Drug-induced parkinsonism: A review

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INTRODUCTION

Drugs which 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). Soon the relationship between parkinsonian symptoms and DA deficiency became apparent among patients who were treated with neuroleptics. This observation led to the most important discovery that identified markedly depleted DA, one of the catecholamines, as the pathogenesis of PD. The list of drugs associated with drug-induced parkinsonism (DIP) has grown ever since, to extend to gastrointestinal (GI) prokinetics, calcium channel blockers, antipsychotics, and antiepileptic drugs that impair DA function directly or indirectly. The main symptoms of DIP are akinesia/bradykinesia and rigidity, which appear in limbs bilaterally rather than unilaterally in a rapidly progressive fashion. DA transporter (DAT) imaging may be used in the differential diagnosis of various etiologies of parkinsonism and also DIP.[2]

EPIDEMIOLOGY

The incidence of DIP in the general population is reported to be 20% of patients with parkinsonism, less than half of PD cases. The incidence of DIP among patients taking neuroleptics varies from 15% to 40% and with classical antipsychotics the incidence varies between 4% and 40%. In the EUROPARKINSON Collaborative Study, DIP was estimated to contribute to 5% in Europe.[3] In population studies, DIP is generally considered the second leading cause of PD with 22%. 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. DIP may remit spontaneously without any change in the dose of neuroleptics, and the long-term effects of antipsychotics may be different from the acute effect of DA receptor blocking.[4] A community-based survey found DIP prevalence rates
of 2.7% and 1.7%, respectively, whereas those of PD were 3.3% and 4.5%, respectively. However, 6.8% of the patients diagnosed with PD were later reclassified as having DIP, thus emphasizing the difficulties in accurately diagnosing DIP and in measuring its prevalence. Age is the most obvious risk factor for DIP, since DA concentrations decrease and nigral cells degenerate with age.

**ETIOLOGY OF DRUG-INDUCED PARKINSONISM**

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 behavior disturbances are possibly the major cause of drug-induced parkinsonism worldwide.

**GI PROKINETICS**

GI prokinetic medicine, have conjointly been related to DIP which includes metoclopramide, levosulpiride, clebopride, and domperidone.[3] These medicine are used clinically to manage motor disorders of the upper GI tract, including purposeful dyspepsia and emesis. The prokinetic impact of those medicine is mediate through their blockade of enteric inhibitory D2 receptors. Besides, binding to receptors within the peripheral finish organs, so causation medicinal drug effects through D2 receptor blockade within the space postrema, they conjointly antagonize central D2 receptors, resulting in adverse effects together with hyperprolactinemia and extrapyramidal side effects (EPS).[6] All prokinetics with D2 receptor antagonizing properties are found to induce EPS, though the extent of symptoms varies. Among the GI prokinetics, metoclopramide is that the most-well-known cause of drug-induced movement disorders. Furthermore, levosulpiride is employed wide in many Asian and European countries to treat nausea, vomiting, and functional dyspepsia. Till recently, the drug-induced movement disorders associated with levosulpiride were under-recognized; however, it’s currently been shown that levosulpiride frequently causes parkinsonism.[7] Whereas metoclopramide typically induces tardive dyskinesia (TD), levosulpiride causes parkinsonism more frequently than TD or alternative EPS. Although metoclopramide and levosulpiride have a similar mechanism of action, they show totally different patterns of adverse effects, the rationale that remains to be clarified.

**CALCIUM CHANNEL BLOCKERS**

This is well described with cinnarizine and flunarizine, and these agents are used as vestibular sedatives in patients with vertigo.[9] A possible mechanism of parkinsonism with calcium channel blockers is D2 blockade, inhibition of energy-dependent vesicular uptake of DA, and mitochondrial damages.[9] It is of note that calcium channel blockers used in cardiac conditions have less clear association with DIP, but it has been reported. It is also noteworthy that the main delay of occurrence of parkinsonism syndrome elicited by calcium channel blockers is longer for the peripheral more than the central dopaminergic antagonism.

**ANTIEPILEPTICS**

This has been reported in several case series with valproate.[10] The proposed pathophysiology behind DIP found with valproate is mitochondrial respiratory chain dysfunction.[11] There is a defective function of the mitochondrial enzyme nicotinamide adenine dinucleotide, Coenzyme Q10, reductase of the respiratory chain in idiopathic PD. Another presumed mechanism of “reversible valproate-induced parkinsonism” is excessive GABAergic activity in the basal ganglia as seen in PD. In a study of 50 patients taking valproate, 3 out of the 50 patients or 6%, were found to have DIP. These patients were not on neuroleptics or other treatment that is known to cause EPS and were taking valproate for a minimum of 1 year.

