

ORIGINAL ARTICLE

## Antisecretory factor-inducing therapy improves the clinical outcome in patients with Ménière's disease

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### Abstract

**Conclusion:** Intake of antisecretory factor (AF)-inducing SPC-flakes<sup>®</sup> significantly reduced vertigo in patients suffering from Ménière's disease (MD). The positive effect may be due to a modulation of the transport of water and ions in the endolymphatic space. **Objective:** To evaluate the effects of a 3-month treatment period with SPC-flakes<sup>®</sup> in patients suffering from MD. **Patients and methods:** A prospective, double-blind, placebo-controlled study was performed. A total of 51 adult patients with MD were included in the study: 27 subjects treated with SPC-flakes<sup>®</sup> and 24 subjects with control cereals. The patients received SPC-flakes<sup>®</sup> or control cereals (1 g per kg body weight per 24 h in two servings) for 3 months. Otoneurological examinations were carried out before and after this period. **Results:** The severity of MD was classified according to the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) grading system. Fourteen of the 27 patients randomized to intake of the AF-inducing SPC-flakes<sup>®</sup> reported decreased vertigo, compared with 2 of 24 in the control group ( $p < 0.001$ ). No consistent change in the otoneurological examinations could be demonstrated in any of the groups of patients.

**Keywords:** Antisecretory factor, specially processed cereals, endolymph homeostasis, vertigo

### Introduction

Ménière's disease (MD) is characterized by recurrent episodes of rotatory vertigo associated with sensorineural hearing loss, tinnitus and a feeling of fullness in the affected ear. The specific cause (s) behind these symptoms are not known, but pathologic findings indicate the presence of endolymphatic hydrops by demonstration of a marked dilatation of the cochlear duct [1,2]. Histopathological findings in the endolymphatic duct and sac have suggested decreased absorptive capacity of the endolymph [1], although this does not seem to be the only cause of the hydrops. Furthermore, endolymphatic hydrops cannot solely explain the pathophysiology of cochlear and vestibular symptoms [3,4]. Thus, dysfunction of many structures of the inner

ear including the stria vascularis, the hair cells and neurons seems increasingly likely to be involved in the pathology of MD [5,6].

A variety of treatment modalities in MD have been tested, including surgical treatments, to reduce the endolymphatic hydrops [7]. The results indicate that impaired production or resorption of endolymph and/or transport across membranes are major factors in the pathophysiology of MD.

Antisecretory factor (AF) is a 41 kDa protein originally isolated due to its ability to inhibit experimental diarrhoea [8]. Endogenous AF activity is increased after exposure to bacterial toxins [8] and increased AF activity in conjunction with the immune system may be a part of the normal, innate defence against the secretory and inflammatory components of diarrhoeal diseases. AF activity can also

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(Received 8 February 2009; accepted 29 April 2009)

ISSN 0001-6489 print/ISSN 1651-2251 online © 2010 Informa UK Ltd. (Informa Healthcare, Taylor & Francis AS)  
DOI: 10.3109/00016480903022842

be increased by the intake of specific food components [9–12]. Thus, the intake of specially processed cereals (SPC-flakes<sup>®</sup>) results in an increase of AF activity in plasma [9]. Clinical studies have shown that intake of SPC-flakes<sup>®</sup> can improve the clinical outcome not only in patients suffering from diarrhoeal diseases, but also in patients suffering from inflammatory bowel diseases [8], endocrine diarrhoea [9] and mastitis [10]. The detailed mechanism of action of AF is not known, but AF appears to act as a modulator of water and ion transport [13].

As disturbances in the secretory processes may play a role in the pathophysiology of MD, we hypothesized that an increased AF activity could positively influence the course of the disease. Thus, we investigated the effect of intake of SPC-flakes<sup>®</sup> in 24 patients with severe MD in an open study [11]. The results demonstrated that the intake of SPC-flakes<sup>®</sup> not only significantly reduced vertigo in 12 of the 24 patients, but was also related to an increased level of active AF in plasma and a positive clinical outcome [11].

The objective of the present study was to test the validity of those promising results in a double-blind, placebo-controlled study on a larger group of patients with MD. The SPC-flakes<sup>®</sup> or placebo cereals were taken as a dietary supplement for a 3-month long experimental period.

## Patients and methods

### Ethics

The purpose and design of the study were explained to the enrolled patients before participation and written informed consent was obtained. The study was approved by the local ethical committee of Gothenburg University.

### Patients

A total of 51 patients with MD were included in the double-blind, placebo-controlled study, with 27 patients receiving SPC-flakes<sup>®</sup> and 24 patients receiving control cereals for a 3-month treatment period. The age, gender and duration of disease of the two groups of patients are shown in Table I. Of the placebo patients, 22 were treated in an open arm for an additional 3-month period with the SPC-flakes<sup>®</sup>.

### Study design

Male and female patients aged 12–80 years and with definite MD (see Clinical evaluation below) were consecutively included in the study. They were recruited from patients who were already being

Table I. Age and gender of the 51 patients participating in the study and the duration of their disease.

