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(54) **COMBINATION OF ANTICHOLINERGICS AND GLUCOCORTICOIDS FOR THE LONG-TERM TREATMENT OF ASTHMA AND COPD**

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(57) **ABSTRACT**

The present invention describes the combination of topically inhaled medicinal formulations comprising an anticholinergic component and a glucocorticosteroid component and its use in the symptomatic and prophylactic treatment of diseases of the respiratory tract, especially with an obstructive component or underlying inflammation like asthma and chronic obstructive pulmonary disease (COPD). It further comprises the presentation of this combination in a locally applied (inhaled) formulation and application in an inhalation device for instance in the Novolizer®.

COMBINATION OF ANTICHOLINERGICS AND GLUCOCORTICOIDS FOR THE LONG-TERM TREATMENT OF ASTHMA AND COPD

[0001] The present invention describes the combination of topically inhaled medicinal formulations comprising an anticholinergic component and a glucocorticosteroid component and its use in the symptomatic and prophylactic treatment of diseases of the respiratory tract, especially with an obstructive component or underlying inflammation like asthma and chronic obstructive pulmonary disease (COPD). It further comprises the presentation of this combination in a locally applied (inhaled) formulation and application in an inhalation device for instance in the Novolizer®.

[0002] One of the most important diseases of the respiratory tract are obstructive airway diseases like COPD or asthma. The prevalence of COPD increases heavily with age. The Global Burden of Disease study, undertaken by the World Bank and World Health Organization, concluded that COPD world-wide will increase from 1990 to 2020 its rank number of death from rank 6 to rank 3, and its rank number of disability-adjusted life years lost from rank 12 to rank 5 (Gulsvik, Monaldi Arch Chest Dis. 2001 June; 56(3): 261-4). Chronic obstructive pulmonary disease (COPD) is increasing worldwide and affects nearly 16 million Americans, and more than $18 billion is spent annually on medications, physician visits, and hospitalizations. COPD is characterized by chronic airflow obstruction with episodic acute exacerbations, which result in increased morbidity and mortality. Patients hospitalized with exacerbations have an overall mortality rate of 3% to 4%, and up to 24% of patients requiring care in the intensive care unit die (Blanchard, Clin Cornerstone. 2003; 5(1): 28-36). Bronchial asthma remains a significant cause of mortality at all ages as well (Sidebotham und Roche, Histopathology. 2003 August; 43(2): 105-17).

[0003] Bronchial asthma causes characteristic histological changes in the mucosa of the airways which includes fibrous thickening of the lamina reticularis of the epithelial basement membrane, smooth muscle hypertrophy and hyperplasia, increased mucosal vascularity and an eosinophil-rich inflammatory cell infiltrate (Sidebotham and Roche, Histopathology. 2003 August; 43(2): 105-17). In COPD, chronic inflammation leads to (partially) fixed narrowing of small airways and alveolar wall destruction (emphysema) (Barnes, Annu Rev Med. 2003; 54: 113-29. Epub 2001 Dec. 3). Thus, both diseases comprise a kind of narrowing of the small airways due to smooth muscle hypertrophy and a kind of inflammatory process as well. The management of the diseases consists therefor on the one hand of a symptomatic reliever medication which dilates the small airways and on the other hand of a causal treatment which controls the underlying inflammation process. Inhaled anticholinergic agents (and β2-adrenoreceptor agonists) are the mainstay in the symptomatic bronchodilating treatment of COPD (GOLD Guideline, 2002) and asthma (GINA Guideline, 2002). And inhaled glucocorticosteroids are the most effective preventer (=controller) medication (Van Asperen, Med J Aust. 2002 Sep. 16; 177 Suppl: S64-6). However, a causal treatment with anticholinergic agents is not possible, nor a rapid symptomatic relief is expected with glucocorticosteroids.

