USE OF MIRTAZAPINE FOR TREATING SLEEP APNEAS

The present invention pertains to the treatment of sleep apneas. Sleep apnea is defined as the cessation of breathing during sleep. It comprises a spectrum of respiration-related disorders with varying severity and morbidity, involving periods, during sleep, in which airflow is disturbed. The usual classification of sleep apneas distinguishes obstructive, central, and mixed apneas, depending on the presence or absence of respiratory efforts during the periods in which airflow has ceased. In the case of the obstructive sleep apnea syndrome, which is the most familiar apnea, sporadic recurring collapse of the patient's upper airway occurs during sleep. If the collapse is complete, there is no air exchange at the nose and the mouth, and breathing is interrupted. The usual result is a partial arousal from sleep, and a return to normal breathing. The patient in most instances does not have any knowledge or memory of these apnea episodes, but finds himself constantly suffering from fatigue and daytime sleepiness for no apparent reason. These recurrent apnea episodes with resultant hypoxemia and fragmented sleep can have serious neurologic and cardiac consequences. While the obstructive sleep apnea is a physical blockade, central sleep apnea is defined as a neurological disorder, causing cessation of all respiratory effort during sleep, usually with decreases in blood oxygen saturation. The effects of both types of apneas are highly similar. Mixed apnea is a combination of the previous two. An episode of mixed sleep apnea usually starts with a central component and then becomes obstructive in nature.

The sleep apnea syndrome today is regarded as a serious problem, as it occurs widely, and there is a true lack of an effective treatment. Surgical and mechanical interventions have been suggested and tried as treatments, as has oxygen administration during sleep, but none of these are recognised to be very suitable. Pharmacological intervention has also been tried, but with little success. In fact, several kinds of respiratory stimulants, theophylline, antidepressants, and progestogens have been used to treat sleep apneas, but none of these has been found to be very effective.

CONFIRMATION COPY

It is an object of the present invention to provide an effective medicine against sleep apneas. To this end, the invention is a method for the treatment of an animal, for example, a mammal including a human patient, suffering from sleep apnea, comprising administering an effective amount of mirtazapine. The invention also involves the use of mirtazapine for the manufacture of a medicament for the treatment of sleep apnea.

Without wishing to be bound by theory, the applicant, with the hindsight of the unexpected effect of the invention, believes that it is the particular serotonergic profile of mirtazapine which is responsible for the efficacy against sleep apnea.

It should be noted that in a 1992 scientific publication (The Journal of Pharmacology and Experimental Therapeutics, Vol. 260 No. 2, pages 917-924), the pharmacological characterisation of the receptors mediating 5-HT (serotonin) - induced apnea has been investigated by studying the inhibitory effects of exogenous 5-HT on respiration and phrenic nerve activity in anaesthetised rats. This study supports the nowadays recognised potential importance of serotonin receptors in respiration, and indicates, int.al., that 5-HT and 2-methyl-5-HT provoked central apneas are antagonised by ondansetron (GR 38032 F), which is a selective $5HT_3$ antagonist.

The invention resides in the finding that an effective medicine against sleep apneas is provided on the basis of the compound mirtazapine. This compound displays a combined serotonergic antagonistic activity to the effect that it simultaneously is a combined 5HT2A, 5HT2C and 5HT3 antagonist. The invention in general pertains to the use of this compound for manufacturing a medicament for treating sleep apneas, Surpisingly, the compound is not only useful as a therapy against sleep apneas of the central type, but also against sleep apneas of the obstructive and mixed types.

Mirtazapine is known, e.g. from US 4,062,848. The compound containing a centre of chirality, it may exist as different enantiomers and enantiomeric mixtures. The present invention includes the use of any particular enantiomer alone, or in a mixture with one

or more steroiseomers, in any proportion including racemic mixtures. The present invention includes any salts of the compound, such as acid addition salts, for example, hydrochloric, fumaric, maleic, citric or succinic acid, these acids being mentioned only by way of illustration and without implied limitation. These compounds can be prepared in accordance with US 4,062,848, incorporated herein by reference.

