Expert Consensus Postprint on Betahistine Mesylate for the Treatment of Vertigo

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Abstract

To standardize scientific medication for vertigo disorders, the Vertigo Professional Committee of the China Medicine Education Association specially established an expert panel. Based on incorporation of existing medical scientific evidence and combined with experts'rich clinical experience, the "Expert Consensus on Betahistine Mesylate in the Treatment of Vertigo" was developed through repeated deliberations. This consensus includes the pharmacological basis of histamine drugs and recommendations on medication recommendation grade, dosage, treatment course, follow-up methods, special population medication, and adverse drug reactions for betahistine mesylate in common vertigo diseases (such as benign paroxysmal positional vertigo, Ménière' s disease, vestibular neuritis, etc.), aiming to help physicians improve their clinical practice standards.

Full Text

Expert Consensus on Betahistine Mesylate in the Treatment of Vertigo

The Vertigo Committee of the Chinese Medical Education Association

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Abstract: To standardize scientific medication use in vertigo management, the Vertigo Committee of the Chinese Medical Education Association convened an expert panel to develop this Expert Consensus on Betahistine Mesylate in the Treatment of Vertigo. Based on existing medical evidence and enriched by the panel' s extensive clinical experience, this consensus was formulated through

repeated deliberations. The document encompasses the pharmacological foundation of histaminergic agents and provides recommendations on betahistine mesylate' s strength of recommendation, dosage, treatment duration, follow-up methods, special population considerations, and adverse drug reactions in common vertigo disorders (including benign paroxysmal positional vertigo, Ménière' s disease, and vestibular neuritis), aiming to enhance clinical practice standards.

Keywords: Vertigo; Benign paroxysmal positional vertigo; Ménière disease; Vestibular neuronitis; Betahistine; Clinical medication

Vertigo disorders exhibit high incidence but pose significant diagnostic and therapeutic challenges. In this context, no prior expert consensus has addressed rational vertigo medication use. Betahistine mesylate represents one of the most commonly prescribed agents for vertigo. The Vertigo Committee of the Chinese Medical Education Association has therefore focused on this widely used medication to promote standardized pharmacotherapy for vertigo, providing clinicians and pharmacists with essential information to improve rational prescribing and optimize medication management for vertigo patients. The consensus includes clinical recommendation grades and evidence levels, presented in and .

1. Consensus Development Methods

The Expert Consensus on Betahistine Mesylate in the Treatment of Vertigo was developed by the Vertigo Committee of the Chinese Medical Education Association. An expert panel was established to systematically review existing medical evidence, integrate extensive clinical experience, and formulate recommendations through iterative discussions. This consensus addresses the pharmacological basis of histaminergic agents and provides guidance on betahistine mesylate' s application in common vertigo disorders, including recommendation strength, dosing, treatment duration, follow-up protocols, special population considerations, and adverse effects, to support clinical decision-making.

2.1 Histaminergic Nervous System and Betahistine

Histamine is a neurotransmitter widely distributed throughout the body with diverse physiological activities. In the central nervous system, the tuberomammillary nucleus (TMN) of the hypothalamus contains a high concentration of histaminergic neuronal cell bodies, whose projections extend to nearly all functional regions, including the cerebral cortex, amygdala, striatum, hippocampus, substantia nigra, retina, and spinal cord. The TMN possesses an extensive projection and connection system ([Figure 1: see original paper]) that regulates multiple brain functions such as sleep-wake cycles, learning and memory, neuroendocrine processes, feeding behavior, and sensorimotor integration. Four histamine receptor subtypes have been identified: H1, H2, H3, and H4. In central neurons, H1, H2, and H3 receptors are all expressed. The H1 receptor is widely distributed in the neocortex, hippocampus, thalamus, hypothalamus, and amygdala, and its activation causes neuronal excitation. The H2 receptor primarily

regulates gastric acid secretion. The H3 receptor, located on presynaptic membranes, functions as an autoreceptor to negatively regulate histamine synthesis and release, and is also present on other neuronal terminals and certain cells to modulate the release of neurotransmitters such as GABA, norepinephrine, and acetylcholine.

