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(54) **Title:** TREATMENT METHOD

(57) **Abstract:** A method of treating a human patient suffering from Eustachian tube malfunction comprising administering to said patient a nasal spray comprising an efficacious amount of betahistine. It has particular applicability to alleviate the symptoms of Meniere's disease in persons suffering from abnormal Eustachian tube function, but also has an applicability to beneficially improve vascular oxygenation of the inner ear.

Treatment Method

Technical Field

This invention concerns the improvement of a person's Eustachian tube function and improvement of vascular oxygenation of the inner ear by use of a betahistine nasal spray. It has particular applicability to alleviate the symptoms of Ménière's disease in persons suffering from abnormal Eustachian tube function, but also has an applicability to beneficially improve vascular oxygenation of the inner ear.

Background

Betahistine is a histamine-like drug administered orally for the treatment of endolymphatic hydrops, such as Ménière's disease. Its action is believed to improve blood supply to the inner ear and it has a possible effect of reducing sensitivity of the vestibular system.

Summary of Invention

In one aspect the invention provides a method of treating a human patient suffering from Eustachian tube malfunction comprising administering to said patient a nasal spray comprising an efficacious amount of betahistine.

In another aspect the invention provides a method of improving vascular oxygenation of an inner ear of a patient comprising administering to said patient a nasal spray comprising an efficacious amount of betahistine.

In another aspect the invention provides a method of a two way improvement of inner ear oxygenation of a patient, via the middle ear and vascular system, comprising administering to said patient a nasal spray comprising an efficacious amount of betahistine.

Preferably said efficacious amount is within the range 0.2 to 5.0 mg of betahistine in solution sprayed into each nostril. More preferably said efficacious amount is within the range 0.5 to 2.0 mg of betahistine in solution sprayed into each nostril. More preferably said efficacious amount is within the range 0.5 to 2.0 mg of betahistine in solution sprayed into each nostril.

Preferably said efficacious amount is sprayed into each nostril as a solution of betahistine in solution adjusted to pH 5.5.

Description of the Invention

Studies have found that around 15-20% of the oxygenation of the inner ear depends on the supply of oxygen via the middle ear. This suggests that good middle ear ventilation is crucial for inner ear function.

It has been found that for some patients with Ménière's disease showed improvement of Eustachian tube function while under betahistine medication. Similarly the insertion of a middle ear ventilation tube, which practically eliminates Eustachian tube dysfunction, can alleviate the symptoms of Ménière's disease. All patients in this category had an enlarged pupil on the side of the affected ear and showed an immediate further enlargement of the pupil when the body was turned against a steadied head, reflecting a functional disorder of the cervical spine. Cervical spine treatment by physiotherapy has shown to lessen Ménière's disease symptoms in these instances, resulting in some people claiming that Ménière's disease is nothing but a neck problem.

While betahistine might have no effect on Eustachian tube function in normal subjects, or might even worsen Eustachian tube function, the effect is different when an imbalance exists of the autonomic nervous system, particularly when the sympathetic is activated as can happen in functional disorders of the upper cervical spine and temporomandibular joints (Upper Quarter Syndrome). In this situation the imbalance of the autonomic nervous system, i.e. an activated sympathetic, reverses the betahistine effect resulting in improvement of Eustachian tube function. It is

achieved by altering the blood supply to the Eustachian tube and alteration of gland secretion.

An explanation for the unexpected beneficial effect of the present invention derives from the multi-step realization that Ménière's disease is, in many instances caused or exacerbated by reduced oxygenation of the inner ear, and that improving ventilation of the middle ear could sufficiently improve oxygenation of the inner ear, and that administering betahistine in a nasal spray could alter gland secretion sufficiently to facilitate Eustachian tube opening to allow sufficiently improved ventilation of the middle ear, which would in turn improve oxygenation of the inner ear and thus alleviate the symptoms of Ménière's disease.

In the invention the betahistine should be administered via a nasal spray. This has a number of advantages, among them, higher concentrations can be used than through oral administration (betahistine has been shown to be non-toxic in high concentrations). Topical application to the nasopharynx is directed to where action is required. Through nasal application betahistine quickly enters the blood stream without incurring the highly variable destruction which occurs in the stomach when administered orally. Improved oxygenation of the inner ear is achieved via the vascular system and improved middle ear ventilation.

The preferred administration rate is in the range 0.5 to 2.0 mg betahistine, as 4 to 8 mg/ml betahistine in solution, with an adjusted pH of 5.5, sprayed into each nostril three times daily. This may be achieved by spraying into each nostril one or two puffs, each of round 150 to 200 µl, of betahistine in solution at a concentration of 4 to 8 mg/ml. As betahistine is considered as non-toxic when administered at much higher levels, the invention envisages the use of much higher dosages of betahistine to fall within the scope of this invention, even though the increase may contribute to change of efficacy.