[0004] Anticholinergic agents are exemplified by the belladonna alkaloids atropine and scopolamine, which inhibit the muscarinic action of acetylcholine on structure innervated by postganglionic cholinergic nerves. These agents typically inhibit bronchoconstriction by relaxing of smooth muscles and cause considerable bronchodilation. Anticholinergic agents also are known to exert central effects which include pupil dilatation and stimulation and/or depression of the central nervous system. Novel anticholinergic pharmaceuticals have been developed which have a limited capacity to pass across the blood-brain barrier, and therefore have a limited capacity to produce central effects. Examples of these agents are the quaternary ammonium compounds methscopolamine, ipratropium, tiotropium and the enantiomers of glycopyrrolate.

[0005] Antimuscarinic treatment of asthma and COPD has a relatively long history leading to its present day use as an effective bronchodilating drug for obstructive pulmonary diseases. Present formulations are, however, limited to oxitropium, ipratropium, and the recently approved tiotropium bromide.

[0006] Anticholinergics are agents of first choice for the symptomatic treatment of patients with COPD. In acute exacerbation of chronic obstructive pulmonary disease, inhaled bronchodilators such as ipratropium bromide have proven useful (Hall et al.). Tiotropium is a long-acting inhaled anticholinergic designed for once-daily bronchodilator treatment of COPD. Tiotropium is a selective antagonist of pulmonary Ml and M3 muscarinic receptor subtypes, that produces a long-lasting (24 hours), dose-dependent bronchodilation and bronchoprotection against constrictive stimuli, e.g. methacholine, following inhalation of single doses. Clinical trials with tiotropium in COPD patients over a maximum treatment duration of one year have confirmed a persisting bronchodilator effect of tiotropium compared with placebo and ipratropium, as well as meaningful clinical improvements in lung function, hyperinflation, exercise tolerance, symptom control and quality of life. Moreover, recent trials indicate that treatment with tiotropium also reduces the frequency of COPD exacerbations and hospitalizations. Comparative trials further suggest that the bronchodilator potency of tiotropium may be superior to those of available COPD treatments. Besides a higher incidence of dry mouth, the side effect profile was comparable to ipratropium bromide.

[0007] In conclusion, present clinical data suggest that tiotropium has the potential of a first-line treatment for patients with COPD (Beeh et al., Pneumologie. 2003 September; 57(9): 519-25). The drug has been shown to improve spirometric parameters, quality of life, and utilization of health care resources (Faulkner et al., Pharmacotherapy. 2003 October; 23(10): 1300-15).

[0008] Anticholinergic drugs have long since been used in the treatment of chronic obstructive pulmonary disease (COPD) and asthma (Joos, Monaldi Arch Chest Dis. 2000 October; 55(5): 411-4). Clinical studies with inhaled tiotropium bromide confirm that it is a potent and long-lasting bronchodilator in COPD and asthma (Barnes et al., Life Sci. 1995; 56(11-12): 853-9). Current therapeutic options for acute severe asthma consist of ipratropium and glucocorticosteroids in combination with beta2 selective drugs (McFadden, Am J Respir Crit Care Med. 2003 October 1; 168(7): 740-59). According to the latest evidence, the goals of treatment of adult asthma may be summarized as relief of

airflow obstruction by administration of inhaled beta-agonists and anticholinergics, and reduction of airway inflammation and prevention of future relapses by using early administration of s corticosteroids (Rodrigo, Curr Opin Allergy Clin Immunol. 2003 June; 3(3): 169-75).

