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(72) Inventor; and
(71) Applicant : **LÖFFLER, Bernd-Michael** [DE/DE]; Knesebeckstraße 68/69, 10623 Berlin (DE).

(74) Agent: **MÜLLER & SCHUBERT**; Neue Promenade 5, 10178 Berlin (DE).

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(54) Title: THERAPEUTIC GAS FOR THE TREATMENT OF MITOCHONDRIAL DISORDERS

(57) Abstract: The use of gaseous oxygen for the production of a therapeutic gas for inhalation by a patient who has been identified as a person with a mitochondrial disorder or a coenzyme Q10 deficiency, for the treatment of mitochondrial disorders or Q10 deficiencies is disclosed. For the first time a non-invasive method is disclosed, upon what the body's own level of Q10 can be raised significantly without further interventions.

Therapeutic Gas for the Treatment of Mitochondrial Disorders

The invention relates to the use of gaseous oxygen for the production of a therapeutic gas for inhalation by patients.

It is known that inhalation of oxygen-deficient air is used for the acclimatization of human bodies to high altitudes, particularly with regard to journeys of people to high mountain areas like the Himalayas or Tibet. But also athletes make use of this method which is known as altitude training to advance their physical ability in standard conditions.

The Interval-Hypoxia-Training (IHT) is a method of acclimatization to altitudes. In this process people inhale oxygen-deficient air (14 - 9% O_2) through a mask what initiates acclimatization activities in the body. Cyclical changes between oxygen-deficient air and ambient air make this altitude training highly efficient.

The Chronic fatigue syndrome (CFS) is a chronic disease which often causes invalidity. It is characterized by a paralyzing mental and corporal exhaustion/exhaustibility as well as by a specific combination of further symptoms. Beside chronic exhaustion, symptoms are, among others, headache, sore throat, joint and muscle pain, difficulties in concentration, disturbance of memory, less restful sleep, sensibility of lymph nodes as well as lasting debasement of fitness condition after exertion.

It is supposed, that CFS might be a result of mitochondrial disorders or oxidative stress, beside other unspecific diseases.

Oxidative stress is a metabolic status in which an amount of reactive oxygen species (ROS) is build or available, that is beyond the physiological levels. Those reactive oxygen species arise in line with metabolic processes of the mitochondrial electron transport chain and cytochrome-P_{50}-oxidases. These oxygen species are the peroxide anion radical O_2^-, hydrogen peroxide (H_2O_2) and hydroxyl radical OH (Schmidt R. F., e.a.: Physiologie des Menschen, Springer, 2007, p. 957 ff.).

Normal organism cells keep their ability to absorb reducing or oxidising substances alive by storing reserves of reducing or oxidising substances. An imbalance between these pools, which overcharges the normal function of repair and detoxication of cells and therefore causes a damage of all cellular and extracellular macromolecules, is called oxidative stress (David Heber, George L. Blackburn, Vay Liang W. Go, John Milner (Ed.): Nutritional Oncology. Academic Press, 2006. p. 314).

A possible treatment of this disease consists in application of Q10 (ubiquinone). Ubiquinone (also named UQ, coenzyme Q, CoQ, Q or coenzyme Q_{10}) is a quinone derivative with a lipophilic isoprenoid side chain, structurally related to vitamin K and vitamin E. The reduced phenolic form is called ubihydrochinone or ubiquinol (QH_2). Q10, coenzyme Q, is an essential vector of electrons and protons between complex I and complex II, respectively, and complex III of the respiratory chain.

Some deficiency symptoms of Q10 also appearing may have different reasons.

The current most known situation of reduction of Q10 by medication is administration of statines to decrease the

cholesterol level and LDL. The synthesis of mevalonic acid gets blocked, which is a collective junction for the production of cholesterol or Q10. Consequences for the patients are partly extensive: muscle pain, restricted walking distance comparable to intermittent claudication, general faintness, tiredness. They are generally not worked therapeutically with.

There is a raising amount of different indications known for lowered Q10, and for giving significant amendments by substitution of Q10 to "therapeutic" Q10 serum level. These are, among others, cardiac insufficiency, migraine, tinnitus. Further there are correlations between lower Q10 levels and cancer, Q10 and immune system and depressions.

The Q10 level is different in various organs and the highest levels are found in myocardial muscle cells. Q10 declines by raising age. Generally it is assumed that Q10 is no vitamin because the body is able to produce enough Q10 by self synthesis. But this is apparently in many situations not the case (e.g. chronic diseases), but also in "as healthy known probands" one can find extensive lowered levels of Q10, without an apparent external cause. The standard value of Q10 is 0.8 - 1.15 mg/l, the preventive medical rated range is > 1.4 mg/l, the therapeutic area is > 2.5 mg/l.

