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SHORT COMMUNICATION

High-dosage betahistine dihydrochloride between 288 and 480 mg/day in patients with severe Menière's disease: a case series

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Abstract The objective of this study was to evaluate the clinical benefit and the side effects of high dosages of betahistine dihydrochloride (288–480 mg/day) in patients with severe Menière's disease (MD). In this case series 11 patients with MD who had not responded sufficiently to a dosage of 144 mg/day of betahistine dihydrochloride were treated on an individual basis with daily dosages between 288 and 480 mg of betahistine dihydrochloride. The number of attacks per month and the side effects were monitored. Non-parametric tests were used for statistical analysis. As a result, the frequency and the severity of vertigo were significantly reduced in all patients. The side effects were mild, self-limiting, and did not require any change in the treatment strategy. Despite the considerable limitations of an observational study—in particular in MD—high dosages of betahistine dihydrochloride between 288 and 480 mg/day seem to be effective in patients who do not sufficiently respond to lower dosages. Moreover, such dosages are well tolerated.

Keywords Menière's disease · Betahistine dihydrochloride · Attacks of vertigo · High-dosage treatment

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Introduction

Menière's disease (MD) is clinically characterized by recurrent attacks of vertigo with hearing loss, tinnitus, and aural fullness [1]. It is presumably caused by an endolymphatic hydrops [2]. As it is the second most frequent cause of peripheral vertigo, it is often diagnosed and treated in specialized care settings [3–5]. Due to the recurrent and unexpected attacks, MD often poses a considerable burden to patients in their daily life [6, 7]. To date a variety of treatment options has been proposed [8], all of which aim to reduce the number of attacks and preserve vestibular and cochlear function. In an open trial, higher-dosage betahistine (48 mg tid) proved to be effective and well tolerated [9]. This has been confirmed by the safety surveillance data over the past 35 years [10].

Here, we report the findings of a retrospective analysis of patient data in which patients with severe MD who had failed to respond significantly to a long-term treatment with betahistine at a dosage of 144 mg/day were treated on an individual basis at higher dosages. The daily dosage of these patients was gradually increased to 288 mg or even up to 480 mg/day. The number of attacks and the side effects were regularly monitored during the treatment period in our outpatient dizziness clinic.

Patients and methods

In this retrospective analysis, 11 patients (4 females), aged 49–83 years (mean ± SD 67±11 years), with clinically definite MD according to the definition of the American Academy of Ophthalmology and Otolaryngology, Head and Neck Surgery [1] received a high dosage of betahistine dihydrochloride and were followed in our outpatient dizziness clinic. All suffered from severe MD and had a high number of attacks per month. They had been treated with betahistine dihydrochloride in increasing dosages for more than 12 months, but had not responded sufficiently to the accepted high dosage of 48 mg tid, i.e., 144 mg per day. Therefore, approximately every 3 months the dosage was further increased.

The results for these 11 patients who received between 288 and 480 mg of betahistine dihydrochloride per day are reported. All patients were followed on a regular basis in our dizziness clinic and also carefully monitored for side effects during quarterly visits (or phone/email contact) and routine laboratory testing (blood cell count, liver enzymes, electrolytes, creatinine, and TSH). The data were retrieved from the patient records and supplemented by a short telephone interview to collect the most recent information on the course of the disease. Statistical analysis was done using PASW statistics 18.

Results

Course of disease

Nine of the 11 patients had unilateral MD (six, right ear; three, left ear). Both labyrinths were affected in two subjects. The disease had lasted 4 to 12 years with a mean duration ± SD from onset of the first attacks of MD of 6.9 ± 2.8 years. The treatment period averaged 4.1 ± 1.4 years (n = 10, 1 missing record), and the daily dosage averaged 360 mg at the date of recording. Whereas patients reported 11.60 ± 10.39 (n =10, 1 missing) attacks of vertigo per month on average before starting the medication, 73% (n = 8) were free of vertigo within at least 1 month (median 7 months, maximum 44 months) before the interview. Figure 1 shows the proportion of patients with ongoing symptoms at the date of recording relative to the increasing dosage of betahistine. Some patients had been intermittently free of vertigo at varying dosages of betahistine in the past, but when relapses occurred, the dosage had to be increased again. At the time of recording the attacks of vertigo in one patient had resolved at a daily dosage of 144 mg; in 3 cases, at 288 mg of betahistine per day, in 2 more subjects, at 360 mg, and in 1 patient at 384 mg per day. Patient eight, who became free of vertigo

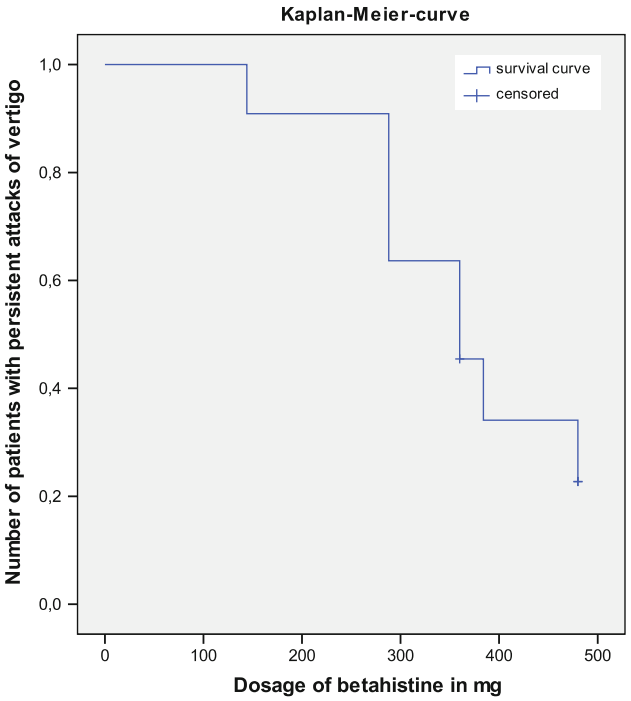

Fig. 1 Proportion of patients with persistent attacks of vertigo

at a dosage of 480 mg per day, was able to decrease the daily dose substantially to 288 mg without recurring episodes of vertigo. In one case (patient 10) the attacks of vertigo ceased at 144 mg per day, but the treatment dosage was further increased due to a severe bilateral hearing loss. Subsequently a moderate recovery of hearing was achieved, and the ability of verbal communication was preserved.

