J Multidisciplinary Scientific Journal

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Commentary

Tardive Dyskinesia and Dopamine Oxidation, Cumulative Effects

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Received: 12 March 2019; Accepted: 29 March 2019; Published: 31 March 2019

Abstract: It is likely that tardive dyskinsesia is caused by the oxidation of dopamine in dopaminergic neurons. This oxidation produces oxygen radicals that damage neurons. Damage accumulates until tardive dyskinesia occurs. The use of dopamine D2 receptor inhibitors should be limited to the lowest doses for the shortest duration possible.

Keywords: Tardive Dyskinesia; dopamine oxidation; free radicals; D2 inhibitors

1. Introduction

Tardive dyskinesia is frequently an irreversible condition marked by rapid, involuntary movements that can be disabling. Tardive dyskinesia can occur spontaneously but is most often caused by drugs that block dopamine D2 receptors and, possibly, through the contribution of a D3 inhibition [1]. However, the importance of presynaptic D2 receptors has not been adequately addressed in previous publications. Tardive dyskinesia is often a slow onset movement disorder, occurring in 68% of patients who have taken chronic antipsychotics for approximately 25 years, with a 5% increase per year of drug use [2]. The condition usually takes months or years of antipsychotic drug use to develop. Additionally, there are several reports of spontaneous dyskinesia occurring in psychotic patients who were never medicated. Spontaneous dyskinesia symptoms are similar to tardive dyskinesia but develop without drug therapy [3–5].

Tardive dyskinesia involves rapid, repetitive, involuntary, and purposeless movements, especially in the facial region, such as blinking, mouth movement, and lip smacking [6]. The torso and legs are other regions frequently affected, and can make walking impossible. The patient moves constantly. Occasionally, respiratory difficulty with grunting breaths can occur. Tardive dyskinesia is usually irreversible. Valbenazine and tetrabenazine can treat, but not cure, the condition. Such drugs inhibit VMAT2 (vesicular monoamine transporter 2), which prevents the release of dopamine from vesicles in dopaminergic neurons. Both drugs also increase suicidality.

Various causes of tardive dyskinesia, including dopamine super sensitivity, have been proposed [7,8]. One unconfirmed theory suggests that inhibition of D2 receptors upregulates D2 receptors and makes D2 receptors particularly sensitive to dopamine, resulting in uncontrollable movements. However, once the drug is cleared from the body, D2 receptors should return to normal and tardive dyskinesia should disappear. Several patients may have partly recovered from tardive dyskinesia, but most patients suffer from the condition for the remainder of their lives.

Drugs associated with the onset of tardive dyskinesia are most commonly used to treat psychosis, schizophrenia, and nausea. Long-term use of antipsychotic medications that block D2 receptors frequently results in tardive dyskinesia. Use of such drugs usually leads to the development of extrapyramidal effects before tardive dyskinesia. However, extrapyramidal effects usually disappear when the D2 receptor blocking agent is stopped. Newer antipsychotic agents may produce fewer occurrences of tardive dyskinesia. Use of metoclopramide, a D2 blocker, used against nausea,

also can cause tardive dyskinesia. The Food and Drug Administration prescribing information for metoclopramide recommends against use of the drug for longer than 12 weeks due to the increased risk of developing tardive dyskinesia. Reports of metoclopramide use also have indicated the onset of tardive dyskinesia in much shorter periods [9,10] Short-term use of metoclopramide, as little as two days, can cause irreversible tardive dyskinesia. Several alternatives to metoclopramide include dronabinol, nabilone, *Cannabis sativa* (medical marijuana), and *Zingiber officinale* (ginger).

Some patients may be more susceptible to the development of tardive dyskinesia, resulting from genetic differences in cytochrome P450 2D6 or other unknown causes. Some genetic variations in cytochrome P450 2D6 increase the risk of developing tardive dyskinesia during metoclopramide therapy [11]. This paper was critically evaluated by Camilleri and Shin, who agreed that genetic variations are important in metoclopramide-induced tardive dyskinesia [12]. Cytochrome P450 2D6 genetics are important in the induction of tardive dyskinesia by metoclopramide [13]. Other risk factors for tardive dyskinesia include smoking [14], female sex, type 2 diabetes [15], and genetic polymorphism of D3, 5HT2A, and 5HT2C receptors [16]. The healthcare community should be aware that some patients may be more susceptible to the development of tardive dyskinesia.

There are at least two distinct populations of D2 receptors in the brain: postsynaptic and presynaptic. Postsynaptic receptors are involved in the transmission of signals from a dopaminergic neuron to the next neuron. Presynaptic D2 receptors regulate the synthesis and release of dopamine by dopaminergic neurons [17]. Inhibition of presynaptic D2 receptors increases the release of dopamine by dopaminergic neurons. This spillover of excess dopamine can cause the intracellular levels of free dopamine to increase inside the neurons. This spillover may lead to neuronal damage that is critical to tardive dyskinesia.

Free intracellular dopamine oxidizes spontaneously or as a result of the actions of mitochondrial monoamine oxidase and aldehyde dehydrogenase [18,19]. This oxidation forms oxygen radicals that damage the cell. Too much damage to the cell causes the death of dopaminergic neurons. The accumulation of this damage and cell death can lead to tardive dyskinesia. Even short-term use of D2 blockers causes damage to dopaminergic neurons. Repetitive short-term use of D2 blockers can result in cumulative damage, potentially leading to tardive dyskinesia. This cumulative effect has been observed in many patients treated with antipsychotic agents [2].

D2 receptor blocker therapy in schizophrenic patients increases the loss of dopaminergic neuronal transporters from the normal 5% per decade to 15% per decade [20], which may demonstrate increased neurodegeneration in these patients. Mitochondrial manganese superoxide dismutase is induced in patients suffering from tardive dyskinesia, suggesting an increased production of oxygen radicals that are detoxified by the enzyme [20].

Dopamine receptor blocking agents increase the turnover of dopamine, leading to oxygen radical formation [21]. Increased dopamine turnover is associated with increased tyrosine hydroxylase activity [22]. Tyrosine hydroxylase activity produces oxygen radicals [23]. Patients suffering from tardive dyskinesia demonstrate abnormal brain imaging in the striatum [8], which is an area with abundant dopaminergic nerve terminals. They also have elevated levels of lipid peroxidation products in the cerebral spinal fluid, a measure of oxidative stress [8].

Additionally, dopamine receptor supersensitivity appears to be involved in supersensitivity psychosis [24]. This phenomenon may be important in the relapse of psychosis and treatment-resistant psychosis.

2. Conclusions

Tardive dyskinesia is the result of damage to the brain caused by D2 receptor blocking drugs [24]. This damage can be cumulative and results in the involuntary movement of various muscles. Damage can also be cumulative with the use of multiple D2 receptor-blocking drugs. When a D2 receptor-blocking drug is stopped and later resumed, there is a possibility of cumulative damage. There are currently no D2 blockers on the market that do not block presynaptic D2 receptors. In the

future, D2 blockers could be developed that do not block presynaptic receptors. These drugs may be safer than drugs currently available.

The FDA recommendation should advise for the shortest effective use of D2 blockers for nausea and recommend against consistent use of such drugs for periods of up to twelve weeks. The FDA should also advise against repetitive, intermittent use of these drugs. The use of antipsychotic drugs should also be for a limited duration to avoid induction of tardive dyskinesia. The doses of these drugs should be kept as low as possible.

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