The object of the invention is providing means to medicate mitochondrial disorders and to elevate the concentration of Q10 in plasma of patients.

The object is solved by use of gaseous oxygen for the production of a therapeutic gas for inhalation according to the main claim.

Thus the object is solved by use of gaseous oxygen for the production of a therapeutic gas for inhalation by a patient who has been identified as a person with a mitochondrial disorder or a Q10 deficiency, for the treatment of mitochondrial disorders or the Q10 deficiencies.

According to the invention the use is preferred, in which the inhalation of the therapeutic gas is performed in at least two sections.

Especially preferred is the use according to the present invention wherein the concentration of the oxygen in the therapeutic gas has a different amount in the respective sections.

Especially preferred is the use according to the present invention wherein the concentration of the oxygen in the therapeutic gas is from about 15 Vol-% to about 9 Vol-%.

Especially preferred is the use according to the present invention wherein the concentration of the oxygen in the therapeutic gas is from about 30 Vol-% to about 55 Vol-%.

According to the present invention the use is especially preferred wherein the respective sections of inhalation last from 1 minute up to 60 minutes.

Furthermore according to the invention the use is especially preferred wherein the total time of inhalation lasts from 10 minutes up to 5 hours.

Also preferred is the use wherein the oxygen partial pressure in the patient is detected during inhalation.

Exceptionally preferred is the use wherein the mitochondrial disorder or the Q10 deficiency to be treated is as-

sociated with: cardiac insufficiency, arrhythmias, cardiac arrest, tinnitus, acute hearing loss, senile ablepsia, age-related macular degeneration, parodontitis, gingivitis, cancer, solid tumour, Attention Deficit/hyperactivity Disorder (ADHD), autism, Attention Deficit Disorder (ADD), parkinsonism, dementia, Alzheimer's disease, olfactory disorders, migraine, neuropathic pain, pruritis, asthma, chronic obstructive pulmonary disease (COPD), apnoea, dialysis, apheresis, incontinence, neurodermatitis, psoriasis, wound healing, type 2 diabetes, overweight, obesity, metabolic syndrome, multiple sclerosis, allergy.

An especially preferred use according to the present invention is to elevate or increase the plasma levels of coenzyme Q10 in a patient.

In other words, the main object of the invention is to provide a method for the treatment of a patient having mitochondrial disorders or coenzyme Q10 deficiencies, and that the method consists of administering a therapeutic gas to the patient, and that the therapeutic gas contains different levels of oxygen, forming either a hypoxic or a hyperoxic therapeutic gas that is administered to the patient in a regime, in which the level is changed from one section to the other from hypoxic to hyperoxic and back to hypoxic and so on.

The "Intermittent Hypoxia-Hyperoxia-Therapy" (IHHT), as it is called by the inventor, is a new therapy method that can be used for a wide range of diseases that are correlated with mitochondrial disorders and/or coenzyme Q10 deficiencies.

In the art there are methods known as intermittent hypoxia ("Intermittent Hypoxia: From Molecular Mechanism To

Clinical Applications"; Lei Xi and Tatiana V Serebrovskaja (Eds.) 2009 Nova Science Publishers Inc. New York). The main difference to known methods (Diving: Normoxia with Hypoxia and simultaneous Hypercapnia (elevation of CO_2 levels in blood); von Ardenne method: Normoxia Hyperoxia, method with ozone (Normoxia-Ozone); so-called Hypobaric Hypoxia: Hypoxia with simultaneous pressure reduction of the air to breath) is that a normobaric hypoxia (15 - 9% O_2) hyperoxia (30 - 55% O_2) method is used.

Furthermore, Hypoxia is described in the art as a dangerous principle as the method is compared to obstructive-sleep-apnoea (OSA). In contrast, OSA differs from IHHT, in that the intervals and the duration of Hypoxia sections are regulated.

Surprisingly it was found, that the concentration of Q10 raises in the blood of the patients, if cycles of inhalation of hypoxygenic and hyperoxygenic gases follow each other. Thereby it is advantageous to carry out these cycles several times following successively one after the other and thereby forming a session and repeating the complete session in predefined intervals.

For the first time a non-invasive method is disclosed, whereby the body's own level of Q10 can be raised significantly without further interventions or medications. Up to now it was only possible to elevate the plasma levels by administering Q10 orally or parenterally to a patient in need of such a medication.

By using cycles of inhalation of hypoxygenic and hyperoxygenic gases it is possible to elevate the plasma levels of Q10 in a patient up to the therapeutic range of 2.5 mg/l without any problem.