Betahistine is a weak agonist of the histamine H1 receptor and a strong antagonist of the H3 receptor, with vasodilatory effects that improve brainstem and inner ear blood circulation, relieve vascular spasm, and reduce endolymphatic hydrops. Additionally, it exhibits antiplatelet aggregation properties and prevents thrombosis formation.

2.2 Relationship Between Histamine Receptors and Vestibular Function

Potential mechanisms by which histamine receptors influence vestibular function include: (1) central arousal level; (2) central histamine synthesis and release; (3) vestibular nucleus excitability; (4) vestibular nerve excitability; and (5) cochlear microcirculation. summarizes the distribution of histamine receptors in the vestibular system and related brain regions, their G protein coupling and downstream signal transduction pathways, cellular functional distribution, and potential mechanisms affecting vestibular function.

3. Pharmacological Highlights

3.1 Pharmacological Mechanism of Betahistine

Betahistine promotes vestibular compensation through multiple pathways ([Figure 2: see original paper]).

3.2 Differences Between Betahistine Mesylate and Betahistine Dihydrochloride

Commonly used betahistine formulations include betahistine mesylate (N-methyl-2-pyridineethanamine dimethanesulfonate; molecular formula $C8H12N2 \cdot 2(CH4O3S)$; molecular weight 328.41 g/mol) and betahistine dihydrochloride (N-methyl-2-pyridineethanamine dihydrochloride; molecular formula $C8H12N2 \cdot 2HCl$; molecular weight 209.12 g/mol), which contain different salt-forming groups. Compared with betahistine dihydrochloride, betahistine mesylate demonstrates relatively higher binding affinity to receptors (H1, H3) and greater gastric dissolution when administered postprandially. Both formulations share similar clinical indications, safety profiles, and adverse reaction patterns.

3.2.1 Receptor Binding Affinity The different salt-forming groups (ligands) in betahistine mesylate and betahistine dihydrochloride result in varying interaction strengths with receptors. Using the Z-Dock method to evaluate

molecular interactions between ligands (mesylate and hydrochloride) and receptors (H1, H3), betahistine mesylate exhibited superior performance in docking models with both H1 and H3 receptors.

3.2.2 Solubility at Different pH Values Due to the presence of hydrochloric acid in gastric fluid, non-hydrochloride salts (such as mesylate) are less susceptible to common ion effects than hydrochloride salts. From a drug solubility perspective, betahistine mesylate demonstrates higher solubility in pH 3-5 environments, where its solubility product (Ksp) is approximately 12.5 times that of the hydrochloride salt. This higher solubility may provide greater bioavailability. Consequently, betahistine mesylate shows enhanced dissolution in postprandial gastric fluid (when pH increases), resulting in improved efficacy compared with preprandial administration.

3.2.3 Pharmacokinetic Studies Betahistine mesylate exhibits a shorter time to peak concentration and longer elimination half-life (t1/2) compared with betahistine dihydrochloride.

3.3 Dose-Response and Duration-Response Relationships of Betahistine Mesylate

Clinical application of betahistine mesylate demonstrates excellent safety and efficacy, with a conventional daily dose of 18-36 mg. Specific dosing and treatment duration should be tailored according to the type of vestibular disorder, therapeutic objectives, and patient tolerance, with maximum doses reaching 108 mg. If patients show favorable response, treatment may be extended to 6 months or 1 year for vertigo prophylaxis. During long-term betahistine therapy, patient status should be evaluated monthly to monitor drug tolerance and adverse reactions. Clinical practice demonstrates dose-response and duration-response relationships, suggesting that increased dosage and adequate treatment duration may yield better clinical benefits.

