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Review Article

VMAT2 inhibitors for the treatment of tardive dyskinesia

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ABSTRACT

Tardive dyskinesia (TD) is an often disabling hyperkinetic movement disorder caused by exposure to dopamine receptor blocking agents. Although initially thought to most commonly occur with typical antipsychotics, the incidence is likely similar with atypical antipsychotics and antiemetics such as metoclopramide. Increased prescribing of these agents as well as low rates of remission have contributed to a rising prevalence of TD. Although this condition was described nearly 60 years ago, it is only within the past year that two novel therapeutic agents were FDA approved. Characterization of the VMAT2 inhibitor tetrabenazine, which was identified as a therapeutic agent for TD in older clinical trials, has yielded two distinct pharmacologic strategies to optimize response. The first strategy, used to create deutetrabenazine, employed deuterization of tetrabenazine to stabilize the pharmacokinetics and eliminate high peak plasma levels. The second strategy was the creation of a prodrug, valbenazine, for the two most active isoforms of tetrabenazine that also resulted in more stable pharmacokinetics and eliminated peak plasma levels. Both agents have been demonstrated to be effective and safe for the treatment of TD in multicenter, controlled trials and their development has led to a resurgence of interest in the characterization and treatment of this movement disorder.

1. Introduction

Tardive dyskinesia (TD) is a serious, often disabling, hyperkinetic movement disorder resulting from exposure to dopamine receptor antagonists, including both typical and atypical antipsychotics, as well as dopamine receptor blocking antiemetic agents such as metoclopramide [1,2]. Classical TD is characterized by abnormal involuntary jaw, face and lingual movements. Severe cases are associated with difficulty speaking, chewing and swallowing, and tongue mutilation. TD can also cause choreiform movements of the limbs, pelvic dyskinesia, and respiratory dyskinesia leading to alternating hyper- and hypoventilation that can be life threatening [2,3]. Other types of movements such as dystonia, myoclonus, tics and stereotypies can also be seen and may be even more disabling [4,5]. In some literature the term Tardive Syndrome (TS) is used to reflect the broad spectrum of delayed-onset, persistent phenomenology resulting from chronic dopamine receptor blocking exposure, but TD is also often used in this manner. For the purpose of this chapter we will use the term TD and the use of classical TD will be more specific for the orobuccolingual dyskinesia.

TD prevalence in neuroleptic exposed populations is thought to be about 30% [6]. A prospective cohort study estimated risk of developing TD for psychiatric patients on neuroleptics to be 5% per year, 25% after 5 years, 49% after 10 years, and 68% after 25 years [7,8]. The number of patients exposed to neuroleptics is believed to be increasing, based on federally reported prescribing data, and this is reflected on the increasing prevalence of TD being observed [2]. The greater use of neuroleptics in adults is to treat affective disorders and in children to treat behavior problems [9]. Even when the offending agent is withdrawn, remission rates are low and estimated to be approximately 13% [1,10,11]. The combination of increasing exposure and low remission rates has highlighted the urgent need to develop effective treatment strategies for TD. Although several off-label treatments have been studied for the management of TD since it's description in the 1950s [12], it is only within the past few years that multicenter trials have been performed and therapeutic agents have been submitted and approved by the Food and Drug Association (FDA) for this indication.

The identification of novel therapeutic agents has relied, in part, on developing an understanding of the pathophysiology of TD. Early data supported the hypothesis that TD was a consequence of D_2 receptor upregulation and supersensitivity related to chronic reduction of dopaminergic neurotransmission, primarily due to postsynaptic receptor blockade [13]. D_2 receptors are expressed on the medium-spiny neurons of the indirect pathway and are inhibitory. Therefore, D_2 receptor hypersensitivity has a net effect of disinhibition of the globus pallidus interna and the STN, leading to hyperkinesia [13]. Support for the hypersensitivity of D_2 receptors is derived from rodent models [14] and clinical observations of exacerbation of dyskinesia when dopamine receptor antagonists are withdrawn and inhibition of dyskinesias when

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dopamine blocking agent doses are increased [15]. PET study findings have been mixed with one study showing increased dopamine D2 receptor binding after long-term treatment with antipsychotics [16], and another showing that dopamine receptor binding was not correlated with severity of dyskinesias [17]. Post-mortem studies did not reveal a difference in the expression of D_2 receptors between patients with and without TD [17]. While striatal D_2 receptor hypersensitivity might be the initial manifestation of dopamine receptor blockage with antipsychotics and antiemetics, ongoing blockade is now believed to create other secondary effects on the plasticity of glutamatergic synapses of striatal interneurons. Aberrant glutamatergic signals to cortical structures that have impaired plasticity provides a rationale for poor remission rates even when the offending agent is discontinued [17].

While the pathogenesis of TD is still being elucidated, by the 1960s evidence that TD is related to increased dopamine signaling led to a search for agents that could modulate dopamine neurotransmission without directly antagonizing postsynaptic receptors. Ideally, such agents would not risk the development or worsening of TD. In the mid-1980s, integral membrane transporters were recognized as necessary to package neurotransmitters into synaptic vesicles of presynaptic neurons. A vesicular monoamine transporter (VMAT) was found to exist in 2 isoforms, with VMAT-1 expressed in the peripheral nervous system and VMAT2 expressed mainly in monoaminergic cells of the CNS. VMAT mediates rapid re-uptake of monoamines from the cytosol into the vesicles through ATP-dependent mechanisms that create a proton electrochemical gradient that promotes influx of neurotransmitters. VMAT can concentrate neurotransmitters by 100,000 fold compared to the cytoplasm to maintain a supply of releasable molecules during period of rapid nerve stimulation [18]. Inhibition of VMAT2 by drugs that bind directly to VMAT decreases the presynaptic uptake and release of dopamine and other monoamines by vesicles into the synapse thereby depleting vesicular and synaptic dopamine levels which, in turn, improves TD symptoms [19]. Three VMAT2 inhibitors are currently available for the treatment of TD: tetrabenazine, deutetrabenazine, and valbenazine (Table 1 summarizes the pharmacokinetic data of each).

