ACLIDINIUM FOR USE IN IMPROVING THE QUALITY OF SLEEP IN RESPIRATORY PATIENTS.

Field of the Invention

The invention relates to a novel use of aclidinium, which can be advantageously used to improve the quality of sleep in respiratory patients.

Background of the Invention

Respiratory diseases, such as asthma and chronic obstructive pulmonary disease (COPD), are a significant global health program, with an increasing incidence throughout the world. They are usually characterised by an inflammatory dysfunction of the airways which results in bronchoconstriction.

In asthma inflammation is driven by exposure to a variety of triggers, including allergens and viruses, which activate components of both the innate and acquired immune responses. In COPD inflammation occurs primarily because of exposure to noxious particles and gases, in particular to cigarette smoke. Rather than a single pathologic condition, COPD is a term encompassing several disorders, such as chronic bronchitis or emphysema.

Asthma and COPD are commonly associated with severe impairment of the physical functions as a consequence of pulmonary symptoms such as dyspnoea (breathlessness), fatigue, cough, wheezing, chest tightness or congestion, and sputum production. Many patients with respiratory diseases complain of the serious impact of these symptoms in the quality of their sleep.

In COPD patients, sleep-related complaints are the third most commonly reported symptoms, after dyspnoea and fatigue (Kinsman et al, *Chest*, 1983, 83, 755-761). In the case of asthma, 80 % of the patients are woken at least occasionally by nocturnal wheeze

and cough, and many patients with severe stable asthma are woken virtually every night (Turner-Warwick, M.; *Am. J. Med.*, 1988, 85 (suppl. 1B), 6-8).

Sleep complaints frequently reported by respiratory patients are for example longer latency to falling asleep, difficulty in staying asleep, frequent arousals and awakenings, superficial sleep, reduction of total sleep time, waking up too early and not being able to get back to sleep, generalised insomnia and, overall, a much poorer quality of sleep. Excessive daytime sleepiness and restricted physical activity during the day due to breathlessness in the morning are also common consequences of the impaired quality of sleep.

These sleep disturbances tend to be more severe with advancing disease and substantially reduce the quality of life of respiratory patients.

Bronchodilating agents like the beta-adrenergic agonists or the antagonists of cholinergic muscarinic receptors (commonly known as anticholinergics or antimuscarinics) are usually prescribed for inhalation to respiratory patients suffering from obstructive airway diseases, such as asthma or COPD. All commercially available anticholinergics are synthetic tropane derivatives, and include ipratropium, oxitropium, and tiotropium. Tiotropium, is the only long-acting anticholinergic currently on the market.

It is well known that the impact of the circadian rhythm on airway responsiveness and airway resistance is much larger in respiratory patients that in normal subjects. As a consequence, respiratory patients are particularly prone to bronchoconstriction at night and in the early morning hours and this is the main factor affecting the quality of their sleep. Therefore, a treatment aimed at overcoming or preventing bronchoconstriction during the night is highly desirable. However, a study by Calverley *et al.*, in *Thorax*, 2003, 58 (10), 855-860 shows that the administration of the long-acting bronchodilator tiotropium in the evening does not produce more bronchodilation during the night than when it is administered only in the morning.

It has now surprisingly been found that aclidinium significantly diminishes the occurrence of the sleep disturbances commonly seen in respiratory patients, increasing thus quality of sleep and overall quality of life.

Aclidinium is 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2] octane, a long-acting muscarinic receptor antagonist in development by Almirall for administration by inhalation in the treatment of respiratory diseases, especially asthma and COPD. It was first disclosed in WO 01/04118.

Aclidinium is rapidly hydrolysed in human plasma to two inactive metabolites, and hence has a reduced potential for systemic side effects and a wider safety margin than currently available inhaled anticholinergic treatments. Its additional effect in improving quality of sleep is an unexpected finding of this invention.

Summary of the Invention

The present invention provides aclidinium, or any of its steroisomers or mixture of stereoisomers, or a pharmaceutically acceptable salt or solvate thereof, for use in improving the quality of sleep in respiratory patients.

Preferably, aclidinium is in the form of a salt with an anion X^-. Most preferably, the anion X^- is bromide.

In a preferred embodiment, the respiratory patient suffers from a disease selected from acute or chronic bronchitis, emphysema, asthma and chronic obstructive pulmonary disease, preferably asthma and chronic obstructive pulmonary disease, most preferably chronic obstructive pulmonary disease.

