

The Use of Tetrabenazine in Movement Disorders

Introduction

Tetrabenazine (TBZ) is a relatively safe and effective treatment for a wide variety of hyperkinetic movement disorders, particularly tardive dyskinesia (TD) and chorea. It has been subject to a number of studies including double blind placebo controlled crossover trials, although there have been no randomised controlled trials and no studies in patients with pre-existing depression.

The mechanism of action of tetrabenazine

TBZ is a synthetic benzoquinolizine derivative¹ which binds to vesicular monoamine transporters (VMATs). Monoamines are concentrated from the cytoplasm into vesicles by VMATs (Figure). The transporters exchange protons for monoamines, using a proton electrochemical gradient generated by a vacuole ATP-dependent H⁺ pump.^{2,3} Many compounds bind to VMATs but three drugs bind selectively: TBZ, reserpine (from the Indian *Rauwolfia* plant) and ketanserin.⁴ Two human isoforms of VMAT exist and have been cloned; VMAT₁⁵ and VMAT₂.⁶ VMAT₂ is located predominantly in the brain and in sympathetic neurones, and VMAT₁ in peripheral endocrine and paracrine cells.⁷ TBZ binds with high affinity to VMAT₂ but with low affinity to VMAT₁.⁸ Reserpine binds with different characteristics and, on the basis of displacement studies, it has been proposed that they bind to the same site on the VMAT but to different conformations.⁹ Reserpine binds irreversibly whereas TBZ displays reversible binding. TBZ thus inhibits the uptake of monoamines into synaptic vesicles and so diminishes their output at synapses.

TBZ additionally blocks postsynaptic dopamine receptors.^{10,11} Despite this, there have been no reports of TD, thus conferring significant advantages over neuroleptics in the treatment of hyperkinetic movement disorders.

Pharmacokinetics

TBZ has a low and erratic bioavailability and is metabolised by first pass metabolism.¹²

Clinical use and adverse effects

Indications

TBZ has been used in a wide range of movement disorders and more recently as a positron emission tomography (PET) ligand.^{13,14,15,16}

Case reports and open label studies

Many case reports and open label studies have reported benefits of TBZ.^{17,18,19,20} For example, Ondo and colleagues in 1999, showed that scores on the Abnormal Involuntary Movement Scale (AIMS) were reduced by 54% in twenty patients with TD post TBZ administration.²⁶ Others, however, have described adverse effects, including oculogyric crises, retrocollis²¹ and neuroleptic malignant syndrome.^{22, 23, 24}

Retrospective studies

A recent, retrospective study showed that TBZ was moderately effective for a large variety of hyperkinetic movement disorders and highly effective for Huntington's disease (HD) chorea, and patients with facial dystonia and dyskinesia.²⁵ A retrospective chart review was conducted in three tertiary care centres and 118 patients were followed up for a mean of twenty-two months with the Clinical Global Impression of Change (CGIC) scale used to assess response to TBZ.

Cross-over studies

Several placebo controlled cross over studies have been described. McLellan, Chalmers and Johnson²⁷ in 1974 published the first double blind crossover trial of TBZ, thiopropazate and placebo, using ten patients with chorea, nine of whom had HD. Each phase of treatment lasted two weeks and assessment was clinical, cinematographic (videos watched by eight neurologists) and with manual dexterity tasks. The authors found that TBZ produced the most effective improvement of chorea. They noted that side effects could occur for the first time after several weeks of treatment.

Jankovic²⁸ in 1982 published a double blind crossover trial of TBZ versus placebo using nineteen patients with a variety of movement disorders. The trial design was similar and again, TBZ significantly reduced the patient's score on the hyperkinesia scale, particularly in patients with TD.

