Introduction

Movement disorders are neurological conditions manifested either by slowness of movement, seen in Parkinson's disease, or abnormal involuntary movements, the so-called hyperkinesias (hyper: too much, kinesis: movement). The hyperkinesias are characterized by excessive, involuntary, repetitive, twisting or random jerk-like movements which may involve the face, limbs, or the entire body. One form of hyperkinesia is tardive dyskinesia, manifested typically by repetitive, chewing mouth and jaw movements. Repetitive (stereotypic) movements associated with tardive dyskinesia may also involve the trunk (rocking movements) and limbs. Tardive dyskinesia is caused by exposure to certain antipsychotics (medications used to treat hallucinations and disorders of thinking) or antiemetics (medications against nausea and vomiting). Although often transient, tardive dyskinesia may be permanent. Other examples of hyperkinesias include chorea (which means "dance" in Greek, and are brief, irregular, continuous jerky-like movements that randomly involve different muscles, as seen in conditions such as Huntington's disease), athetosis (subtle twisting and writhing movements often accompanying chorea, seen for example in cerebral palsy), ballism (large amplitude, flinging movements usually of one arm or leg, most commonly following a lesion, such as a stroke, in a specific region in the brain called the subthalamic nucleus), motor and phonic tics (typically associated with Tourette syndrome), dystonia (intermittent or sustained muscle contractions producing abnormal, often repeated, postures and/or movements), myoclonus (brief muscle jerks), stereotypies (constant repetition of certain gestures and seemingly purposeful coordinated movements such as seen in chewing movements of orofacial tardive dyskinesia or body-rocking movements in
children with autism), and akathisia (subjective feeling of "inner" restlessness and inability to stay still).

The neurochemical alterations underlying involuntary movement disorders are not well understood, but excess dopamine or increased sensitivity of dopamine receptors have been postulated to play a dominant role in many hyperkinetic movement disorders, particularly tardive dyskinesia, Huntington's disease and Tourette syndrome. The traditional antipsychotic or antiemetic drugs, also called neuroleptics, block dopamine receptors and are sometimes used to treat the various hyperkinetic movement disorders. However, these drugs carry the risk of tardive dyskinesia and, therefore, are not appropriate for the chronic therapy of movement disorders. Other drugs that act by reducing the dopaminergic transmission and thus ameliorate hyperkinesias include reserpine, tetrabenazine (TBZ; Xenazine), deutetetabenazine (DBZ; Austedo) and valbenzine (VBZ; Ingrezza). These drugs cause depletion of dopamine in the brain, but reserpine also causes dopamine depletion in the peripheral nervous system and therefore may cause low blood pressure, diarrhea and other adverse effects. The primary pharmacologic action of TBZ, DBZ and VBZ is depletion of dopamine in the central nervous system by inhibiting the human vesicular monoamine transporter isoform 2 (hVMAT2).

Tetrabenazine (TBZ)

In 1979, the Food and Drug Administration granted Dr. Jankovic Investigational Exemption for a New Drug, a special permission to use TBZ in various movement disorders. Since that time Dr. Jankovic and his colleagues at the Parkinson's Disease Center and Movement Disorders Clinic at Baylor College of Medicine have accumulated long-term experience with this drug in well over a thousand patients with a large variety of hyperkinesias. Data from double-blind, placebo-controlled trials conducted at Baylor and also as part of a large multicenter study (TETRA-HD) as well as longitudinal data based on observational experience at Baylor over the
past quarter century was submitted to the FDA. In December 2007, an independent advisory committee concluded that TBZ is effective and safe and unanimously recommended to the FDA an approval of TBZ (Xenazine) for the treatment of chorea associated with Huntington's disease, which was finally granted on Aug. 15, 2008. This approval was provided under the FDA's orphan products program, which is aimed at developing treatments for conditions affecting fewer than 200,000 people (Huntington's disease affects 30,000 people in the United States). Although not approved by the FDA yet, TBZ is also used to treat patients with Tourette's syndrome and tardive dyskinesia.