[0009] Inhaled glucocorticosteroids are the most effective therapy in controlling chronic asthma symptoms (Barnes, J Aerosol Med. 1996 Spring; 9(1): 131-41). Randomized, controlled clinical studies confirm the efficacy of early intervention with inhaled glucocorticosteroids in patients with mild persistent asthma. Regular use of an inhaled glucocorticosteroids can reduce the number of exacerbations and hospitalizations in patients of all ages and with all disease severities (Chapman, Clin Ther. 2003; 25 Suppl C:C_2-C_{14}). Within inhaled glucocorticosteroids, fluticasone is endowed of a potent antiinflammatory activity, due to its high affinity for the the glucocorticoid receptor (allowing the use of 50% of the dose of other ICS) and of a negligible oral bioavailability (<1%), indicating a low potential for systemic exposure. Due to its high therapeutical index, fluticasone can be used in the management of severe asthma or other airway diseases at doses devoid of relevant unwanted systemic effects. Scientific literature has broadly demonstrated its efficacy and safety, even at high doses and in the long term use (Solidoro et al., Minerva Pediatr. 2003 August; 55(4): 345-55). When combined with delivery devices suitable for a spectrum of patient groups, the physical and pharmacokinetic properties of budesonide lend it many of the characteristics of an ideal inhaled glucocorticosteroid, including favorable efficacy and tolerability profiles (O'Connell, Clin Ther. 2003; 25 Suppl C:C42-60). Whereas budesonide has clinical efficacy similar to that of other currently available ICSs, it has a good safety profile—and hence a favorable therapeutic margin—that is supported by long-term clinical data (Skoner, Clin Ther. 2003; 25 Suppl C:C61-74).

[0010] The practice of using inhaled steroids (ICS) in chronic obstructive pulmonary disease (COPD) is common but controversial (O'Riordan, J Aerosol Med. 2003 Spring; 16(1): 1-8). Glucocorticosteroids are probably scarcely effective in COPD patients without overlapping concomitant asthma (Caramori et al., Pulm Pharmacol Ther. 2003; 16(5): 247-77). The routine prescription of these agents to asymptomatic patients with well-preserved lung function is not indicated. However, more selective use of inhaled glucocorticosteroids in patients with moderately severe disease (FEV1<50% predicted) may produce clinical benefit as measured by an increase in FEV1, reduced symptoms and fewer exacerbations (O'Riordan, J Aerosol Med. 2003 Spring; 16(1): 1-8). Glucocorticosteroids should mainly be used to reduce exacerbations and improve the health status of these patients (Man et al., JAMA. 2003 Nov. 5; 290(17): 2313-6). But it has to be admitted that current pharmacological treatment of COPD is unsatisfactory, as it does not significantly influence the severity of the disease or its natural course.

[0011] As the current treatment of asthma and COPD is not satisfactory improved, the problem underlying the present invention was to provide effective and more convenient therapeutic interventions.

[0012] A solution is given by the combination of inhaled glycopyrrolate with an inhaled glucocorticoid like budesonide, fluticasone, ciclesonide, or beclometason.

[0013] Glycopyrrolate belongs to the so-called quaternary ammonium anticholinergic drugs and antagonizes the neurotransmitter acetylcholine at its muscarinic receptors. This effect leads to a considerable smooth muscle relaxation resulting in a prolonged bronchodilating effect. Due to the fast onset and the long duration of action anticholinergic agents are the first choice for the symptomatic treatment of COPD.

[0014] Topically inhaled glucocorticosteroids such as budesonide and fluticasone suppress inflammation in asthmatic airways by affecting the transcription of several steroid-responsive genes and have become first-line therapy for the long-term asthma control.

[0015] Surprisingly, the combination of a symptomatic and a causal treatment is superior to that of the monocompounds resulting in over-additive effects and/or diminished side-effects, respectively. Therefore, the combination can be useful in the treatment of obstructive airway diseases of different origins like COPD or asthma.

[0016] Surprisingly it has been revealed that the use of topically inhaled anticholinergic agents such as glycopyrrolate, including one of its enantiomers, especially R,R-glycopyrrolate or their physiologically acceptable salts or a mixture thereof administered in combination with topically inhaled glucocorticosteroids is effective and safe in the treatment of asthma and chronic obstructive pulmonary disease (COPD) which allows for lower doses or which decreases side-effects.

[0017] Consequently, the combination of such drugs leads to a better efficacy which is surprisingly overadditive and an improved tolerability with less side-effects than expected.