Whilst the above description includes the preferred embodiments of the invention it is to be understood that many variations, alterations and/or additions may be introduced

into the constructions and arrangements of parts previously described without departing from the essential features or the spirit or ambit of the invention.

It will be also understood that where the word "comprise", and variations such as "comprises" and "comprising" are used in this specification, unless the context requires otherwise such use is intended to imply the inclusion of a stated feature or features, but is not to be taken as exclusive the presence of other feature or features.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that such prior art forms part of the common general knowledge.

Claims

1. A method of treating a human patient suffering from Eustachian tube malfunction comprising administering to said patient a nasal spray comprising an efficacious amount of betahistine.

In another aspect the invention provides a method of improving vascular oxygenation of an inner ear of a patient comprising administering to said patient a nasal spray comprising an efficacious amount of betahistine.

2. A method of a two way improvement of inner ear oxygenation of a patient, via the middle ear and vascular system, comprising administering to said patient a nasal spray comprising an efficacious amount of betahistine.

3. A method according to claim 1 or 2 wherein said efficacious amount is within the range 0.2 to 5.0 mg of betahistine in solution sprayed into each nostril.

4. A method according to claim 3 wherein said efficacious amount is within the range 0.5 to 2.0 mg of betahistine in solution sprayed into each nostril.

5. A method according to any one of claims 1 to 4 wherein said efficacious amount is sprayed into each nostril as a solution within the range 4 to 8 mg/ml of betahistine in solution adjusted to pH 5.5.

INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/4402 (2006.01) A61K 9/08 (2006.01) A61P 27/16 (2006.01) A61P 11/02 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PATENW, HCAPLUS, MEDLINE, BIOSIS, EMBASE: betahistine, nasal spray, Eustachian, auditory, pharyngotympanic, ear, otologic, dysfunction, blockage, oxygenation, topical and related terms.

AustralianClinicalTrials, International Clinical Trials Registry Platform Search Portal: betahistine

eSpaceNet, PubMed: Franz Karl-Heinz Gunther, Karl-Heinz Gunther, Franz Lilian

Applicant & inventors' names searched in internal databases provided by IP Australia.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 May 2018	11 May 2018
Name and mailing address of the ISA/AU	**Authorised officer**
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INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/AU2018/000041**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/143572 A1 (THE UNIVERSITY OF MELBOURNE) 03 December 2009 See whole document, in particular abstract, page 3 lines 27-29, page 8 lines 9-15, page 5 lines 23-25, page 6 lines 13-17, page 7 lines 6-12, page 7 line 23 – page 8 line 4, page 9 line 29 – page 10 line 3, page 10 lines 28-31, page 11 lines 10-18 and page 12 lines 17-20.	1-5
X	OTIFEX THERAPEUTICS, "A Phase Ib, Randomised, Placebo-Controlled, Double-Blind Study to Evaluate Potential Benefits of Two Concentrations of Betahistine Dihydrochloride Spray Administered as a Single Intranasal Dose in Adult Male and Female Volunteers with Eustachian Tube Dysfunction", *World Health Organisation International Clinical Trials Registry Platform*, Registered 25 June 2015 [online], [retrieved on 8 May 2018] Retrieved from < http://apps.who.int/trialsearch/Trial2.aspx?TrialID=ACTRN12615000657527> See whole document, in particular Key inclusion & exclusion criteria, Intervention and Secondary Coutcome(s).	1-5
X	FRANZ *et al.*: "Topical application of betahistine improves eustachian tube function in an animal model" ACTA OTO-LARYNGOLOGICA, 2011, vol. 131, no. 11, pp. 1155–1159 See whole document, in particular abstract, page 1156 left column paragraph 1, page 1156 left column paragraph 3, page 1158 left column paragraph 6 – right column paragraph 1 and page 1158 right column paragraph 3.	1-5
A	BROOKES: "The pharmacological treatment of Meniere's disease" CLINICAL OTOLARYNGOLOGY AND ALLIED SCIENCES, 1996, vol. 21, no. 1, pp. 3-11 See whole document	

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/AU2018/000041**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		**Patent Family Member/s**	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
WO 2009/143572 A1	03 December 2009	WO 2009143572 A1	03 Dec 2009
		AU 2009253739 A1	03 Dec 2009
		AU 2009253739 B2	06 Feb 2014
		BR PI0912126 A2	03 Nov 2015
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		CN 102046170 B	28 Nov 2012
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		EA 022565 B1	29 Jan 2016
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		EP 2293794 B1	22 May 2013
		HK 1155387 A1	30 Aug 2013
		JP 2011520992 A	21 Jul 2011
		JP 5543963 B2	09 Jul 2014
		KR 20110022624 A	07 Mar 2011
		KR 101621726 B1	17 May 2016
		NZ 589742 A	29 Jun 2012
		US 2011166190 A1	07 Jul 2011
		US 8642631 B2	04 Feb 2014

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.