In another embodiment, aclidinium is administered as a pharmaceutical composition suitable for inhalation, preferably in the form of a dry powder. The composition can be administered by means of any inhaler device, more preferably the Genuair®.

Typically, a dry powder formulation comprises a pharmaceutically acceptable carrier selected from mono-, di- or polysaccharides and sugar alcohols. Preferably, the carrier is lactose.

Aclidinium is administered at least once a day, preferably in the morning or in the evening. More preferably aclidinium is administered twice daily. In a most preferred embodiment aclidinium is administered twice daily, one in the morning and another one in the evening.

The effective dose of aclidinium to be used per inhalation is the equivalent to a metered nominal dose from 100 to 1000 micrograms of aclidinium bromide in a dry powder for inhalation, more preferably 200 or 400 micrograms of aclidinium bromide.

In another preferred embodiment, aclidinium is co-administered with an additional medication suitable for the treatment of respiratory diseases, selected for example from one or more of the following: corticosteroids, beta-adrenergic agonists, PDE4 inhibitors, antihistamines, anti-IgE antibodies, leukotriene D4 inhibitors, inhibitors of egfr-kinase, p38 kinase inhibitors and/or NK1-receptor antagonists. The additional medications can be present in the same pharmaceutical composition as aclidinium or in separate pharmaceutical compositions. Preferably, the additional medication is selected from corticosteroids, beta-adrenergic agonists and/or PDE4 inhibitors.

The improvement by aclidinium of the quality of sleep of the respiratory patient can be measured by observing the reduction of one or more of the following:

a) Latency to falling asleep
b) Total number of awakenings
b) Early awakenings
c) Difficulty in staying asleep
d) Superficial sleep

e) Insomnia

f) Daytime sleepiness or fatigue

g) Restriction of activities during the morning

and/or by the increase of total sleep time.

Among the clinical factors that may contribute to the improvement of the quality of sleep by aclidinium are reductions in one or more of the following respiratory complaints during sleep time:

a) Cough severity and/or frequency

b) Sputum production

c) Wheezing

d) Chest tightness

e) Chest congestion

f) Bronchoconstriction

g) Breathlessness

h) Need of rescue medication

The invention further provides a pharmaceutical composition comprising aclidinium for improving the quality of sleep in respiratory patients.

The invention further provides the use of aclidinium in the manufacture of a medicament for improving the quality of sleep in respiratory patients.

The invention further provides a method of improving the quality of sleep in respiratory patients, which method comprises administering to said patient an effective amount of aclidinium, as defined above.

Detailed description of the invention

Typically, the aclidinium is administered in the form of a salt with an anion X^-, wherein X^- is a pharmaceutically acceptable anion of a mono or polyvalent acid. More typically, X^- is an anion derived from an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulphuric acid and phosphoric acid, or an organic acid such as methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid or maleic acid. Most preferably the aclidinium is in the form of aclidinium bromide.

The compound of the invention may exist in both unsolvated and solvated forms. The term solvate is used herein to describe a molecular complex comprising a compound of the invention and an amount of one or more pharmaceutically acceptable solvent molecules. The term hydrate is employed when said solvent is water. Examples of solvate forms include, but are not limited to, compounds of the invention in association with water, acetone, dichloromethane, 2-propanol, ethanol, methanol, dimethylsulfoxide (DMSO), ethyl acetate, acetic acid, ethanolamine, or mixtures thereof. It is specifically contemplated that in the present invention one solvent molecule can be associated with one molecule of the compounds of the present invention, such as a hydrate.

The words "treatment" and "treating" are to be understood as embracing amelioration of symptoms of a disease or condition and/or elimination or reduction of the cause of the disease or condition and/or prevention of the appearance of the disease or its symptoms..

The term “therapeutically effective amount” refers to an amount sufficient to effect treatment when administered to a patient in need of treatment.

Aclidinium can also be used in combination with other drugs known to be effective in the treatment of the diseases or the disorders indicated above. For example aclidinium can be combined with corticosteroids or glucocorticoids, beta-adrenergic agonists, PDE4 inhibitors, antihistamines, anti-IGE antibodies, leukotriene D4 antagonists, inhibitors of egfr kinase, p38 kinase inhibitors and/or NK-1 receptor agonists.