EXPERIMENTAL PART

[0018] The influence of R,R-glycopyrrolate in combination with glucocorticoids on TNFα release was investigated by using human peripheral blood mononuclear cells (PBMCs). The study was approved by our institutional Ethics Committee according to the International Declarations of Helsinki and Tokyo.

[0019] PBMCs were isolated from heparinized blood samples of healthy donors by density gradient centrifugation. An equal volume of Hanks buffer (Life Technologies, Heidelberg, Germany) is added to heparinized whole blood samples. 15 ml Histopaque-1077. (Sigma, Deisenhofen, Germany) are overlayed with a maximum of 40 ml of blood/Hanks mixture were centrifuged for 30 min at room temperature (2000 rpm). A visible band containing PBMCs is transferred to a fresh tube and washed twice with Hanks-buffer. Finally cells are seeded in RPMI 1640 Medium (Life Technologies, Heidelberg, Germany) with Glutamax I (Gibco BRL, Eggenstein) and 10% FCS (Boehringer Mannheim, Penzberg, Germany). After isolated, PBMCs were cultured in RPMI 1640 medium supplemented with 10% fetal calf serum (FCS) at 37° C. 5% CO_2 overnight. Monocytes were isolated from other cells by adherence method, non-adherent cells were removed by changing the medium.

[0020] Cells are re-suspended at 106 cells/ml and incubated in 500 μl volumes in 24-well tissue culture plates (Falcon Becton Dickinson Labware) at 37° C., 5% CO_2. After pre-incubation with test substances (0.5 μl/500 μl medium) for 30 min, cells were stimulated with lipopolysac-

charide (LPS) (1 μg/ml). At indicated times cells were sedimented by centrifugation, the supernatants were harvested and kept frozen at −80° C. until protein determination; the cells were lysed by RLT lysis Buffer (Qiagen, Hilden, Germany) and frozen at −80° C. until analysis.

[0021] Cytokine measurements in culture supernatants are done by sandwich ELISA using matched antibody pairs (Pharmingen, Heidelberg, Germany). ELISA plates (Maxisorb, Nunc) are coated overnight with anti-cytokine monoclonal antibody (mAb) in 0.1 M carbonate buffer, pH 9.5. After being washed, plates are blocked with Assay Diluent (Pharmingen, Heidelberg, Germany) for 1 h and washed again. Appropriately diluted supernatant samples and standards are distributed in duplicates and the plates are incubated for 2 h at room temperature. Plates are washed, incubated for 1 h with working detector (biotinylated anti-cytokine antibody and Avidin-horseradish peroxidase conjugate). After washing, substrate (TMB and hydrogen peroxide) is added. The reaction is stopped by adding of 1M H_3PO_4. Plates are read at 450 nm (reference 570 nm) in a microplate reader (Dynatech). The results are expressed as a percentage of the control level of cytokines production by cells stimulated in the absence of the compound.

[0022] Upon LPS-stimulation, basal TNFα release from monocytes increased from 328 pg/ml up to 7,258 pg/ml. R,R-glycopyrrolate alone did not inflence the LPS-induced TNFα release up to 10 μmol/l. The glucocorticoid budesone inhibited the TNFα release in a concentration-dependent manner. The IC_{50} value of budesonide amounted to 0.55±0.13 nmol/l. The simultaneous addition of 10 μmol/l of R,R-glycopyrrolate surprisingly and highly significantly reduced the IC_{50} to 0.13±0.03 nM (p=0.0251).

[0023] The data show that R,R-glycopyrrolate significantly enhances the anti-inflammatory activity of glucocorticoids with increased efficacy which is surprisingly overadditive and a better tolerability with reduced occurrence of side-effects than at administration of the monocompounds.

[0024] The combination therapy disclosed by this invention comprises administering a glucocorticosteroid together with a long-acting anticholinergic bronchodilator to prevent onset of a pulmonary disease event or to treat an existing condition and to reduce obstruction and airway inflammation.

