

**A. INGREDIENT NAME:**

**BETAHISTINE DIHYDROCHLORIDE**

**B. Chemical Name:**

N-Methyl-2-(2-pyridyl)ethylamine dihydrochloride

**C. Common Name:**

Ger., Egypt, Greece, Neth, Switz, U. K. Serc. \*See file for various names in different countries.

**D. Chemical grade or description of the strength, quality, and purity of the ingredient:**

Quality Assay Tot. base (%): 98.965

**E. Information about how the ingredient is supplied:**

White to off white crystals, is odorless, crystals obtain from alcohol

**F. Information about recognition of the substance in foreign pharmacopeias:**

**G. Bibliography of available safety and efficacy data including peer reviewed medical literature:**

Seipel, J. H. and Meyer, J. S. Dementia. *J Clin., I Pharm.* 1975;15: 144 & 1974; 14: 280.

Tighilet, B., Leonard, J. and Lacour, M. Betahistine dihydrochloride treatment facilitates vestibular compensation in the cat. *Journal of Vestibular Research*, 1995; 5(1): 53-66.

Oostervald, W. J. Betahistine dihydrochloride in the treatment of vertigo of peripheral vestibular origin. A double-blind placebo-controlled study. *Journal of Laryngology & Otology*. 1984; 98(1): 37-41.

1998-3454B1-02-15-BDLO2

Petermann, W. and Mulch, G. Long-term therapy of Meniere's disease. Comparison of the effects of betahistine dihydrochloride and hydrochlorothiazide. *Fortschritte der Medizin*, 1982; 100(10): 431-435.

Fraysse, B., Bebear, J. P., and Dubreuil, C. Betahistine dihydrochloride versus flunarizine. A double-blind study on recurrent vertigo with or without cochlear syndrome typical of Meniere's disease. *Acta Oto-Laryngologica*, 1991; 490 (Suppl): 1-10.

Pfaltz, C. R. and Aoyagi, M. Calcium-entry blocker in the treatment of vestibular disorders. *Acta Oto-Laryngologica*, 1988; 460 (Suppl): 135-142.

Oosterveld, W. J. Effect of betahistine dihydrochloride on induced vestibular nystagmus: a double blind study. *Clinical Otolaryngology*, 1987; 12(2): 131-135.

#### **H. Information about dosage forms used:**

Scored tablets

#### **I. Information about strength:**

4mg in Canada

8mg in U. K.

#### **J. Information about route of administration:**

Orally

#### **K. Stability data:**

Melting point: 152° C to 154 C

Incompatibilities:

Acids

Acid Chlorides

Acid Anhydrides

Oxidizing Agents

#### **L. Formulations:**

#### **M. Miscellaneous Information:**



Database: Medline <1966 to present>

<1>

Unique Identifier

95227410

Authors

Tighilet B. Leonard J. Lacour M.

Title

Betahistine dihydrochloride treatment facilitates vestibular compensation in the cat.

Source

Journal of Vestibular Research. 5(1):53-66, 1995 Jan-Feb.

Abstract

Unilateral lesion of the vestibular system induces posturo-locomotor deficits that are compensated for with time. Drug therapy is currently used to improve the recovery process and to facilitate vestibular compensation. Betahistine dihydrochloride is an histamine-like substance that has been employed in vestibular pathology; it was found effective in many forms of vertigo and in vestibular-related syndromes. Investigations performed in animal models have shown betahistine-induced neuronal modulations in the vestibular nuclei complex and interactions with the H1 and H3 histamine receptors. Potentially, this substance is therefore capable to interfere with some recovery mechanisms and to improve the behavioral adaptations. But there is at present a total lack of data concerning the influence of betahistine treatment on vestibular compensation in animal models. The aim of this study was to understand the pharmacological activity of betahistine in the restoration of posture and locomotor balance functions in unilateral vestibular neurectomized cats. Posture recovery was assessed by quantifying the surface reaction of the cat's support as measured while standing erect on its four legs, at rest. Locomotor balance recovery was determined using the rotating beam test, by measuring the maximal performance (max. P.) of the cat and its locomotion speed regulation during the postoperative time period. We have compared the recovery profile and time course of these static (posture) and dynamic (equilibrium) functions in three groups of cats. Two experimental groups were treated at daily doses of 50 mg/kg and 100 mg/kg, respectively. Betahistine dihydrochloride was given orally until complete recovery of posturolocomotor functions. One untreated control group served as the reference. Results showed that postoperative treatment strongly accelerated the recovery process in both

treated groups, inducing a time benefit of around 2 weeks as compared to the controls. Maximum performance of the cats on the rotating beam as well as locomotion speed regulation were highly correlated to the postoperative development of the cat's support surface, indicating that compensation of the static vestibulospinal deficits conditioned the subsequent locomotor balance recovery. These behavioral data showed that betahistine dihydrochloride constitutes a useful drug therapy for the symptomatic treatment of central vestibular disorders in our animal model of unilateral vestibular lesion. Improvement of vestibular compensation under betahistine postoperative treatment, as evidenced here for the posture and locomotor balance functions, is discussed both in terms of aspecific effect (histamine-induced increase of the level of vigilance) or more direct action in the vestibular nuclei (histamine-induced rebalance of neuronal activity on both sides).