4. Clinical Applications

4.1.1 Betahistine in Benign Paroxysmal Positional Vertigo (BPPV)

Recommendations: (1) For BPPV patients with chronic dizziness or residual vestibular symptoms following successful canalith repositioning; (2) For prophylactic treatment of recurrent BPPV. (Grade A recommendation)

According to China' s latest BPPV guidelines, canalith repositioning maneuvers constitute the primary treatment, while pharmacotherapy addresses potential inner ear damage from concurrent vestibular disorders associated with BPPV recurrence. This consensus specifically identifies betahistine for patients with residual symptoms post-repositioning.

Analysis of residual symptoms following successful BPPV treatment reveals that persistent dizziness, instability, and cervical discomfort are most common, with incidence correlating with the number of repositioning attempts. Numerous domestic and international reports demonstrate that betahistine reduces both the duration and severity of residual dizziness, either as monotherapy or in combination with other treatments.

Pre-treatment assessment: Recommended 1 week after initial treatment (repositioning maneuver). **Recommended evaluation methods:** Ocular vestibular-evoked myogenic potentials (oVEMP) when available (Grade B recommendation) and dynamic/static balance assessment (Grade B recommendation).

Post-treatment monitoring: Monthly assessment is recommended following medication initiation. Treatment should be discontinued when complete functional recovery is achieved (symmetrical oVEMP amplitudes, normalized modified sensory organization test results), symptoms fully resolve, or patients show no benefit (after 3 months of treatment) (Grade B recommendation).

4.1.2 Betahistine in Ménière' s Disease

Recommendation: For prevention of Ménière' s disease attacks. Conventional dose: 18-36 mg/d, maximum 108 mg/d. (Grade A recommendation)

Per China' s latest Ménière' s disease guidelines, the primary treatment goal during the interictal period is controlling or preventing vertigo attacks. Beyond patient education and lifestyle modifications, betahistine is the first-line pharmacological recommendation.

Notably, betahistine' s prophylactic effect in Ménière' s disease demonstrates dose- and duration-dependent effects, emphasizing high-dose, adequate-duration therapy (at least 2 tablets per dose, 3 times daily for 12 months), with the high-dose group showing the fewest attacks. If high-dose therapy proves ineffective after 3 months, dosage may be increased to ultra-high levels (20-30 tablets daily). However, the authors' latest dose-finding randomized double-blind study demonstrated significant disease control after 9 months, independent of dosage. Nevertheless, animal studies confirm dose-dependent increases in cochlear stria vascularis blood flow with betahistine. Therefore, adequate-duration therapy (assessment every 3 months, 3-9 months) receives Grade A recommendation, while high-dose therapy receives Grade B recommendation due to conflicting evidence.

Pre-treatment assessment: Recommended before initiating maintenance oral therapy in patients experiencing attacks despite baseline treatment (patient education and lifestyle modifications). **Recommended evaluation methods:** Caloric testing and head impulse test (Grade B recommendation); vertigo attack scales (select simple, convenient tools) (Grade B recommendation); dynamic/static balance assessment (Grade B recommendation). Electrocochleog-

raphy is not recommended for routine follow-up due to its invasive nature and complexity.

Follow-up: Reassessment every 3 months to evaluate treatment benefit. If no benefit is observed at 6-9 months, escalation to advanced therapies is recommended. With significant improvement and attack-free status for at least 6 months, dosage may be reduced to maintenance levels. All dose reductions or discontinuations should occur under physician supervision with appropriate evaluation.

4.1.3 Betahistine in Vestibular Migraine

Recommendation: Given current understanding limitations, betahistine is primarily used for: (1) Symptom control during attacks; (2) Promoting vestibular compensation. (Grade B recommendation)

Vestibular migraine represents a common episodic vestibular syndrome, though betahistine' s therapeutic role remains controversial. The histaminergic system plays a crucial role in migraine pathophysiology, with antihistamine agents potentially preventing migraine progression through H3 receptor antagonism, reducing histamine levels and other neurotransmitter release. Betahistine' s multi-receptor pharmacology suggests potential efficacy, though randomized controlled trials are needed. Additionally, evidence indicates peripheral vestibular system damage during vestibular migraine attacks and functional imaging demonstrates central compensation processes similar to those following peripheral vestibular damage during interictal periods. Betahistine modulates peripheral vestibular input and promotes central vestibular compensation.