[0025] The compounds may be administered together in a single dosage form. Or they may be administered in different dosage forms. These drugs are usually administered as an aerosol (with or without propellant), or as an inhaled powder for instance with the Novolizer®. This invention contemplates either co-administering both drugs in one delivery form such as an inhaler, that is putting both drugs in the same inhaler. Formulations are within the skill of the art and may contain all usual excipients, adjuncts, and additives.

[0026] The active ingredients may be given from 1 to 8 times a day, sufficient to exhibit the desired activity. Preferably, the active components are given about once or four times a day, more preferably once or twice a day. The compounds of the combination may be administered at the same time. Or they may be administered either close in time or remotely, such as where one drug is administered in the morning and the second drug is administered in the evening. Or in another scenario, one drug could be taken twice daily and the other once daily, either at the same time as one of the twice-a-day dosing occurred, or separately. Preferably both drugs should be taken together at the same time.

[0027] The inhaled anticholinergic drug, racemic glycopyrrolate, one of its enantiomers, especially R,R-glycopyrrolate or a mixture thereof and its salts, solvates and hydrates can be administered in an amount of between 5 and 500 μg/day adult human with the preference of 15 to 300 μg/day in dependence of the magnitude of symptoms. A dosage range between 5 and 100 μg/day is especially preferred.

[0028] Glucocorticosteroids (budesonide or ciclesonide or fluticasone or mometasone or flunisolide, or beclometason or loteprednol) can be administered inhaled in conformity with approved labeling in an amount of 100 to 1.600 μg/day preferably between 200 and 400 μg/day.

[0029] The combination may be used prophylactically or after the onset of symptoms has occurred. In some instances the combination(s) may be used to prevent the progression of a pulmonary disease or to arrest the decline of a function such as lung function.

[0030] The following examples describe the invention without limiting it.

Example 1

Powder Inhalation with 250 μg Fluticasone and 20 μg Glycopyrrolate Per Single Dose

[0031] A quantity of 250 g micronized fluticasone is mixed with 1000 g alpha lactose monohydrate, the mixture is given on a sieve of 0.5 mm mesh size and finally mixed again. 20 g micronized glycopyrrolate is mixed with 100 g alpha lactose monohydrate, the mixture is given on a sieve of 0.8 mm mesh size and finally mixed again. The two mixtures received are blended and filled up with alpha lactose monohydrate to 15000 g. Subsequently, it is mixed again and the powder mixture received is filled in powder inhalers releasing 15 mg of powder per single dose. Per single dose, 250 μg fluticasone and 20 μg glycopyrrolate are released from a powder inhaler and supplied to the patient's airways.

Example 2

Dosage Aerosol with 100 μg Fluticasone and 10 μg Glycopyrrolate Per Single Dose

[0032] A quantity of 1000 g 1,1,1,2,3,3,3 heptafluoropropane (=HFA 227) is cooled down at a temperature of −55° C. and, while stirring, mixed with a solution of 11.7 g polyoxethylene-25-glyceryl-trioleate (trade name: Tagat TO) in 11.7 g absolute ethanol. Subsequently, 1500 mg micronized fluticasone and 150 mg micronized glycopyrrolate is added, and the suspension produced is intensively homogenized. While further cooling and stirring, the suspension is filled up with refrigerated propellant 227 to 1170 g and after mixing again filled in metal cans which are closed with metering valves releasing 50 μl of the suspension per actuation. Thus, 100 μg fluticasone and 10 μg glycopyrrolate are released per actuation.

1. A combination of topical anticholinergics with glucocorticoids or their physiologically acceptable salts for the treatment of diseases of the respiratory tract.

2. The combination according to claim 1 wherein the anticholinergic is selected from the group consisting of racemic glycopyrrolate, one of its enantiomers or diastereoisomers or their physiologically acceptable salts or a mixture thereof.

3. The combination according to claim 2 wherein the anticholinergic is R,R-glycopyrrolate or a physiologically acceptable salt thereof.