<2>

Unique Identifier

84113189

Authors

Oosterveld WJ.

Title

Betahistine dihydrochloride in the treatment of vertigo of peripheral vestibular origin. A double-blind placebo-controlled study.

Source

Journal of Laryngology & Otology. 98(1):37-41, 1984 Jan.

Abstract

A double-blind, cross-over, placebo-controlled study of betahistine dihydrochloride (12 mg, t.i.d.) was carried out in patients with vertigo of peripheral vestibular origin. Twenty-four patients completed the study, which consisted of two six-week treatment periods. The patients were diagnosed as suffering from Meniere's disease (15 patients), vertigo due to other (specified) causes (five patients), or vertigo of unknown origin (four patients). Patients were examined by the investigator at the start of the study and were re-assessed at three-weekly intervals. In addition, they recorded the nature, frequency and severity of their symptoms on diary cards. Both the incidence and severity of dizziness (the predominant presenting complaint) were found to be significantly reduced during betahistine treatment ( $p = 0.004$ ). The occurrence of nausea and vomiting was also significantly reduced during betahistine treatment ( $p = 0.014$  and  $0.036$ ).

respectively). There were no statistically significant differences in the results of audiometric or vestibulometric tests, or in the severity of tinnitus or deafness, between the two treatment periods. The overall comparisons of the two periods made by both the patients and the investigator were significantly in favour of betahistine (p less than 0.001). All diagnostic groups responded favourably to betahistine, confirming the efficacy of betahistine in the symptomatic treatment of peripheral vestibular vertigo. No unwanted signs or symptoms were reported.

<3>

Unique Identifier

82165791

Authors

Petermann W. Mulch G.

Title

[Long-term therapy of Meniere's disease. Comparison of the effects of betahistine dihydrochloride and hydrochlorothiazide]. [German]

Source

Fortschritte der Medizin. 100(10):431-5, 1982 Mar 11.

Abstract

During the last few years betahistine-dihydrochloride has been used extensively in the conservative treatment of M. Meniere. The question has arisen as to whether betahistine-dihydrochloride is more effective than diuretics. The effect of betahistine-dihydrochloride was compared to that of hydrochlorothiazide on 32 M. Meniere-patients. The patients were initially kept under observation for 3 months without medication apart from symptomatic anti-vertigo agents. The patients were then assigned to 2 groups each of 16 subjects and received either 3 X 8 mg betahistine-dihydrochloride or 3 X 25 mg hydrochlorothiazide for 6 months under double-blind conditions. Before and during treatment subjective symptoms such as vertigo, attacks of dizziness, tinnitus, sensation of blockage in the ear and general well-being were assessed at 4-weekly intervals. Apart from this the objective symptoms as measured by pure tone audiograms, Frenzel-test and electronystagmography were recorded. At the moment betahistine-dihydrochloride seems to be the drug of choice for Meniere-patients with a fluctuating auditory threshold. During the 6 months treatment period an impressive reduction in the frequency, severity and duration of the attacks of vertigo as well as an improvement in the general condition was found in all patients. In contrast the

diuretic hydrochlorothiazide seemed to show a distinct therapeutic effect on vertigo and general well-being principally during the first few months of treatment in patients with a constant auditory threshold.

&lt;4&gt;

Unique Identifier

92108928

Authors

Frayse B. Bebear JP. Dubreuil C. Berges C. Dauman R.

Title

Betahistine dihydrochloride versus flunarizine. A double-blind study on recurrent vertigo with or without cochlear syndrome typical of Meniere's disease.

Source

Acta Oto-Laryngologica - Supplement. 490:1-10, 1991.

Abstract

This study was designed to compare the efficacy and safety of betahistine dihydrochloride and flunarizine. All patients included in this multicenter, double-blind, randomized trial showed a specific pattern of vertigo, i.e. recurrent paroxysmal vertigo with or without the cochlear symptoms typical of Meniere's disease. Fifty-five patients were treated for 2 months (28 in the betahistine group and 27 in the flunarizine group). Analysis of intra-group symptom changes demonstrated a greater efficacy for betahistine. Statistically significant decreases in duration and severity of attacks, and in the presence of vegetative symptoms were seen in the betahistine group after the first and second months of treatment, whereas in the flunarizine group this was the case only at the end of the first month of treatment. Furthermore in the betahistine group, statistically significant decreases occurred for the other major criteria, including number of attacks, evidence of vestibular dysfunction, and presence of cochlear symptoms. Adverse effects were similar to those reported in previous studies of both products: stomach pains only with betahistine, and drowsiness, asthenia, and depression with flunarizine.