As the plasma level of coenzyme Q10 is believed to be highly related with many diseases of the heart, brain, eyes, lungs, bladder, kidneys, skin, nervous system, sense of hearing, and also with pain and cancer, it is a great advantage to elevate the plasma level in a patient without external administration of the coenzyme Q10. The body's-own production of coenzyme Q10 is stimulated by the inhalation of hypoxygenic and hyperoxygenic gases.

Further it was found that by a capable oral therapy with so-called "mitogen substances" (e.g. acetyl salicylic acid, vitamins, alpha liponic acid, minerals, Zn, Mn, etc.) the effect of the oral therapy with Q10 can be clearly amplified. Consequently, the same applies to the method of the invention so that co-medication with mitogen substances may be carried out.

It is apparent from the description of the invention that the levels of oxygen in the respective hypoxygenic and hyperoxygenic gases may be adjusted and easily optimized for a certain disease. It is possible for a skilled artesian to optimize those levels using the teaching of the present invention without deviating from the scope of the claims given herein.

The following examples explain the invention in greater detail.

Example 1:

18 test persons were chosen and concluded the test. The test persons get randomized after an initial check-up into a control group (N=8) and a treatment group (N=10).

Within three weeks all of the test persons graduated ten inhalation proceedings of 36 minutes in each case. The persons belonging to the control group respired ambient air through an air supply tube of the respiration apparatus (tube not connected), the treatment group respired for 6 minutes 12 Vol.-% O_2 , afterwards for 3 minutes 44 Vol.-% O_2. This cycle was repeated three times, so that altogether four cycles were completed, forming an inhalation session of 36 minutes. The lowest value for pCO_2 was defined to 80%.

After completion of the ten treatment units all test persons were examined again.

The inhalation was arranged by using an ordinary respiration apparatus. Analogous apparatus are known from the IHT. Those apparatuses were accordingly modified, so that next to hypoxygenic gases also hyperoxygenic gases with an oxygen content of 30 - 55 Vol-% can be ventilated.

Monitoring of oxygen partial pressure of the test persons blood was performed using a commercially available equipment as for example given in DE 92 08 590 U1.

The results of the collected physiological parameters of the test persons are presented in Table 1. The values of NPE (3-nitro phenyl acetic acid) and citrulline have been measured in the urine, the values for MMS (methyl malonic acid), Q10 (coenzyme Q_{10}), and Mito Act (mitochondrial activity) in the blood of the test persons.

Table 1

Para-meter		Control group			Treatment group			
		Mean	SD	pTT	Mean	SD	pTT	uTT
NPE	before	7,52	11,70	0,37	10,09	15,17	0,244	
	after	29,05	71,17		33,11	46,57		
Citrulline	before	5,89	3,39	0,94	8,29	9,59	0,845	
	after	5,38	6,05		7,59	4,46		
MMS	before	0,94	0,46	0,25	1,02	1,37	0,325	
	after	1,05	0,33		0,53	0,33		
Q10	before	0,78	0,26	0,02	0,96	0,31	0,000	0,23
	after	0,91	0,31		1,37	0,35		0,02
Mito Act	before	86,28	12,41	0,16	84,74	6,59	0,004	0,77
	after	94,03	5,14		94,57	4,31		0,84

Statistical analysis:

Mean: Mean value

SD: Standard deviation.

pTT: paired T-Test, 2-tailed for unequally variance of the groups within the groups for indicated values before/after treatment.

uTT: unpaired T-Test between treatment group and control group.

Example 2:

A patient showing symptomatic disorders caused by chronic borreliosis was treated 1 minute with 13 Vol-% hypoxia and 9 minutes with 38 Vol-% hyperoxia in 6 cycles forming a session of one hour duration.

A significant improvement of the skin structure and the aspect of the skin was achieved after 10 sessions. The improvement remained for about 3 months.

Claims

1. Use of gaseous oxygen for the production of a therapeutic gas for inhalation by a patient who has been identified as a person with a mitochondrial disorder or a coenzyme Q10 deficiency, for the treatment of mitochondrial disorders or coenzyme Q10 deficiencies.

2. Use according to claim 1, wherein inhalation of the gas is performed in at least two sections.

3. Use according to claim 1 or 2, wherein the concentration of the oxygen in the therapeutic gas has a different level in the respective sections.

4. Use according to any of the claims 1 to 3, wherein the concentration of the oxygen in the therapeutic gas is from about 15 Vol-% to about 9 Vol-%.

5. Use according to any of the claims 1 to 3, wherein the concentration of the oxygen in the therapeutic gas is from about 30 Vol-% to about 55 Vol-%.

