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Drug induced parkinsonism
A review

Abstract The use of neuroleptics as psychotherapeutic agents has resulted in extrapyramidal syndromes including parkinsonism. This specific drug-induced parkinsonism (DIP) mimics idiopathic Parkinson's disease with the typical parkinsonian triad but the symptomatology of this disorder is a rather akinetic rigid syndrome with lesser incidence of resting tremor. This disorder is usually dose-dependent and related to individual susceptibility to neuroleptics. Recent PET techniques with selective radioactive ligands enable us to study extrapyramidal side effects and dopamine D2 receptor occupancy. Now we know that more than 80 % D2-receptor occupancy is consistent with the appearance of DIP, whereas a low occupancy between 40–70 % induces no DIP. Conventional neuroleptics in regular doses usually cause more than 80 % D2 occupancy with resultant parkinsonian symptoms, whereas regular doses of atypical neuroleptics cause only less than 40–70 % D2 occupancy without parkinsonism. The other mechanism to explain the lower incidence of DIP in patients with atypical neuroleptics is the "fast-off" hypothesis. D2 receptor occupancy by atypical antipsychotic drugs is rather loose and transient, so they easily dissociate to allow normal dopamine transmission. Newer calcium entry blocking agents such as flunarizine and cinnarizine are known to cause similar DIP. The pathomechanism of this disorder was studied by SPECT and the dose dependent dopamine D2-receptor occupancy by these drugs was noted to explain DIP. The first management for this disorder is to withdraw the offending drugs if possible or switch from conventional neuroleptics to atypical agents. If it is impossible to change the drugs, it is better to add anticholinergics. For the elderly, it is recommended to use amantadine to prevent anticholinergic side effects.

Key words drug-induced parkinsonism · antipsychotic drugs · atypical neuroleptics · dopaminergic D2 receptor · D2 receptor occupancy

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Introduction

Drugs that either block dopamine receptors or deplete dopamine storage produce a functional dopaminergic deficient state, and hence cause clinical symptoms that mimic idiopathic Parkinson's disease (PD). Historically, the emergence of this typical drug-induced parkinsonism (DIP) after the use of phenothiazines was reported shortly after introduction of the drug in the early 1950s. Soon the relationship between parkinsonian symptoms and dopamine (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. This discovery automatically led to the development of L-dopa for treating patients with PD.

Parkinsonian symptoms induced by neuroleptics or dopamine depleting drugs cannot be distinguished clinically from those seen in PD. The main symptoms of DIP are akinesia/bradykinesia and rigidity, which appear in limbs bilaterally rather than unilaterally in a rapidly progressive fashion. Masked face and reduced blinking are also noted. Rigidity is less frequent, with cogwheel rigidity usually observed symmetrically in both limbs.

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Tremor is the least common of the major clinical symptoms, usually seen symmetrically in both hands during posture and action. A pill-rolling tremor at rest, a characteristic symptom of PD, is very rare among patients with DIP. Postural instability due to decreased response to body displacements results in loss of balance and falls. Flexed posture is another abnormality, which is probably due to truncal rigidity. Arm swing is also reduced and shuffling is quite common while walking. There is a tendency to run forward with small steps.

DIP usually appears later than akathisia and dystonia after taking neuroleptics with 50 % of cases within the first 30 days and 90 % within 72 days [1]. But Freyhan reported that the majority of patients developed parkinsonian symptoms before the 20th day [2], and Medinar found parkinsonism within the first week [3]. Patients treated with lower doses of neuroleptics or antiparkinsonian drugs improve over a period of 7–8 weeks, but some of the parkinsonian symptoms continue in 50 % of the patients with DIP despite anticholinergic drug treatment. Some of these patients later develop or transform to PD, probably reflecting early subclinical dopaminergic deficiency prior to administration of neuroleptics.

Epidemiology

The incidence of DIP in the general population is reported to be 20 % of patients with parkinsonism, less than half of PD cases [4]. The incidence of DIP among patients taking neuroleptics varies from 15 to 40 %, depending upon the type and dose of neuroleptics [5].

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 [1]. Many patients who develop DIP have had a predisposing subclinical depletion of DA and recent reports support this explanation [6, 7]. DIP may remit spontaneously without any change in the dose of neuroleptics, and the long-term effects of neuroleptics may be different from the acute effect of DA receptor blocking.

Pathophysiology

DIP is usually dose-dependent for each potent neuroleptic drug, and all patients eventually would develop DIP if high enough doses of the drugs were used. This was studied extensively by the recent use of PET with selective radioactive ligands, and now we know that DA receptor occupancy is directly related to parkinsonism [8–10]. The mechanism of action of neuroleptics is hypothesized to be related to the degree of D2-dopamine receptor occupancy. This was confirmed by several reports that regular doses of classical neuroleptics block D2 receptors in 70–89 % of cases, while atypical neuroleptics blocks the receptors in only between 38 and 63 % of cases [10]. This D2 receptor occupancy clearly explains the appearance of DIP and more than 80 % occupancy of D2 receptors always causes parkinsonism while less than 80 % occupancy does not usually cause DIP. The occupancy of regular doses of clozapine and other atypical neuroleptics is less than 60–70 %. But higher dosage of atypical neuroleptics, if used, produces increased D2 blocking, resulting in parkinsonism. The mechanism of action of atypical neuroleptics has been studied in more detail. The degree of receptor binding of classical antipsychotics is much tighter than that of atypical neuroleptics [11]. Radioactive haloperidol and chlorpromazine dissociated very slowly over a 30 minutes time span, whereas radioactive clozapine and quetiapine dissociated rapidly in less than 60 seconds. This phenomenon is called the "fast-off-D2" theory [12]. Therefore, atypical neuroleptics will clinically help patients by transiently occupying D2 receptors and rapidly dissociating to result in normal dopamine neurotransmission.

Another hypothesis of the atypicality of newer antipsychotics is that these drugs block 5-HT2A receptors as well as D2 receptors [13]. The inhibitory action of 5-HT2A receptors on DA secretion can be blocked by atypicals, hence higher endogenous dopamine concentration is available at dopaminergic terminals which helps dopamine transmission. However, this serotonin-dopamine balance theory has not yet been proved scientifically.

The newer calcium-entry blockers, such as flunarizine and cinnarizine are structurally related to neuroleptics such as piperazine derivatives. These drugs have been well documented as a cause of DIP. The elderly are particularly vulnerable to these agents. Theoretical explanations of this include the inhibition of calcium entry into striatal neurons and direct dopaminergic blocking effects. It was recently proved that D2 receptor-binding potential was blocked and reduced to 14–63 % by ^{131}I-benzamide SPECT study [14]. Older age and long-term use of the agents are predisposing factors for this illness and preexisting basal ganglia dysfunction due to old age, and vascular disease can explain why DIP occurs more in the elderly.

Treatment

Treatment of DIP should be considered, if disabling parkinsonian symptoms are observed. Those patients usually need antipsychotic drugs for a primary psychiatric illness, therefore the dose of neuroleptics should be checked carefully and, if overdosed, the first approach is to reduce the responsible dopamine D2 blocking agents or switch to less potent drugs. If it is impossible to stop or change the drugs because of the degree of psychiatric

illness, then anticholinergic drugs or amantadine should be considered to ameliorate DIP. Elderly patients can gain more benefit from amantadine because of fewer anticholinergic side effects [15]. Promethazine may be tried for patients with akathisia as well as DIP because of its strong antihistaminic effect.

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