&lt;5&gt;

Unique Identifier

90125179

Authors

Cullen JR. Hall SJ. Allen RH.

Title

Effect of betahistine dihydrochloride compared with

cinnarizine on  
Source  
Clinical Otolaryngology  
Abstract

The effect of beta-histamine  
induced vestibular nystagmus  
chair, in 6 head positions  
slow acceleration  
Electronystagmography  
pretreatment control  
t.i.d. and cinnarizine  
duration of nystagmus  
No difference was  
pretreatment rotation  
greater than 0.05  
0.05) was seen in  
acceleration, and  
stop after treatment

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<5>

Unique Identifier  
89269630

Authors

Pfaltz CR. Aoyagi M.

Title

Calcium-entry blocker  
disorders.

Source

Acta Oto-Laryngologica

Abstract

Based upon the results  
in a series of 100  
objective vestibular  
observations during  
by means of calcium  
regress fairly well  
after betahistine  
therapy (TP). Clinical  
action of calcium  
based on the results  
which was carried  
chair. The most  
objective assessment  
vestibular response  
show a progressive  
depressive or  
flunarizine up  
those obtained in

Abular

, 1988.

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betahistine dihydrochloride and 15 mg cinnarizine. Patients were allocated at random to receive 2 tablets 3-times daily of one or other drug for 3 consecutive months before being crossed over to the alternative medication for a further 3 months. Severity of symptoms was assessed at 4-week intervals using the Clinical Global Impression scale and patients kept a record in a daily diary of the frequency and duration of attacks. Details were also recorded of any side-effects reported. The results were analyzed for 46 patients who completed the 6-month study period. Both drugs were shown to be equally effective in reducing the duration and severity of symptoms. Significantly fewer attacks of vertigo, however, occurred during betahistine therapy. Side-effects were the most common reason for dropping out whilst on cinnarizine (9 patients) and were complained of by 38 patients during the study (16 only when on betahistine, 19 only on cinnarizine, 3 whilst on both drugs). The most frequently reported were drowsiness or lethargy affecting 16 patients on cinnarizine and 7 on betahistine.



## **BETAHISTINE DIHYDROCHLORIDE**

### **Toxicity:**

Has caused asthma, drowsiness, lethargy, nausea, headache. Could cause eye and skin irritation, and inhalation should be prevented. Could cause recurrence of peptic ulcers due to its histamine-like activity.

Has been used to treat Meniere's disease.



## REFERENCES

1. Tighilet B, Leonard J, Lacour M. Betahistine dihydrochloride treatment facilitates vestibular compensation in the cat. *Journal of Vestibular Research* 1995; 5(1):53-66.
2. Oosterveld WJ. Betahistine dihydrochloride in the treatment of vertigo of peripheral vestibular origin. A double-blind placebo-controlled study. *Journal of Laryngology & Otology* 1984; 91(1):37-41.
3. Petermann W, Mulch G. [Long-term therapy of Meniere's disease. Comparison of the effects of betahistine dihydrochloride and hydrochlorothiazide]. [German] *Fortschritte der Medizin* 1982; 100(10):431-5.
4. Fraysse B, Bebear JP, Dubreul C, et al. Betahistine dihydrochloride versus flunarizine. A double-blind study on recurrent vertigo with or without cochlear syndrome typical of Menieres disease. *Acta Oto-Laryngologica - Supplement* 1991; 490:1-10.
5. Cullen JR, Hall SJ, Allen RH. Effect of betahistine dihydrochloride compared with cinnarizine on induced vestibular nystagmus. *Clinical Otolaryngology* 1989; 14(6):485-7.
6. Pfaltz CR, Aoyagi M. Calcium-entry blockers in the treatment of vestibular disorders. *Acta Oto-Laryngologica - Supplement* 1988; 460:135-42.
7. Oosterveld WJ. Effect of betahistine dihydrochloride on induced vestibular nystagmus: a double blind study. *Clinical Otolaryngology* 1987; 12(2):131-5.
8. Deering RB, Prescott P, Simmons RL, et al. A double-blind crossover study comparing betahistine and cinnarizine in the treatment of recurrent vertigo in patients in general practice. *Current Medical Research & Opinion* 1986; 10(4):209-14.