Long term data

Jankovic and colleagues have published open label long-term data on the use of TBZ.^{29,30} In the more recent larger study,²⁹ 526 patients were treated with TBZ and 400 analysed. Among those who were not analysed, seventeen discontinued TBZ within the first two weeks of treatment due to intolerable adverse effects and fourteen discontinued due to lack of efficacy. Most patients had been tried on a variety of other medication but their symptoms were poorly controlled. The drug was



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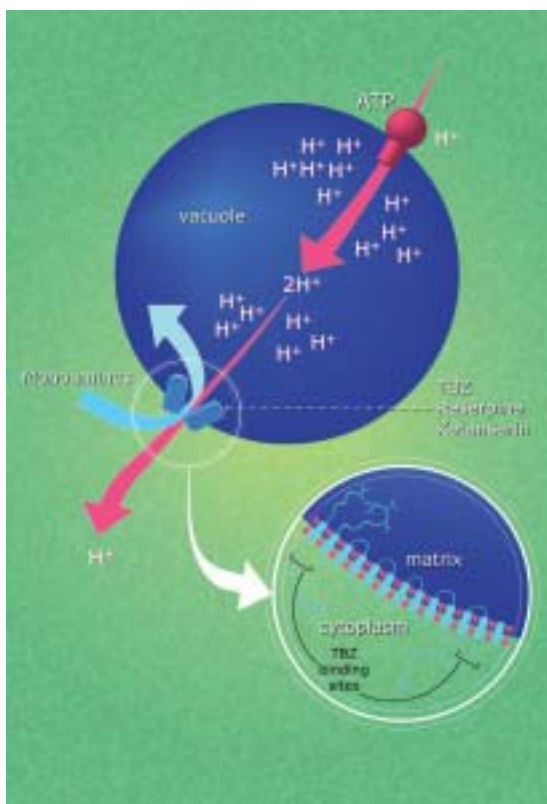


Figure: An ATP-dependent H⁺ pump on the vesicle membrane generates a proton electrochemical gradient. This gradient drives the entry of cytoplasmic monoamines into the vesicle via the VMAT (monoamine/2H⁺ exchange). TBZ binds reversibly and reserpine, irreversibly, to the VMAT, preventing the vesicular accumulation of monoamines. TBZ also blocks postsynaptic dopamine receptors. The VMAT has 12 transmembrane domains, with the C and N terminals in the cytoplasm, and three putative glycosylation sites in the vesicular lumen. TBZ binds to transmembrane domains I and II, and X and XII.

started at 25 mg once a day and increased until the movement disorder was controlled or adverse effects appeared. Most patients determined their long-term response within the first six weeks of treatment. Responses were graded on a 5-point scale, evaluated by the same neurologist, patient and relatives, 1 being an excellent response. Mean follow up was 28.9 +/- 31.1 months. Patients with TD responded best (89.3% with a grade of 1) although in all groups but the HD patients, the score had reduced slightly at the end of evaluation (e.g. to 84.9% in the case of TD). 82.8% of HD patients scored 1, as did 62.9% of dystonia patients; but patients with Tourette's syndrome responded least well (57.4% scored grade 1).

Side effects were common (81.8%) although this may have reflected the author's strategy of increasing the dose to the maximum recommended, or until side effects were experienced, or complete control achieved. 36.5% of patients experienced drowsiness, 28.5% Parkinsonism, 15% depression, 11% insomnia, 10.3% anxiety, 2.3% acute dystonic reaction and lesser numbers of side effects including confusion, orthostatic hypotension, and hallucinations. Seventy-three patients reported no side effects at all, and all the side effects were dose related, reversible upon reduction of the dose or cessation of the drug (which occurred in 23% of patients). Interestingly, lithium enhanced the action of TBZ in 67.6% of the thirty-four patients in whom it was tried.

Kazamatsuri, Chien and Cole¹⁷ noted in a long-term study in 1973, that the beneficial effect of TBZ may decline within a few days or weeks. Other long term studies have been published and, for example, shown benefit from TBZ with mild infrequent side effects.^{18, 25}

Use of TBZ in HD

Most of the published evidence has shown that TBZ significantly improves TD and the chorea in HD. Over 90% of patients with HD will display chorea at some stage of the illness, particularly in the early phase but other more disabling movement disorders are common, and tend to develop later in the illness, displacing chorea.³¹ The decision to treat chorea with TBZ must be balanced against the risk of developing more disabling Parkinsonism (albeit at high doses) and depression, both of which are common in HD. These effects can be ameliorated by TBZ withdrawal. Pragmatically, TBZ should be avoided in patients with pre-existing depression.

Anti-choreic medication, if indicated at all, should be tailored to the individual patient and antipsychotic medication, for example, may be a more appropriate choice in patients with concomitant psychiatric disorders.

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