Betahistine hydrochloride in Ménière's disease

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Summary

A double-blind, placebo-controlled, cross-over clinical trial was performed to assess the effect of betahistine hydrochloride (Serc) in Ménière's disease. The diagnosis was based on paroxysmal attacks of rotational vertigo, with tinnitus, and a fluctuating sensori-neural deafness, together with the results of auditory and vestibular tests. Twenty-eight patients were admitted to the trial over 3 years. Twenty-two patients completed the trial. In total, they received betahistine 32 mg daily, for a period of 16 weeks, and placebo also for the same length of time, preceded in every case by a 4-week pre-treatment period. Daily symptom score cards were kept. There was a statistically significant improvement in favour of the drug with regard to vertigo, tinnitus and deafness. Vertigo was the most responsive symptom. No adverse reactions were observed.

Introduction

James Seymour (1951) described the functional significance of the stria vascularis in Ménière's disease, and suggested the pathological condition was a selective sclerosis of the stria capillary networks. He also showed that hydrops was a secondary reaction due to osmosis, and not to raised intra-labyrinthine pressure.

Hinchcliffe (1972) referred to the production of vasodilatation as a natural corollary to the belief that labyrinthine ischaemia is important in Ménière's disease. Thus a variety of vasodilator drugs have been used. These include nicotinic acid, β -pyridylcarbinol, buphenine hydrochloride, and cyclandelate, but none has been subjected to a double-blind, clinical trial.

Histamine is a well established drug in the treatment of Ménière's disease. It is not active when given orally and repeated parenteral administration is difficult. Betahistine was found during the search for an alternative drug which could be administered orally. Experimental studies have shown that it produces vasodilatation of the capillaries, arterioles and arterial venous arcades in the stria vascularis and spiral ligament (Martinez, 1972). The purpose of the

investigation was to assess the effect of betahistine on the symptoms of Ménière's disease in a double-blind, placebo-controlled, cross-over trial lasting 9 months.

Materials and methods

Patients

Twenty-eight patients with Ménière's disease were admitted to the trial. Diagnosis was based on paroxysmal attacks of rotational vertigo, tinnitus and fluctuating sensori-neural deafness. Nausea and vomiting with the attacks were common. Twenty-two patients, eleven male and eleven female, completed the trial. Their ages ranged from 28 years to 63 years (mean, 45) and the duration of illness from 2 years to 20 years (mean, 7). Six patients withdrew because they were unable to co-operate.

Full clinical, neurological, and cardiovascular examinations were carried out. In every patient the central nervous system was normal, neck movements full and adequate. Carotid impulses were equal and normal. Blood pressure was not significantly elevated, and there was no evidence of relevant atherosclerotic disease. Tympanic membranes, conductive hearing mechanism and eustachian tube function were normal. Audiological investigation included tuning fork tests, air and bone conduction audiometry, loudness balance and short increment sensitivity index (SISI). Vestibular analysis was by clinical balance tests, positional tests and caloric tests (bithermal at 30°C and 44°C). Radiology of the skull, internal auditory meati, and cervical spine, as well as haematology (haemoglobin and cell counts) and serology (Wasserman reaction) were carried out. Patients had to be capable of keeping simple score cards and all agreed to submit to the trial conditions.

Trial design

Betahistine was compared with placebo in a double-blind, cross-over trial lasting 36 weeks. After pre-treatment periods of 4 weeks on placebo, they entered, on a randomized and double-blind basis, a cross-over trial of four 8-week periods.

Betahistine was given in two of the treatment periods, and placebo during the other two periods.

Each patient was instructed on how to maintain the symptom score card. They were asked to record the severity of the vertigo, tinnitus, deafness, fullness in the ear, nausea and vomiting, on a four-point scale. The pre-treatment period allowed the investigator to be satisfied that the patient understood the scoring system, and helped to exclude placebo responders. All patients had symptoms on admission to the trial.

In addition to the score cards, the investigator maintained a record of symptoms as reported during each 4-week follow-up interview. The initial investigations were repeated at the end of the pre-treatment period, and after each 8-week treatment period.

Drugs and dosage

The tablets were 8 mg of betahistine and placebo tablets, identical in taste and appearance. Placebo was considered justified since the investigator could break the code if any unbearable relapse occurred. Patients took four tablets daily (two at 08.00 hours, one at 14.00 hours and one at 20.00 hours). No other drugs were given for Ménière's disease during the trial. A letter was sent to the patient's general practitioner, informing him of the details of the trial, and asking that no other medication be used without notifying the investigator.

Results

The trends in total score values were tested for statistical significance using Wilcoxon's signed ranked test. Tables 1 and 2 summarize the main results.

The most striking effect of betahistine is seen to be a considerable improvement of vertigo, judged both by the patients' score cards and by the clinical assessment of the investigator. Audiograms demonstrated an improvement of hearing due to betahistine, a finding which is once more supported by the patients' own scores. Finally, both tables reveal an improvement with respect to tinnitus. All these results are substantiated by statistical significance in favour of betahistine.

No adverse reactions occurred, and no statistically significant differences in heart rate or blood pressure were found between betahistine and placebo periods.

Discussion

Since Ménière's disease is episodic, results of drug therapy are difficult to interpret. The treatment periods of many trials have been too short (Elia, 1966; Hicks, Hicks and Cooley, 1967). This trial was designed to try to overcome this.

The assessment of symptoms by the investigator closely paralleled the patient's own record keeping. This confirms the results of Hommes (1972). No

TABLE 1. Summary of scores recorded by the patients

Symptom	Treatment means (average total score per patient per month)		Level of statistical significance (one-sided Wilcoxon Signed Rank Test)
	Placebo	Betahistine	
Vertigo	12.4	9.5	0.007
Tinnitus	21.3	19.5	0.04
Deafness	10.7	9.1	0.05
Vomiting	3.5	3.7	0.60
Fullness in the ear	3.2	3.6	0.70

TABLE 2. Summary of double-blind clinical assessment by the investigator

Symptoms	Number of patients			Level of statistical significance (one- sided Sign Test)
	Assessment for betahistine periods better than for placebo	Assessment for placebo periods better than for betahistine	Similar assessments for both treatments	
Vertigo	14	3	5	0.006
Tinnitus*	10	2	7	0.02
Deafness	7	1	14	0.04
Above three symptoms combined	15	5	2	0.02

* Three patients did not have tinnitus.

patient showed evidence of psychosomatic factors playing an aetiological role. A statistically significant difference has been demonstrated between betahistine and placebo, in the treatment of Ménière's disease. Vertigo responded best of all, but further specific audiological and vestibular studies will be valuable (Bertrand, 1971).

It is submitted that betahistine is now a proved, useful therapeutic agent in the treatment of Ménière's disease, especially in the control of vertigo.

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