Side effects

Mild side effects including gastrointestinal complaints (n = 4), fatigue (n = 1), and altered taste (n = 1) were reported by 46% of the patients. It was not necessary to discontinue the treatment in any case. Routine laboratory testing identified one patient as having non-seriously elevated levels of gamma-glutamyltransferase (level 37 U/l normal range 6–28 U/l), possibly associated with the medication. The blood samples of three other subjects showed various pathologies (one had anemia and elevated levels of TSH, one had thrombocytopenia and monocytosis, and one had elevated levels of blood glucose, HbA1c, lactate dehydrogenase, alpha 1-microglobulin, and hyperlipidemia). These could with certainty be ascribed to the patients' concomitant diseases.

Concomitant diseases and co-medication

Table 1 shows the major concomitant diseases and co-medication of all the patients. Given the age of the patients,

Table 1 : Concomitant disease and co-medication

Patient	Sex	Age	Concomitant disease	Co-medication
1	m	51	PFO with brain stem stroke, allergic rhinitis, depressive disorder, hypothyreosis	L-Thyroxine, fluoxetine
2	m	63	COPD, atrial fibrillation, diabetes mellitus type 2 with polyneuropathy, reflux oesophagitis, hypertension, Hashimoto thyroiditis, diverticulosis, BPH, BPPV	L-Thyroxine, enalapril, amiodarone, phenprocoumone
3	f	77	Chronic cephalgia, diverticulosis, hypertension, strumectomy, breast cysts, chronic back pain	Metoprolol, mirtazapine, manidipine,
4	f	63	Diverticulitis, gastritis, hyperlipidemia, hysterectomy, ovariectomy, splenectomy, food allergies	Atorvastatin, bisoprolol
5	f	49	Vestibular migraine, food allergies, mammary carcinoma	None
6	m	79	Hypertension, glaucoma, anxiety disorder, RLS, polyneuropathy, essential tremor, DVT, BPH	Bisoprolol, amlodipine, irbesatane, HCT
7	m	76	Chronic anemia, hypothyreosis, femoral endoprotheses	L-Thyroxine
8	m	58	Hyperlipidemia, polyneuropathy, atrial fibrillation, hypophysectomy, sleeping disorder	Phenprocoumone, L-thyroxine, bisoprolol, hydrocortisone, testosterone, genotropine
9	f	68	Migraine, hyperlipidemia, multiple allergies	Metoprolol, HCT, atorvastatin
10	m	75	DVT, coronary heart disease, BPH, hyperlipidemia, hypertension, penicillin allergy	Ramipril, bisoprolol, phenprocoumone, simvastatin
11	m	83	Macroprolactinoma, primary hyperparathyreoidism, Parkinson's disease, chronic back pain	Atorvastatin, acetylsalicylic acid, L-dopa, esomeprazole, L-thyroxine + potassium iodide

m male, *f* female

there was a broad variety of co-morbidities and an array of co-medications.

Discussion

To date a broad range of therapies has been proposed for MD. However, the evidence of their benefit is still lacking for many [8]. This case series confirms that long-term high-dosage betahistine prophylaxis is a potent, safe, non-invasive, and systemic treatment option.

The major methodological limitations of this case series are obvious. There was no prospective and/or systematic approach, the number of patients was quite small, and the medication was individually adjusted not administered according to a standardized treatment plan. There was also no regular testing of cochlea function. Nevertheless, the results are promising.

As proposed earlier in an open trial [9] and in an ongoing placebo-controlled multi-center trial (EudraCT-Nr. 2005-000752-32), a high dosage and long-term treatment with betahistine proved again to be very effective in severe courses of MD. In 73% of the patients vertigo resolved completely. The remaining subjects reported considerably reduced frequency and severity of Menière's attacks. Although betahistine is thought to mainly affect vestibular symptoms [11], high-dosage betahistine positively influenced even cochlear function in one of our patients.

Considering the mean age of our subjects, the diversity of concomitant diseases and hence the variety of co-medication, it was imperative to pay special attention to the safety surveillance. No serious adverse events were documented; this agrees with prior work [10]. Almost half of our patients reported mild side effects, namely gastrointestinal complaints, fatigue, and altered taste. One patient had moderately elevated levels of gamma–glutamyltransferase, probably associated with betahistine. All of these side effects, except for altered taste, have been described previously [10]. They were mostly self-limiting and did not require any modification of the treatment strategy. In exceptional cases, we believe that betahistine might even be safely used in patients with contraindications [10] such as COPD/asthma (s. patient 2), provided the dosage is slowly increased and the clinical tolerance is carefully monitored.

In conclusion, very high-dosage and long-term treatment with betahistine dihydrochloride seems to be an effective treatment option for patients with severely progressing MD. It also has a good safety profile. However, further studies are needed for confirmation.

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