Corticosteroids that can be combined with aclidinium in the present invention particularly include those suitable for administration by inhalation in the treatment of respiratory diseases or conditions, e.g., prednisolone, methylprednisolone, dexamethasone, naflocort, deflazacort, halopredone acetate, budesonide, beclomethasone dipropionate, hydrocortisone, triamcinolone acetonide, fluocinolone acetonide, fluocinonide, clocortolone pivalate, methylprednisolone aceponate, dexamethasone palmitoate, tipredane, hydrocortisone aceponate, prednicarbate, alclometasone dipropionate, halometasone, methylprednisolone suleptanate, mometasone furoate, rimexolone, prednisolone farnesylate, ciclesonide, deprodone propionate, fluticasone propionate, halobetasol propionate, loteprednol etabonate, betamethasone butyrate propionate, flunisolide, prednisone, dexamethasone sodium phosphate, triamcinolone, betamethasone 17-valerate, betamethasone, betamethasone dipropionate, hydrocortisone acetate, hydrocortisone sodium succinate, prednisolone sodium phosphate and hydrocortisone probutate. Budesonide and mometasone are especially preferred.

Beta-adrenergic agonists that can be combined with aclidinium in the present invention particularly include β2 adrenergic agonists useful for treatment of respiratory diseases or conditions, for example, selected from the group consisting of arformoterol, bambuterol, bitolterol, broxaterol, carbuterol, clenbuterol, dopexamine, fenoterol, formoterol, hexoprenaline, ibuterol, isoprenaline, mabuterol, meluadrine, nolomirole, orciprenaline, pirbuterol, procaterol, reproterol, ritodrine, rimoterol, salbutamol, salmeterol, sibenadet, sulfonterol, terbutaline, tulobuterol, vilanterol, olodaterol, KUL-1248, LAS-100977, carmoterol and indacaterol, in free or pharmaceutically acceptable salt form. Preferably, the β2 adrenergic agonist is a long-acting β2 adrenergic agonist, e.g., selected from the group consisting of formoterol, salmeterol, carmoterol , vilanterol, olodaterol, LAS-100977 and indacaterol in free or pharmaceutically acceptable salt form.

PDE4 inhibitors that can be combined with aclidinium in the present invention include denbufylline, rolipram, cipamfylline, arofylline, filaminast, piclamilast, mesopram, drotaverine hydrochloride, lirimilast, roflumilast, cilomilast, 6-[2-(3,4-Diethoxyphenyl)thiazol-4-yl]pyridine-2-carboxylic acid, (R)-(+)-4-[2-(3-

Cyclopentyloxy-4-methoxyphenyl)-2-phenylethyl]pyridine, N-(3,5-Dichloro-4-pyridinyl)-2-[1-(4-fluorobenzyl)-5-hydroxy-1H-indol-3-yl]-2-oxoacetamide, 9-(2-Fluorobenzyl)-N6-methyl-2-(trifluoromethyl)adenine, N-(3,5-Dichloro-4-pyridinyl)-8-methoxyquinoline-5-carboxamide, N-[9-Methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydropyrrolo[3,2,1-jk][1,4]benzodiazepin-3(R)-yl]pyridine-4-carboxamide, 3-[3-(Cyclopentyloxy)-4-methoxybenzyl]-6-(ethylamino)-8-isopropyl-3H-purine hydrochloride, 4-[6,7-Diethoxy-2,3-bis(hydroxymethyl)naphthalen-1-yl]-1-(2-methoxyethyl)pyridin-2(1H)-one, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluroromethoxyphenyl)cyclohexan1-one, *cis* [4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol, ONO-6126 (Eur Respir J 2003, 22(Suppl. 45): Abst 2557) and the compounds claimed in the PCT patent application number WO03/097613, and PCT/EP03/14722 and in the Spanish patent application numer P200302613.

Aclidinium for use in the present invention may be administered by any suitable route to provide local antimuscarinic action. It is preferably administered by inhalation, e.g., as a powder, spray, or aerosol, preferably as a dry powder. Pharmaceutical compositions comprising aclidinium may be prepared using conventional diluents or excipients and techniques known in the galenic art.

Medicaments for administration in a dry powder for inhalation desirably have a controlled particle size. The optimum particle size for inhalation into the bronchial system is usually 1-10 μm, preferably 2-5μm. Particles having a size above 20 μm are generally too large when inhaled to reach the small airways. To achieve these particle sizes the particles of the active ingredient as produced may be size reduced by conventional means, e.g. by micronisation or supercritical fluid techniques. The desired fraction may be separated out by air classification or sieving. Preferably, the particles will be crystalline.