4.1.4 Betahistine in Vestibular Neuritis (Acute Unilateral Vestibulopathy)

Recommendation: Improves vertigo symptoms and activities of daily living. (Grade A recommendation)

Vestibular neuritis, or acute unilateral vestibulopathy, is a common acute vestibular syndrome. Treatment includes acute-phase vestibular suppressants, corticosteroids, and vestibular rehabilitation therapy (VRT). Betahistine combined with VRT facilitates central vestibular compensation following peripheral vestibular damage. Randomized, double-blind, controlled studies demonstrate that betahistine reduces recovery time for static posture, eye movements, spatial perception, and patient self-assessed stability compared with placebo, confirming its role in modulating vestibular tone imbalance at the vestibular nucleus level.

Randomized controlled trials show that betahistine mesylate (12 mg per dose, 3 times daily for 4 weeks) reduces vertigo symptoms by 70% from baseline, improves activities of daily living (ADL) scores, and promotes recovery of neuro-otological signs in vestibular neuritis patients. Regarding safety, the EudraCT

(2009-013702-14) study demonstrated good safety and tolerability with higher-dose betahistine (144 mg/d) over 4 weeks in vestibular neuritis patients.

4.1.5 Betahistine in Vascular Vertigo/Dizziness

Recommendations: (1) Improving cerebral blood flow; (2) Vestibular rehabilitation. (Grade B recommendation)

As a weak H1 receptor agonist, betahistine promotes arousal and dilates cerebral vessels to increase brain perfusion. As a strong H3 receptor antagonist, it increases histamine synthesis and release through H3 autoreceptor blockade. Multiple animal studies demonstrate that betahistine mesylate increases cerebral blood flow and improves vertigo symptoms in vascular vertigo/dizziness, with a regimen of 12 mg per dose, 3 times daily showing superior efficacy.

summarizes recommended betahistine applications across vertigo disorders.

4.2 Special Populations

4.2.1 Betahistine Mesylate in Elderly Patients

Elderly patients, particularly those with chronic hepatic or renal impairment, require dose reduction based on individual assessment.

4.2.2 Betahistine Mesylate in Pregnant, Lactating Women and Children

Currently, reliable references are lacking. Based on expert experience, pediatric use receives Grade C recommendation with Level V evidence. For pregnant and lactating women, betahistine is not recommended due to safety considerations.

5. Safety and Adverse Reactions

Recommendation: Both conventional and high-dose (108 mg/d) betahistine mesylate demonstrate excellent safety and tolerability in vertigo treatment, with low adverse reaction rates. (Grade A recommendation)

As a primary symptomatic treatment for Ménière' s disease and vertigo of other etiologies, betahistine exhibits favorable safety and tolerability with low adverse event risk, with some reports showing similar incidence to placebo. In a study of 2,254 cases, 26 patients (1.15%) experienced adverse reactions, including occasional (0.1%-5.0%) gastrointestinal symptoms such as nausea and vomiting, and occasional (0.1%-5.0%) allergic reactions such as rash.

In special populations, betahistine exposure during pregnancy carries risk of congenital malformations. A double-blind prospective randomized crossover study found that psychomotor effects following betahistine 72 mg per dose, 3 times daily were similar to placebo, suggesting good safety and tolerability for special populations such as drivers.

Betahistine mesylate is the most commonly used formulation in clinical vertigo management, though practice has lacked standardization. This consensus provides recommendations for common clinical scenarios to improve rational prescribing and standardize medication use for vertigo patients. Additionally, while controlling vertigo symptoms, the consensus emphasizes monitoring vestibular functional recovery as a key assessment parameter to guide treatment.

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Author Declaration: No conflicts of interest exist. This expert consensus aims to assist clinical decision-making by providing evidence-based frameworks and strategies, and does not carry legal authority. Physicians must select the most appropriate treatment based on individual patient circumstances. Adherence to these recommendations does not guarantee satisfactory outcomes in all cases.

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