4. The combination according to claim 1 wherein the glucocorticoids are selected from the group consisting of budesonide, fluticasone, ciclesonide, mometasone, flunisolide, beclometason and loteprednol and their physiologically acceptable salts.

5. The combination according to claim 4 wherein the glucocorticoid is budesonide or a physiologically acceptable salt thereof.

6. The combination according to claim 4 where the glucocorticoid is fluticasone or a physiologically acceptable salt thereof.

7. (canceled)

8. A pharmaceutical for the treatment of asthma and respiratory diseases containing an anticholinergic and at least a glucocorticoid or their physiologically acceptable salts.

9. The pharmaceutical according to claim 8, wherein the anticholinergic, glucocorticoid or physiologically acceptable salt(s) thereof are available in an appropriate particle size dispersion when inhaled.

10. The pharmaceutical according to claim 8, that is an inhalable aerosol with or without propellant.

11. The pharmaceutical according to claim 8, that it an inhalable dry powder

12. The pharmaceutical according to claim 8, that is an inhalable suspension or solution.

13. The pharmaceutical according to claim 8, wherein the active ingredients are presented in fixed or free combination for simultaneous, sequential or separate administration together with excipients, adjuncts, and additives in a pharmaceutical form suitable for inhalative application.

14. The pharmaceutical according to claim 8, presented in an inhaler.

15. The pharmaceutical according to claim 8, where the anticholinergic is selected from the group consisting of racemic glycopyrrolate, an enantiomer thereof, a diasterioisomer thereof, physiologically acceptable salts thereof and mixtures thereof.

16. The pharmaceutical according to claim 15, containing R,R glycopyrrolate and budesonide or their physiologically acceptable salts as active substance.

17. The pharmaceutical according to claim 15, containing R,R glycopyrrolate and fluticasone or their physiologically acceptable salts as active substance.

18. (canceled)

19. (canceled)

20. (canceled)

21. (canceled)

22. (canceled)

23. (canceled)

24. (canceled)

25. A method for producing a pharmaceutical for the treatment of asthma/allergies and/or respiratory diseases in mammals comprising combining a topical anticholinergic and at least a glucocorticoid or physiologically acceptable salts thereof to obtain a pharmaceutical.

26. The method according to claim 25 wherein the anticholinergic is selected from the group consisting of racemic glycopyrrolate, an enantiomer thereof, a diastereoisomer thereof, a physiologically acceptable salt thereof and a mixtures thereof.

27. The method according to claim 25 wherein the anticholinergic is R,R-glycopyrrolate or a physiologically acceptable salt thereof.

28. A method of treating asthma/allergies and/or respiratory diseases in a mammal comprising administering an effective amount of the pharmaceutical of claim 25 to said mammal.

29. The method according to claim 28 wherein the mammal is selected from the group consisting of cats, dogs, and horses.

30. The method according to claim 28 wherein the disease is characterized by an obstructive component or underlying inflammation.

31. The method according to claim 30 wherein the disease is asthma or chronic obstructive pulmonary disease (COPD).

32. The method according to claim 28 wherein an adult human is treated with a daily dosage of R,R glycopyrrolate between 5 and 500 □g/day and a daily dosage of glucocorticoid is between 100 to 1.600 μg/day.

33. The method of claim 32 wherein the daily dosage of R,R glycopyrrolate is 15 to 300 μg/day.

34. The method of claim 32 wherein the daily dosage of glucocorticoid is between 200 and 400 μg/day.

35. The method according to claim 28 wherein an adult human is treated with a dosage of R,R glycopyrrolate between 5 and 100 □g/day and a daily dosage of glucocorticoid between 100 to 1.600 μg/day.

36. The method of claim 35 wherein the dosage of glucocorticoid is between 200 and 400 μg/day.

37. A method of producing a medicament for inhalative administration for the treatment of bronchial asthma and chronic obstructive pulmonary disease (COPD) comprising combining an anticholinergic with a glucocorticoid or their physiologically acceptable salts to obtain a medicament.

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