In a preferred embodiment, the aforementioned compound is combined with a selective serotonin reuptake inhibitor (SSRI). SSRI's, and pharmaceutically acceptable salts thereof, are known and have been available since the early 1980s. They include zimelidine, fluoxetine and fluvoxamine. Other SSRI's are for example citalopram, ericlamine, femoxetine, ifoxetine, cyanodothiepin, sertraline, paroxetine, and litoxetine. SSRI's are known to the skilled person, and may be prepared by any method known in the art. For example, fluoxetine or pharmaceutically acceptable salts thereof, can be prepared in accordance with US 4,314,081, incorporated herein by reference.

A further benefit of mirtazapine, is that it also has antidepressant and anxiolytic properties, which helps to overcome secondary symptoms of which sleep apnea patients may suffer. Moreover mirtazapine improves the quality of sleep in general, which up to date has not been achieved with treatments of sleep apnea.

The compounds used according to the invention are to be administered in dosages of from 0,01 to 30 mg per kilogram body weight of the recipient per day, preferably in the range of 0,1 to 5 mg per kg body weight. In most instances, the preferred dosage of mirtazapine is 5 to 45 mg per day, and more preferably 15-30 mg. The SSRI dose may vary depending on the potency and efficacy of the specific active substance, but will generally be in the range of from 5 to 300 mg per day. E.g. citalopram and paroxetine will have a suitable dose of 40-50 mg, while the doses for fluvoxamine and sertraline will be 200-300 mg per day. In general, a suitable dose of an SSRI or a pharmaceutically acceptable salt thereof for administration to a human will be in the range of 0.01 to 50 mg per kilogram body weight of the recipient per day, preferably in the range of 0.1 to 3 mg per kilogram body weight per day. The preferred SSRI is

fluoxetine which, administered in a dose within the range of 0.01 to 10 mg per kilogram body weight of the recipient per day, preferably in the range of 0.1 to 1 mg per kilogram body weight per day, together with the above preferred dose of mirtazapine forms the best choice for providing a highly effective medicament for the treatment of sleep apneas of the obstructive and mixed types.

The method of treatment of sleep apneas wherein the compounds according to the invention are administered for therapy to an animal e.g. a mammal including a human, may be carried out in conventional manner, using all kinds of methods, including parenteral, peroral or rectal administration. Administration in the form or oral dosage units, such as tablets or capsules, is preferred. In the method of the invention according to which the aforementioned compounds are used for manufacturing a medicine, the compound can be mixed with all kinds of pharmaceutically acceptable carriers, depending on the method of administration intended. For the preferred, peroral, method of administration, the active compound is taken up in known manner in a composition from which granules or tablets are prepared.

The term "dosage unit" generally refers to physically discrete units suitable as unitary dosages for humans, each containing a predetermined quantity of active material calculated to produce the desired effect, for instance tablets, pills, powders, suppositories, capsules and the like.

Methods and compositions for making such dosage units are well-known to those skilled in the art. For example, conventional techniques for making tablets and pills, containing active ingredients, are described in the standard reference, Gennaro et al., Remington's Pharmaceutical Sciences, (18th ed., Mack Publishing Company, 1990, see especially Part 8: Pharmaceutical Preparations and Their Manufacture).

For making dosage units, e.g. tablets, the use of conventional additives, e.g. fillers, colorants, polymeric binders and the like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used in the one or more of the compositions.

Suitable carriers with which the compositions can be administered include lactose, starch, cellulose derivatives and the like used in suitable amounts. Lactose is a preferred carrier. Mixtures of carriers can also be used.

The manufacture of the dosage units according to the invention can involve standard pharmaceutical methods known to the skilled person without further elucidation.

Test Example

The efficacy of the compounds according to the invention is tested by studying the effects of administration of mirtazapine (in the range of from 0.05 to 25 mg/kg) in adult Sprague-Dawley rats by monitoring sleep, respiration and blood pressure for a minimum of 6 hours. This follows an accepted physiological animal model (ref. Monti et al., *Pharmacol.Biochem.Behav.*, 51:125-131;1995). The effective suppression by mirtazapine of sleep apneas in the rat model is indicative for similar efficacy in humans.