6. Use according to any of the claims 1 to 5, wherein the respective sections of inhalation last from 1 minute up to 60 minutes.

7. Use according to any of the claims 1 to 6, wherein the total time of inhalation lasts from 10 minutes up to 5 hours.

8. Use according to any of the claims 1 to 7, wherein the oxygen partial pressure in the patient is measured during inhalation.

9. Use according to any of the claims 1 to 8, wherein the mitochondrial disorder or the Q10 deficiency to be treated is associated with: cardiac insufficiency, arrhythmias, cardiac arrest, tinnitus, acute hearing loss, senile ablepsia, age-related macular degeneration, parodontitis, gingivitis, cancer, solid tumour, attention deficit/hyperactivity disorder (ADHD), autism, attention deficit disorder (ADD), parkinsonism, dementia, Alzheimer's disease, olfactory disorders, migraine, neuropathic pain, pruritis, asthma, chronic obstructive pulmonary disease (COPD), apnoea, dialysis, apheresis, incontinence, neurodermatitis, psoriasis, wound healing, type 2 diabetes, overweight, obesity, metabolic syndrome, multiple sclerosis, allergy.

10. Use according to any of the claims 1 to 9, for the increase of the level of coenzyme Q10 in the plasma of a patient.

INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K33/00 A61P3/00
ADD.

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)
A61K A61P

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 practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Carol Hutner: "Oxygen therapy for mitochonfrial myopathy - Letter to the Editor", , 10 January 2002 (2002-01-10), pages 1-4, XP002622862, Retrieved from the Internet: URL:http://the-medical-dictionary.com/myopathy_article_6.htm [retrieved on 2011-02-16] the whole document ----- -/--	1,6,7,9

[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 document but published on or after the international filing date

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"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.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Estañol, Inma

INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Julie Koziol: "/International Symposium on Hyperbaric Oxygen Therapy Cutting Edge Forums and ideas for Brain Injury", South Florida Hospital News and Healthcare Report , vol. 1, no. Issue 1 27 July 2004 (2004-07-27), pages 1-2, XP002622863, Retrieved from the Internet: URL:http://southfloridahospitalnews.com/page/International_Symposium_on_Hyperbaric_Oxygen_Therapy_Offers_Cutting_Edge_Forums_and_Ideas_For_Brain_Injury/375/1/index.php [retrieved on 2011-02-16] the whole document	1,6,7,9
X	DAVE K R ET AL: "Hyperbaric oxygen therapy protects against mitochondrial dysfunction and delays onset of motor neuron disease in Wobbler mice.", NEUROSCIENCE, vol. 120, no. 1, 4 August 2003 (2003-08-04), pages 113-120, XP002622864, ISSN: 0306-4522 the whole document	1,6,7,9
A	US 5 792 090 A (LADIN DANIEL [US]) 11 August 1998 (1998-08-11) the whole document	1-10
A	WO 2008/131070 A1 (LADIZINSKY DANIEL A [US]) 30 October 2008 (2008-10-30) the whole document	1-10
A	US 6 479 533 B1 (YAROSH DANIEL B [US]) 12 November 2002 (2002-11-12) the whole document	1-10
A	WO 2008/086025 A2 (EDISON PHARMACEUTICALS INC [US]; MILLER GUY M [US]; SHRADER WILLIAM D) 17 July 2008 (2008-07-17) the whole document	1-10
A	US 2006/281809 A1 (MILLER GUY M [US] ET AL) 14 December 2006 (2006-12-14) the whole document	1-10

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/066288

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	SCATENA ROBERTO ET AL: "Mitochondrial damage and metabolic compensatory mechanisms induced by hyperoxia in the U-937 cell line", JOURNAL OF BIOCHEMISTRY AND MOLECULAR BIOLOGY, vol. 37, no. 4, 31 July 2004 (2004-07-31), pages 454-459, XP002622831, ISSN: 1225-8687 the whole document -----	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2010/066288

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5792090 A	11-08-1998	NONE	
WO 2008131070 A1	30-10-2008	EP 2136751 A1	30-12-2009
		US 2008262413 A1	23-10-2008
US 6479533 B1	12-11-2002	NONE	
WO 2008086025 A2	17-07-2008	AU 2008205263 A1	17-07-2008
		CA 2674368 A1	17-07-2008
		CN 101610782 A	23-12-2009
		EA 200900970 A1	30-12-2009
		EP 2101808 A2	23-09-2009
		JP 2010515736 T	13-05-2010
		US 2010056429 A1	04-03-2010
US 2006281809 A1	14-12-2006	US 2010222436 A1	02-09-2010