Achieving a high dose reproducibility with micronised powders is difficult because of their poor flowability and extreme agglomeration tendency. To improve the efficiency of

dry powder compositions, the particles should be large while in the inhaler, but small when discharged into the respiratory tract. Thus, an excipient, for example a mono-, di- or polysaccharide or sugar alcohol, such as lactose, mannitol or glucose is generally employed. The particle size of the excipient will usually be much greater than the inhaled medicament within the present invention. When the excipient is lactose it will typically be present as lactose particles, preferably crystalline alpha lactose monohydrate, e.g., having an average particle size range of 20-1000 μm, preferably in the range of 90-150 μm. In one embodiment, the lactose particles for use in formulations of the invention have a d10 of 90 - 160 μm, a d50 of 170 – 270 μm, and d90 of 290 – 400 μm.

Suitable lactose materials for use in the present invention are commercially available, e.g., from DMW Internacional (Respitose GR-001, Respitose SV-001, Respitose SV-003); Meggle (Capsulac 60, Inhalac 70, Capsulac 60 INH); and Borculo Domo (Lactohale 100-200, Lactohale 200-300, and Lactohale 100-300).

The ratio between the lactose particles and the aclidinium by weight will depend on the inhaler device used, but is typically, e.g., 5:1 to 200:1, for example 50:1 to 150:1, e.g., 60-70:1.

In a preferred embodiment, the aclidinium is administered in the form of a dry powder formulation of aclidinium bromide in admixture with lactose, in a ratio by weight of aclidinium to lactose of 1:50 to 1:150, suitable for administration via a dry powder inhaler, wherein the aclidinium particles have an average particle size of from 2 to 5μm in diameter, e.g., less than 3 μm in diameter, and the lactose particles have have a d10 of 90 - 160 μm, a d50 of 170 – 270 μm, and d90 of 290 – 400 μm.

Dry powder compositions for topical delivery to the lung by inhalation may, for example, be presented in capsules and cartridges of for example gelatine or blisters of for example laminated aluminium foil, for use in an inhaler or insufflator. Each capsule or cartridge may generally contain between 0.001-50 mg, more preferably 0.01-5 mg of active

ingredient or the equivalent amount of a pharmaceutically acceptable salt thereof. Alternatively, the active ingredient (s) may be presented without excipients.

Packaging of the formulation may be suitable for unit dose or multi-dose delivery. In the case of multi- dose delivery, the formulation can be pre-metered or metered in use. Dry powder inhalers are thus classified into three groups: (a) single dose, (b) multiple unit dose and (c) multi dose devices.

Aclidinium is preferably administered with a multi-dose inhaler, more preferably with the Genuair® (formerly known as Novolizer SD2FL), which is described the following patent applications Nos: WO97/000703, WO03/000325 and WO2006/008027.

Dosages will vary depending on, e.g., the individual, the mode and frequency of administration, and the nature and severity of the condition to be treated. Daily dosages for a 70 kg adult human may typically for example be on the order of 100-1000 micrograms of active agent in the form of dry powder for inhalation.

Example 1

In a Phase IIa randomized, double-blind, crossover trial, patients with moderate to severe COPD received aclidinium 400 micrograms twice-daily (in the morning, 9 am, and in the evening, 9 pm) and placebo for 15 days, with a 9-15 day washout between treatment periods.

Sleep quality was assessed with daily records on a patient diary card using a 0-4 score according to the following criteria:

0	No awakenings
1	Early awakening or awakening once during the night
2	Early awakening or awakening two or more times during the night
3	Awakening for most time during the night

4	The patient could not sleep at all

Patients treated with aclidinium showed a significantly improved quality of sleep compared to untreated patients.

Example 2

In a double-blind, randomised, placebo-controlled Phase III trial, the quality of sleep and the use of rescue medication was assessed during twice-daily treatment of aclidinium bromide in COPD patients.

COPD patients with FEV1/FVC <70% were randomised (1:1:1) to aclidinium 200 micrograms, 400 micrograms, or placebo. The quality of sleep was reported daily using electronic diaries and a questionnaire, which assessed symptom frequency and severity and its effect on morning activities. Rescue medication use was also assessed.

At Week 12, aclidinium significantly improved the quality of sleep compared to placebo. Aclidinium 200 mcg and 400 mcg significantly reduced the severity of breathlessness and cough at night, the frequency of awakenings and the difficulty to fall back sleep. Additionally, the production of sputum and the use of rescue medication were also reduced.