* C L M S *

Claims:

1. The use of mirtazapine or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating sleep apneas.

2. A use according to claim 1, characterised by the additional use of an SSRI.

3. A use according to any one of the preceding claims, characterised in that the medicament is a dosage unit for oral administration.

4. A method for the treatment of sleep apneas in an animal, comprising administering a therapeutically effective amount of mirtazapine or a pharmaceutically acceptable salt thereof.

5. A method according to claim 4, wherein additionally an SSRI is administered.

6. A method according to claim 4 or 5, wherein the animal is a human.

7. A method according to any one of the claims 4-6, wherein the administration is conducted orally.

This Sheet Has Been Replaced

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/07330

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/55

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)
IPC 6 A61K

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	M. RADULOVACKI ET AL.: "SEROTONIN 5-HT3-RECEPTOR ANTAGONIST GR 38032F SUPPRESSES SLEEP APNEAS IN RATS" SLEEP, vol. 21, no. 2, 1998, pages 131-136, XP002063050 see the whole document ---	1-7
Y	M. YOSHIOKA ET AL.: "PHARMACOLOGICAL CHARACTERISATION OF 5-HYDROXYTRYPTAMINE-INDUCED APNEA IN THE RAT" THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 260, no. 2, 1992, pages 917-924, XP002063051 cited in the application see the whole document ---	1-7
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 March 1999	08/04/1999

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, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hoff, P

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	TH. DE BOER: "THE PHARMACOLOGIC PROFILE OF MIRTAZAPINE" JOURNAL OF CLINICAL PSYCHIATRY, vol. 57, no. S4, 1996, pages 19-25, XP002063052 see the whole document	1-7
Y	EP 0 518 767 A (MERRELL DOW PHARMA) 16 December 1992 see abstract see page 14, line 14 - line 25	1-7
A	G.L. STIMMEL ET AL.: "MIRTAZAPINE: AN ANTIDEPRESSANT WITH NORADRENERGIC AND SPECIFIC SEROTONERGIC EFFECTS" PHARMACOTHERAPY, vol. 17, no. 1, 1997, pages 10-21, XP002063053 see the whole document	1-7
A	J. TOUCHON: "UTILISATION DES ANTIDEPRESSEURS DANS LES TROUBLES DU SOMMEIL: CONSIDERATION PRATIQUES" L'ENCEPHALE, vol. 21, no. 7, 1995, pages 41-47, XP002063054 see abstract see page 42, right-hand column, paragraph 1 see page 44, right-hand column, paragraph 3	1-7
A	WO 97 22339 A (HEDNER JAN ;KRAICZI HOLGER (SE)) 26 June 1997 see abstract see page 11, line 20 - line 43 see page 12, line 12 - line 20; claims 11-13	1-7

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 98/07330

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 4-7
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 98/07330

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0518767 A	16-12-1992	EP 0517984 A	16-12-1992
		AU 649836 B	02-06-1994
		AU 1803792 A	24-12-1992
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		FI 922695 A	12-12-1992
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WO 9722339 A	26-06-1997	AU 701911 B	11-02-1999
		AU 1217697 A	14-07-1997
		CA 2240717 A	26-06-1997

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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		(43) International Publication Date: 27 May 1999 (27.05.99)

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(71) Applicant *(for all designated States except US)*: AKZO NOBEL N.V. [NL/NL]; Velperweg 76, NL–6824 BM Arnhem (NL).

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(75) Inventor/Applicant *(for US only)*: ANDREWS, John, Stuart [GB/GB]; 7 Rowan Grove, Quarter, Hamilton ML3 7TT (GB).

(74) Agent: KRAAK, Hajo; P.O. Box 20, NL–5340 BH Oss (NL).

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(54) Title: USE OF MIRTAZAPINE FOR TREATING SLEEP APNEAS

(57) Abstract

The compound mirtazapine is found to be effective in treating sleep apneas. Optionally, mirtazapine is combined with an SSRI such as fluoxetin.