2. Tetrabenazine

Tetrabenazine (TBZ) was developed initially in the 1950s as a possible antipsychotic [19]. It was not until 2008 that it was approved in the US, but the approval was for treatment of chorea in Huntington's disease. Nevertheless, because of its effectiveness in treating chorea, it was used off label for TD much earlier. In 1972, Kazamatsuri et al. reported the first clinical trial for the treatment of TD with TBZ. They chose TBZ as a therapeutic agent based on the supposition that if abnormal movements of TD result from overactivity of dopaminergic neurons, then abnormal movements should be suppressed both by drugs that exert a presumed blocking action at the dopaminergic synapse and by drugs that decrease release of synaptic dopamine. Given that dopamine blocking agents were known to cause TD, dopamine vesicular and synaptic depleting agents were deemed more appropriate for the treatment of TD. Of the two such agents on the market at the time, TBZ and reserpine, TBZ was preferred because of its VMAT2 selectivity, shorter duration and reversible action on VMAT, relative lack of hypotensive side effects, and less severe depressive effect [20].

Among movement disorders specialists, TBZ has been considered the treatment of choice for moderate to severe TD. However, only two small blinded trials have been conducted and reported to evaluate the efficacy of this medication. In the initial aforementioned study by Kazamatsuri et al., 24 patients with psychiatric disease on the chronic wards of Boston State Hospital were enrolled in a placebo-controlled, double-blind trial. In this blinded cross-over design, all patients were observed over a 4-week baseline period, a 4-week placebo period during which neuroleptics were completely withdrawn, a 6 week tetrabenazine trial while off neuroleptics, and then crossed back over to placebo for 2 weeks again while maintained off neuroleptics. The primary outcome measure was the mean frequency of dyskinetic movements per minute as calculated by a blinded rater. At the end of the sixth week of TBZ at doses of 100–150 mg/day, dyskinesia resolved in 8 patients (33%), was markedly reduced in 6 (25%), and slightly decreased or was unchanged in 6 patients. Four patients did not complete the study: two developed severe malaise and were withdrawn, one withdrew because of a “psychotic exacerbation”, and one left the ward and was not available for follow-up observation. Paired *t*-test revealed a significant decrease of TD movements by 60% on TBZ when compared to placebo [20]. The second trial was reported in 1999. Ondo et al. (Table 2) enrolled 20 patients in an open-label study with up to 150 mg TBZ. Mean scores on the blinded videotaped Abnormal Involuntary Movement Scale (AIMS) assessment improved by 54% ($p < 0.0001$). Eleven patients rated themselves as markedly improved, 6 as moderately improved, and 2 as mildly improved. One patient withdrew from the study because of sedation [21]. Two retrospective reports further supported the efficacy of TBZ for the treatment of TD [22,23]. A retrospective chart review of 149 TD patients on TBZ revealed a high frequency of adverse effects, including drowsiness (25%), parkinsonism (15.4%), depression (7.6%), and akathisia (7.6%) [22]. Suicidality has also been reported and is a serious adverse effect of TBZ [24]. The frequency and severity of these adverse effects has limited the routine use of TBZ for TD [25].

Though at the time of the initial studies the mechanism of action was unknown, TBZ is now recognized to be a VMAT2 inhibitor, which is the mechanism by which it blocks reuptake of monoamines into vesicles and decreases presynaptic dopamine release. TBZ is rapidly metabolized and converted into 2 isomers, α-dihydrotetrabenazine (DH-TBZ) and β-DH-TBZ, which have a high affinity for VMAT2 and are the pharmacologically active agents. These isomers are metabolized by the cytochrome P450 system, in part by the 2D6 isozyme. Because of the short half-life (Table 1) and existence of 2D6 polymorphisms, use of TBZ carries recommendations for 3 times daily dosing and for CYP 2D6 genotyping to screen for poor metabolizer status when exceeding 50 mg/day. High peak concentrations and plasma fluctuations of this drug are thought to contribute to the tolerability concerns that restrict its use (Table 1) [26]. These issues led to the development of two different pharmacologic strategies to moderate the metabolism of TBZ and improve tolerability.

Table 1
Pharmacokinetics of VMAT2 inhibitors.

	Tetrabenazine	Deutetrabenazine	Valbenazine
Starting dose	12.5 mg daily	12 mg	40 mg
Max total dose	50 mg	48 mg	80 mg
Dosing	TID	BID	Daily
C_{max}	1–2 h	3–4 h	4–8 h
Half life	5–7 h	9–10 h	15–22 h
Metabolism	CYP2D6	CYP2D6	CYP2D6

3. Deutetrabenazine

Deuterium is a nontoxic isotope of hydrogen. Due to its increased mass relative to hydrogen, deuterium forms a stronger bond with carbon that requires 8 times more energy to break than a carbon-hydrogen bond. While deuterated tetrabenazine (Deut-TBZ) retains the VMAT2 affinity of non-deuterated TBZ, the substitution of deuterium for hydrogen at specific positions prolongs its plasma half-life and reduces metabolic variability (Table 1). The longer half-life enables less frequent daily dosing (Table 1) with lower peak concentration, which is believed to result in an improved risk-benefit profile [27].

Deut-TBZ was first studied as a treatment for chorea in Huntington's disease. In a double-blind, placebo-controlled, parallel-group study, 90 patients were randomized to receive Deut-TBZ or placebo twice daily.