Both aclidinium doses also significantly reduced the severity of early morning breathlessness and the impact of breathlessness and cough on morning activities.

Example 3

In a Phase IIa randomised, double-blind, double-dummy, crossover trial, patients with moderate-to-severe COPD received inhaled aclidinium 400 µg BID, tiotropium 18 µg QD and placebo for 15 days, with a 9-15 day washout between treatment periods.

The incidence of sleep difficulties was recorded daily on a patient diary card. As in Example 1, the scores ranged from 0 for none to 1-4 for increasing severity of the sleep difficulties. The change in the score produced by each treatment with respect to the baseline was then measured.

The average score (+/- SEM) of the patients treated with tiotropium was –0.011 (0.091), which is practically identical to the baseline and very similar to the score of 0.061 (0.088), observed in the patients treated with placebo. There is no statistically significant difference between these two scores ($p>0.05$). In contrast, the score of the patients treated with aclidinium was –0.123 (0.089). In this case there is a statistically significant difference with placebo ($p<0.05$).

These phase IIa results demonstrate that the remarkable improvement of sleep quality produced by aclidinium is not observed when the patients are treated with tiotropium, the reference anticholinergic drug currently in the market. This unexpected effect of aclidinium is therefore not obvious and involves an inventive step.

CLAIMS

1. Aclidinium or any of its steroisomers or mixture of stereoisomers, or a pharmaceutically acceptable salt or solvate thereof, for use in improving the quality of sleep in respiratory patients.

2. Aclidinium for use according to claim 1, wherein the aclidinium is in the form of aclidinium bromide.

3. Aclidinium for use according to claim 1 or 2, wherein the respiratory patient suffers from asthma or chronic obstructive pulmonary disease (COPD).

4. Aclidinium for use according to any preceding claim, wherein the aclidinium is in the form of a dry powder formulation suitable for inhalation.

5. Aclidinium for use in a dry powder formulation according to claim 4, providing a metered nominal dose of aclidinium equivalent to from 100 to 1000 micrograms of aclidinium bromide per inhalation, preferably 200 or 400 micrograms of aclidinium bromide.

6. Aclidinium for use according to any preceding claim, wherein aclidinium is administered one or more times per day, preferably twice daily.

7. Aclidinium for use according to any preceding claim, wherein aclidinium is co-administered with a therapeutically effective amount of a corticosteroid, a beta-adrenergic agonist and/or a PDE4 inhibitor.

8. Aclidinium for use according to any of the preceding claims, wherein the quality of sleep is improved by reducing one or more of the following:

a) Latency to falling asleep

b) Total number of awakenings
b) Early awakenings
c) Difficulty in staying asleep
d) Superficial sleep
e) Insomnia
f) Daytime sleepiness or fatigue
g) Restriction of activities during the morning

and/or by increasing total sleep time.

9. Pharmaceutical composition comprising aclidinium, as defined in any preceding claim, for use in improving the quality of sleep in respiratory patients, as defined in any preceding claim.

10. Use of aclidinium, as defined in any preceding claims, in the manufacture of a medicament for improving the quality of sleep in respiratory patients, as defined in any preceding claim.

11. A method of improving the quality of sleep in respiratory patients, which method comprises administering to said patient an effective amount of aclidinium, as defined in any preceding claim.

12. Aclidinium, as defined in claim 1 or 2, for use in treating a respiratory disorder, preferably asthma or chronic obstructive pulmonary disease, in a patient suffering from impaired sleep.

13. Aclidinium for use according to claim 12, wherein the impaired sleep involves one or more of the following:
a) delay in falling asleep,
b) one or more awakenings, preferably 2 or more, more preferably 3 or more, during the night,

b) early awakenings,
c) difficulty in staying asleep,
d) superficial sleep,
e) insomnia,
f) daytime sleepiness or fatigue, and
g) restriction of activities during the morning.

14. Use of aclidinium as defined in claim 1 or 2, in the manufacture of a medicament for treating a respiratory disorder, preferably asthma or chronic obstructive pulmonary disease, in a patient suffering from impaired sleep.

15. Use according to claim 14, wherein the impaired sleep involves one or more of the following:
a) delay in falling asleep,
b) one or more awakenings, preferably 2 or more, more preferably 3 or more, during the night,
b) early awakenings,
c) difficulty in staying asleep,
d) superficial sleep,
e) insomnia,
f) daytime sleepiness or fatigue, and
g) restriction of activities during the morning.