Cereals	Sex	Age: mean (range)	Disease duration: mean (range)
Placebo flakes	10 females, 14 males	56 years (41–72)	14 years (1–30)
SPC-flakes <sup>®</sup>	13 females, 14 males	57 years (12–79)	12 years (1–37)

treated at Sahlgrenska University Hospital. The study was run in a double-blinded fashion, with the study code kept secret at the Department of Audiology, Sahlgrenska University Hospital, until all data had been processed. The patients were randomized by lottery to receive either active treatment with SPC-flakes<sup>®</sup> or placebo consisting of cereals without AF induction capacity. At the clinic, the patients were given packages of cereals sufficient for a 3-month treatment period. The cereals were consumed together with milk twice daily as a dietary supplement, at a dose of 1 g/kg body weight/day. No changes were made in the patient's ordinary medication. The patients randomized to placebo were offered SPC-flakes<sup>®</sup> in an additional open arm of the study known to all patients before entering the study.

### Clinical evaluation

Clinical otoneurological status was determined and audiological tests including pure tone average (PTA) and speech audiometry were carried out 1 month before commencement of cereal intake. The same procedure was iterated after the 3-month diet period. The level, 1–6, of the patient's functional handicap was assessed according to the Gibson score [14], following the grading system set up by the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS), before and after the 3-month period of cereal intake. Electronystagmography and oculomotor tests had been performed previously in the patients.

### Statistics

The method for analysing systematic and random differences between paired ordinal data according to Svensson et al. [15] was used, the relevant measures here being relative position (RP: –1 to 1) and relative variance (RV: 0 to 1). RP describes the systematic shift in position; in this case, a negative value would mean that there was a systematic improvement, while a positive value would indicate a systematic deterioration. RV is a measurement of random shifts in position; a high value means that is a

lot of 'noise' in the system. In addition, Pearson's chi-square test was performed to compare the outcome in functional score for the groups consuming SPC-flakes<sup>®</sup> and placebo cereals, respectively.

## Results

### Double-blind arm

The AAO-HNS functional score for each individual patient before and after 3 months of the cereal diet supplement is shown for the placebo group in Figure 1 and for the group on SPC-flakes<sup>®</sup> in Figure 2. Patients with the highest initial AAO-HNS values are presented on the left-hand side of the figures, followed by data from patients with lower values on the right-hand side.

A decrease in the AAO-HNS value represents a positive effect of the diet supplement. In the placebo group, the AAO-HNS factor remained unchanged in 22 of 24 patients. In the two other patients, nos 9 and 18, the AAO-HNS factor decreased by 3 and 2 units, respectively (Figure 1).

In the group treated with SPC-flakes<sup>®</sup>, the AAO-HNS factor decreased in 14 of the 27 patients and remained unaffected in 13 patients (Figure 2). Six of the patients with the initial AAO-HNS factors of 5 and 6, the most severe symptoms, and eight of the others, reported decreased symptoms.

### Statistics

The RP for the placebo group was  $-0.092$ , with a standard error (SE) of  $0.0638$ ; this indicates that while there was a small tendency for the placebo group to improve, the results are not statistically significant. The RP for the group treated with SPC-flakes<sup>®</sup> was  $-0.3843$ , with an SE of  $0.0805$ ; this indicates that the improvement in this group was highly significant ( $p < 0.001$ ).

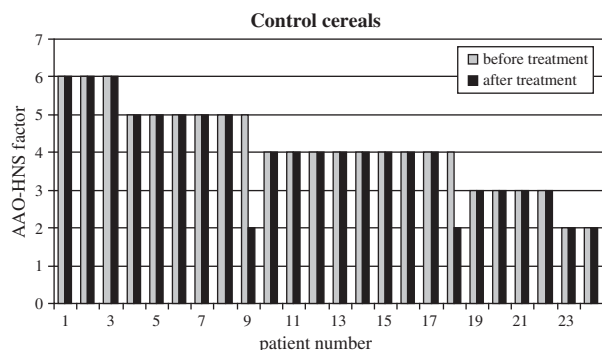


Figure 1. AAO-HNS factors for the patients ( $n = 24$ ) treated with control cereals. The grey and black lines represent the levels before and after, respectively, the 3-month period of treatment. The AAO-HNS factor decreased in 2 of the 24 patients.

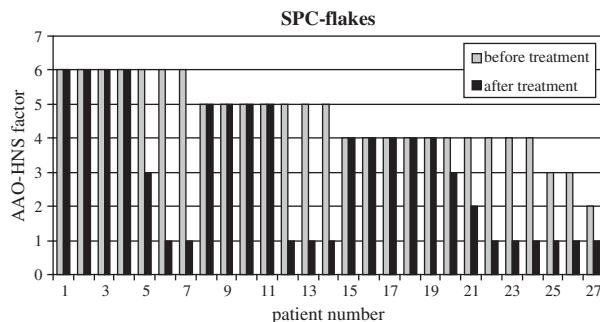


Figure 2. AAO-HNS factors for the patients ( $n = 27$ ) treated with SPC-flakes<sup>®</sup>. The grey and black lines represent the levels before and after, respectively, the 3-month period of treatment. In 14 of the 27 patients, the AAO-HNS factor decreased at the end of the treatment period.