**ANTIPSYCHOTIC AGENTS**

Centrally acting DA receptor antagonists accounted for nearly half of all DIP cases. All typical antipsychotics had the potential to cause EPS, including parkinsonism, acute dystonia, akathisia, and TD. Typical antipsychotics include chlorpromazine, promazine, haloperidol, perphenazine, fluphenazine, and pimozide.[12] About 80% of patients taking typical antipsychotic drugs exhibit more than one kind of EPS. Their risk is likely influenced by their antimuscarinic properties. Several second- and third-generation atypical antipsychotics also cause EPS or may unmask and exacerbate PD. Centrally acting DA receptors are widely distributed in the brain, and typical antipsychotics may act on DA receptors in the striatum. Therefore, all patients taking antipsychotics have some risk of developing parkinsonism and other EPS. Parkinsonism usually appears days to weeks after starting antipsychotics, but in rare cases, the onset delay may be several months or more. The risk of EPS was thought to be low for atypical antipsychotics. Atypical antipsychotics include clozapine, risperidone, olanzapine, quetiapine, and aripiprazole.[14] It was originally thought that their relatively low frequency of associated EPS was due to them being more strongly antagonistic toward serotonin-2A receptors than toward DA receptors. This serotonin-DA hypothesis has long been considered a useful model for developing atypical
antipsychotics that exhibit superior antipsychotic efficacy with a lower incidence of EPS compared to typical antipsychotics. In 1989, clozapine became the first atypical antipsychotic drug to be approved by the US Food and Drug Administration. It is effective in schizophrenia patients with drug-resistant negative symptoms, with an almost complete absence of EPS. DIP due to clozapine has not been reported, and it was found to improve psychosis without aggravating parkinsonism even in PD patients.

**CLINICAL FEATURES OF DRUG-INDUCED PARKINSONISM**

Differentiating DIP from PD or other Parkinsonian syndromes can be elusive on many occasions. Drug-induced parkinsonism might have acute to subacute onset with a temporal relationship to a newly started medication, occasionally within a few days. The average duration was found to be approximately 3 months DIP is generally characterized clinically as bilateral and symmetric parkinsonism, with more prominent bradykinesia and rigidity than in patients with PD. Typically 30–50% of patients with DIP show asymmetric parkinsonism and tremor at rest. Tremors mark the onset of the disease in a third of cases, and the complete triad of parkinsonism is found only in 25% of patients with DIP these characteristics are considered to support a PD diagnosis. The similar clinical manifestations of DIP and PD indicate that patients with DIP may have been in a preclinical stage of PD and that their parkinsonism may have been unmasked by the offending drugs. This is supported by findings that parkinsonism persists or even progresses after cessation of the drug in many DIP patients.

**PATHOPHYSIOLOGY OF DRUG-INDUCED PARKINSONISM**

DA receptors in the brain consist of those of the D1 family, comprising D1 and D5 receptors, and the D2 family, comprising D2, D3, and D4 receptors. The D2 receptor blockade in the mesocortical and mesolimbic pathways have an essential therapeutic role in controlling psychotic symptoms, and EPS emerge 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. The blockade of D2 receptors by antipsychotic drugs in the striatum leads to disinhibition of GABA - and encephalin - containing striatal neurons at the origin of the indirect pathway without alteration of the direct pathway, 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 globus pallidus/substantia nigra pars reticulata. Based on the computed positron-emission tomography, 60–80% of D2 blockade is required for antipsychotic effect. If more than 80% of D2 receptors are occupied, DIP will develop.

**CONCLUSION**

DIP is important because it is a common etiology of Parkinsonism and is frequently either unrecognized or misdiagnosed as PD. Thus, DIP requires a high index of suspicion and knowledge of the diverse offending drugs to be managed effectively. DAT imaging may be useful for accurately diagnosing patients with DIP and may help to identify the clinical characteristics and exact prognosis of this disorder. About 50% of patients with DIP and other movement disorders are treated with DRBAs for conditions unrelated to psychosis, including depression, GI disturbance, anxiety, and insomnia. Physicians should avoid prescribing DRBAs and CCBs for inappropriate reasons and should monitor these patients’ neurological signs when prescribing these drugs.

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**REFERENCES**


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