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USE OF MIRTAZAPINE FOR TREATING SLEEP APNEAS

The present invention pertains to the treatment of sleep apneas. Sleep apnea is defined as the cessation of breathing during sleep. It comprises a spectrum of respiration-related disorders with varying severity and morbidity, involving periods, during sleep, in which airflow is disturbed. The usual classification of sleep apneas distinguishes obstructive, central, and mixed apneas, depending on the presence or absence of respiratory efforts during the periods in which airflow has ceased. In the case of the obstructive sleep apnea syndrome, which is the most familiar apnea, sporadic recurring collapse of the patient's upper airway occurs during sleep. If the collapse is complete, there is no air exchange at the nose and the mouth, and breathing is interrupted. The usual result is a partial arousal from sleep, and a return to normal breathing. The patient in most instances does not have any knowledge or memory of these apnea episodes, but finds himself constantly suffering from fatigue and daytime sleepiness for no apparent reason. These recurrent apnea episodes with resultant hypoxemia and fragmented sleep can have serious neurologic and cardiac consequences. While the obstructive sleep apnea is a physical blockade, central sleep apnea is defined as a neurological disorder, causing cessation of all respiratory effort during sleep, usually with decreases in blood oxygen saturation. The effects of both types of apneas are highly similar. Mixed apnea is a combination of the previous two. An episode of mixed sleep apnea usually starts with a central component and then becomes obstructive in nature.

The sleep apnea syndrome today is regarded as a serious problem, as it occurs widely, and there is a true lack of an effective treatment. Surgical and mechanical interventions have been suggested and tried as treatments, as has oxygen administration during sleep, but none of these are recognised to be very suitable. Pharmacological intervention has also been tried, but with little success. In fact, several kinds of respiratory stimulants, theophylline, antidepressants, and progestogens have been used to treat sleep apneas, but none of these has been found to be very effective.

CONFIRMATION COPY

It is an object of the present invention to provide an effective medicine against sleep apneas. To this end, the invention is a method for the treatment of an animal, for example, a mammal including a human patient, suffering from sleep apnea, comprising administering an effective amount of mirtazapine. The invention also involves the use of mirtazapine for the manufacture of a medicament for the treatment of sleep apnea.

Without wishing to be bound by theory, the applicant, with the hindsight of the unexpected effect of the invention, believes that it is the particular serotonergic profile of mirtazapine which is responsible for the efficacy against sleep apnea.

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The invention resides in the finding that an effective medicine against sleep apneas is provided on the basis of the compound mirtazapine. This compound displays a combined serotonergic antagonistic activity to the effect that it simultaneously is a combined 5HT2A, 5HT2C and 5HT3 antagonist. The invention in general pertains to the use of this compound for manufacturing a medicament for treating sleep apneas, Surpisingly, the compound is not only useful as a therapy against sleep apneas of the central type, but also against sleep apneas of the obstructive and mixed types.

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or more steroiseomers, in any proportion including racemic mixtures. The present invention includes any salts of the compound, such as acid addition salts, for example, hydrochloric, fumaric, maleic, citric or succinic acid, these acids being mentioned only by way of illustration and without implied limitation. These compounds can be prepared in accordance with US 4,062,848, incorporated herein by reference.

In a preferred embodiment, the aforementioned compound is combined with a selective serotonin reuptake inhibitor (SSRI). SSRI's, and pharmaceutically acceptable salts thereof, are known and have been available since the early 1980s. They include zimelidine, fluoxetine and fluvoxamine. Other SSRI's are for example citalopram, cericlamine, femoxetine, ifoxetine, cyanodothiepin, sertraline, paroxetine, and litoxetine. SSRI's are known to the skilled person, and may be prepared by any method known in the art. For example, fluoxetine or pharmaceutically acceptable salts thereof, can be prepared in accordance with US 4,314,081, incorporated herein by reference.