The RV for the placebo group was  $0.0799$ , with an SE of  $0.0799$ , meaning that there is considerable individual variation in the response to the treatment. The RV for the group treated with SPC-flakes<sup>®</sup> was  $0.3215$ , with an SE of  $0.0895$  – again indicating a considerable variation in the effect of the treatment.

Pearson's chi-square test, comparing the outcome in the two groups, showed a statistically significant difference between the two groups ( $p < 0.001$ ).

### Open arm

After completion of the double-blind part of the study, 22 of the patients who had been randomized to placebo cereals chose to proceed with the intake of the SPC-flakes<sup>®</sup> for a further period of 3 months. In 17 of the patients, a decrease in the AAO-HNS factor was registered at the end of the treatment period, whereas in the remaining 5 patients no effect was seen (Figure 3).

### Otoneurological examinations

No consistent effect in the otoneurological examinations could be demonstrated in response to the dietary

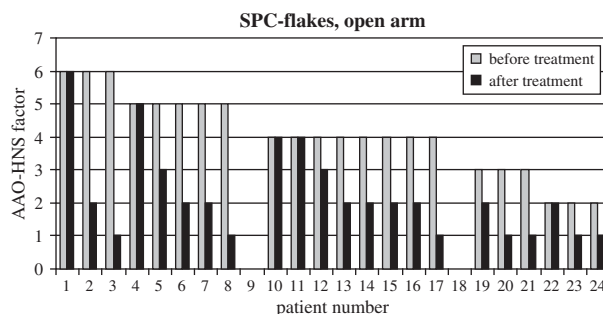


Figure 3. AAO-HNS factors before and after the 3-month treatment with SPC-flakes<sup>®</sup> in 22 patients, previously treated with control cereals. The grey and black lines represent the levels before and after the period of treatment, respectively.

treatment, and the PTA levels were unaffected in the majority of patients. The positive effect of the treatment with SPC-flakes<sup>®</sup> was thus mainly due to an effect on the vertigo component of the disease.

## Discussion

The present double-blind, placebo-controlled study shows that intake of AF-inducing SPC-flakes<sup>®</sup> can reduce vertigo in patients with MD. These results confirm the findings from a previous open pilot study [11]. The variability of clinical manifestations of MD has led to a search for objective tests for the disorder. The hearing test gives important diagnostic information, while there is no vestibular test that is uniformly positive in MD. The results of caloric vestibular tests in subjects with MD may vary considerably from decreased or no reaction to normal vestibular reaction in the same patient. For this reason, AAO-HNS [14] has recommended clinicians to report the patient's individual functional capacity and quality of life using factors 1–6, where factor 1 is a very mild disease while a patient with factor 6 is severely handicapped by the illness. Using this standard, 14 of the 27 patients randomized to intake of the AF-inducing SPC-flakes<sup>®</sup> reported decreased vertigo, compared with 2 of 24 in the group randomized to control cereals. However, no effect on the hearing ability was seen in either of the dietary groups.

The results thus show that about 50% of the patients experienced a reduced vertigo as a result of treatment with SPC-flakes<sup>®</sup>. A similar percentage of positive results has been reported in other studies on the effects of various regimes for treatment of MD [16], reflecting the complicated nature of the disease. The response to the SPC treatment was individual and appeared to be relatively independent of the severity of the vertigo. Thus, 6 of 14 patients with the most severe symptoms, with AAO-HNS factor 5 and 6, reported marked effect of the treatment, similar to 8 of the 13 patients with less severe symptoms.

After the double-blinded part of the study, patients who had been randomized into the placebo group were offered SPC-flakes<sup>®</sup> for a further 3-month long period of treatment. Seventeen of the 22 patients in this group responded favourably and reported decreased vertigo at the end of the treatment. Since this was an open, additional part of the study, these results are probably influenced by the expectations of the patients and also by a higher compliance.

The mechanism of action of AF is not well understood, but a number of experimental and clinical studies indicate that AF can normalize water and ion transport [13]. In this process, interaction with

the lipid raft protein flotillin-1 could be of importance [17], an interaction that may result in a down-regulation or re-organization of aquaporin channels. We have shown previously that AF and flotillin-1 are expressed in the inner ear of the rat [11], as well as in the human cochlea and endolymphatic sac [18]. The expression of AF in various cell types, facing the endolymphatic space, is compatible with a role for AF in the production and/or modification of the endolymph.

In summary, we have shown that the dietary intake of the AF-inducing SPC-flakes<sup>®</sup> significantly reduces vertigo in patients with MD. We suggest that AF is involved in the homeostasis of endolymph.

## Acknowledgements

Financial support was provided by the Göteborg Medical Society, the Swedish State under the LUA agreement (grant # 7157), Sahlgrenska University Hospital (grant # 8303) and the Magnus Bergvall Foundation. SPC-flakes<sup>®</sup> and control cereals were a gift from Lantmännen AS-Faktor AB. We thank Professor I. Bosaeus and Anders Starmark for statistical analyses, and I. Jonsson and K. Björnhammar for careful handling of patients and technical support.

**Declaration of interest:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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