Although considered safe when appropriately administered and monitored, TBZ does have potential side effects, such as drowsiness, changes on electrocardiogram (prolonged QT interval), slowness of movement (parkinsonism), mood changes (depression), nervousness/anxiety and restlessness (akathisia). The labeling for TBZ draws special attention to potential depression and suicidality and recommended genotyping patients (for CYP2D6) to determine if they are slow metabolizers when dosage above 50 mg per day is prescribed (see package insert for additional precautions, contraindications and other prescribing information). The side effects of TBZ are reversible, meaning that they resolve with either dose reduction or drug cessation. Most importantly, there has been no documented cases of TBZ-induced tardive dyskinesia, and, therefore, this dopamine depleting agent has a distinct advantage over the dopamine-blocking agents (neuroleptics) in the treatment of a variety of hyperkinetic movement disorders. Combination of tetrabenazine with some other medications might cause potentially dangerous side effects so make sure your neurologist and other prescribing physicians are aware of all medications you are taking including over-the-counter drugs. If you have any additional questions about Xenazine, please call the Xenazine Information Center at (888) 882-6013.
Deutetrabenazine (DBZ)

DBZ is chemically similar to TBZ, except for the incorporation of deuterium (“heavy hydrogen”, a type of hydrogen with higher mass allowing for stronger chemical bonds), which makes the drug more resistant to metabolism by the human body. This creates several advantages compared to TBZ: steadier drug levels in the blood, lower peak concentration, lower doses and less frequent (twice daily vs three times daily) drug administration while maintaining the same relative effect. For these reasons, DBZ is felt to be better tolerated compared to TBZ. The mechanism of action and side effects of DBZ are the same as TBZ.

DBZ has been studied in several large trials, including several with participation of patients and clinicians at Baylor, involving patients with Huntington’s disease (FIRST-HD), Tourette syndrome and tardive dyskinesia (ARM-TD and AIM-TD). In the FIRST-HD trial, while reporting significant symptomatic benefit, less than a third as many patients as in TETRA-HD (TBZ) reported side-effects of sleepiness, difficulty falling asleep, fatigue and depression. Although this reaffirms the clinical experience that DTBZ may be better tolerated than TBZ, a direct comparison between the two studies/drugs should be avoided due to several differences in the study populations and how the studies were executed. Due to the body of evidence presented in FIRST-HD, DBZ received FDA approval in 2017 as a treatment for chorea in Huntington’s disease. Based on the positive results of ARM-TD and AIM-TD, DBZ further received FDA approval for the treatment of tardive dyskinesia in 2017. The drug currently being marketed for these indications by Teva Pharmaceutical Industries Ltd. under the trade name Austedo. Similar to TBZ, DBZ is also used off-label for Tourette’s syndrome and tardive dyskinesia. The side-effects of DBZ are similar to those of TBZ and similarly resolve upon dose reduction or drug withdrawal. DBZ has not been associated with tardive dyskinesia. DBZ is typically dosed as 6-24mg twice daily. If you have any additional questions about Austedo, please call Teva’s Shared Solutions at (800) 887-8100.

Valbenazine (VBZ)
VBZ is a purified prodrug of TBZ, meaning that it is metabolized (converted) into some of the same active substances as TBZ. Due to its pharmacological profile, VBZ is administered once daily compared to three times daily for TBZ, and is felt to be better tolerated than TBZ. The mechanism of action and side effect profile of VBZ are the same as TBZ and DBZ.

VBZ has been studied for the treatment of Tourette’s syndrome (T-Forward and T-Force GREEN) and tardive dyskinesia (KINECT-3 and -4). Since VBZ had been designated as a “breakthrough therapy” by the FDA in 2014, this helped pave the way for priority review of the drug when the results of KINECT-3, a multicenter, randomized trial, became available. This led to the FDA’s first ever approval of a drug for the treatment of tardive dyskinesia on April 11th, 2017. It is currently being marketed for this indication by Neurocrine Biosciences Inc. under the trade name Ingrezza. VBZ is also used off-label for chorea in Huntington’s disease and Tourette’s syndrome. The side-effects of VBZ are similar to those of TBZ and DBZ and similarly resolve upon dose reduction or drug withdrawal. VBZ has not been associated with tardive dyskinesia. VBZ is typically dosed as 80mg once daily. If you have any additional questions about Ingrezza, please call the INBRACE Support Program at (844) 647-3992.

Selected References


Additional Information

For further information about the manufacturing and distribution of these medications, visit Xenazine® (www.xenazineusa.com), Austedo® (www.austedo.com), and Ingrezza® (www.ingrezza.com).

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