A further benefit of mirtazapine, is that it also has antidepressant and anxiolytic properties, which helps to overcome secondary symptoms of which sleep apnea patients may suffer. Moreover mirtazapine improves the quality of sleep in general, which up to date has not been achieved with treatments of sleep apnea.

The compounds used according to the invention are to be administered in dosages of from 0,01 to 30 mg per kilogram body weight of the recipient per day, preferably in the range of 0,1 to 5 mg per kg body weight. In most instances, the preferred dosage of mirtazapine is 5 to 45 mg per day, and more preferably 15-30 mg. The SSRI dose may vary depending on the potency and efficacy of the specific active substance, but will generally be in the range of from 5 to 300 mg per day. E.g. citalopram and paroxetine will have a suitable dose of 40-50 mg, while the doses for fluvoxamine and sertraline will be 200-300 mg per day. In general, a suitable dose of an SSRI or a pharmaceutically acceptable salt thereof for administration to a human will be in the range of 0.01 to 50 mg per kilogram body weight of the recipient per day, preferably in the range of 0.1 to 3 mg per kilogram body weight per day. The preferred SSRI is

fluoxetine which, administered in a dose within the range of 0.01 to 10 mg per kilogram body weight of the recipient per day, preferably in the range of 0.1 to 1 mg per kilogram body weight per day, together with the above preferred dose of mirtazapine forms the best choice for providing a highly effective medicament for the treatment of sleep apneas of the obstructive and mixed types.

The method of treatment of sleep apneas wherein the compounds according to the invention are administered for therapy to an animal e.g. a mammal including a human, may be carried out in conventional manner, using all kinds of methods, including parenteral, peroral or rectal administration. Administration in the form or oral dosage units, such as tablets or capsules, is preferred. In the method of the invention according to which the aforementioned compounds are used for manufacturing a medicine, the compound can be mixed with all kinds of pharmaceutically acceptable carriers, depending on the method of administration intended. For the preferred, peroral, method of administration, the active compound is taken up in known manner in a composition from which granules or tablets are prepared.

The term "dosage unit" generally refers to physically discrete units suitable as unitary dosages for humans, each containing a predetermined quantity of active material calculated to produce the desired effect, for instance tablets, pills, powders, suppositories, capsules and the like.

Methods and compositions for making such dosage units are well-known to those skilled in the art. For example, conventional techniques for making tablets and pills, containing active ingredients, are described in the standard reference, Gennaro et al., Remington's Pharmaceutical Sciences, (18th ed., Mack Publishing Company, 1990, see especially Part 8: Pharmaceutical Preparations and Their Manufacture).
For making dosage units, e.g. tablets, the use of conventional additives, e.g. fillers, colorants, polymeric binders and the like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used in the one or more of the compositions.

Suitable carriers with which the compositions can be administered include lactose, starch, cellulose derivatives and the like used in suitable amounts. Lactose is a preferred carrier. Mixtures of carriers can also be used.

The manufacture of the dosage units according to the invention can involve standard pharmaceutical methods known to the skilled person without further elucidation.

Test Example

The efficacy of the compounds according to the invention is tested by studying the effects of administration of mirtazapine (in the range of from 0.05 to 25 mg/kg) in adult Sprague-Dawley rats by monitoring sleep, respiration and blood pressure for a minimum of 6 hours. This follows an accepted physiological animal model (ref. Monti et al., *Pharmacol.Biochem.Behav.*, 51:125-131;1995). The effective suppression by mirtazapine of sleep apneas in the rat model is indicative for similar efficacy in humans.

Claims:

1. The use of mirtazapine or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating sleep apneas.

2. A use according to claim 1, characterised by the additional use of an SSRI.

3. A use according to any one of the preceding claims, characterised in that the medicament is a dosage unit for oral administration.

4. A method for the treatment of sleep apneas in an animal, comprising administering a therapeutically effective amount of mirtazapine or a pharmaceutically acceptable salt thereof.

5. A method according to claim 4, wherein additionally an SSRI is administered.

6. A method according to claim 4 or 5, wherein the animal is a human.

7. A method according to any one of the claims 4-6, wherein the administration is conducted orally.