism.[28] Metoclopramide-induced parkinsonism is not rare.[33] However, metoclopramide has potent antidopaminergic properties, therefore it’s contraindicated in parsionian patients.[34] Although the drug is relatively safe, a growing body of literature has noted movement disorder after its administration.[33] The use of metoclopramide was associated with considerable morbidity, including impairment in ambulation and increased use of benzodiazepines.[30]

Metoclopramide has also been observed to worsen extrapyramidal symptoms in Parkinsonian patients and probably should not be administered to such patients. Prolonged blockade of central dopaminergic receptors can result in DIP, a side effect of metoclopramide, thought to involve both D2-receptors.[34]

When the administration of metoclopramide was discontinued, all symptoms diminished rapidly and the conditions of all the patients but one improved until they became entirely free of symptoms. The patients completely recovered within two weeks to one year, the average period being 4.2 months.[28] The management of gastrointestinal symptoms such as nausea and vomiting in patients with PD is more adequate with domperidone rather than with metoclopramide.[25]

Anticholinergics including trihexyphenidyl, benztropine, amantadine, and levodopa have been empirically tested for their ability to relieve symptoms of DIP, but this has produced no clear evidence of their effects in DIP patients.[2]

Although metoclopramide has been safely given to parkinsonian patients, both to enhance levodopa absorption and decrease levodopa-induced nausea and vomiting, this use must be viewed cautiously pending further investigations.[31]

The patient should be reassured about the fact that DIP usually reverses with the cessation of the offending drug. If the patient should be prescribed a drug that is known to cause DIP patient should be educated about the possible alternative treatment options with a lower risk of DIP or a completely safer drug. [Prescription of domperidone instead of metoclopramide particularly in patients with Parkinson's disease].

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