corticosteroid in the trachea and in the oropharyngeal area, wherein orally administered steroids could be eliminated or, at least, the oral dose of these drugs could be significantly reduced.

[019] It is, therefore, an object of this invention to provide a method, a device and/or a composition for efficacious treatment for severe and uncontrolled forms of asthma by providing means for delivery of a sufficiently high dosage of a corticosteroid for treatment of said severe uncontrolled asthma and wherein an oral delivery of corticosteroids could be either completely eliminated or reduced, and wherein said treatment would be able to deliver higher dosages of corticosteroid selectively into alveoli and bronchi of the lower peripheral lungs of an asthmatic patient without depositing said drug into a mouth or pharyngeal cavity or causing other undesirable adverse side effects.

[020] A further object of the invention is to provide a device capable of delivering an inhalable glucocorticoid composition efficiently to the lower lungs while minimizing its deposition in other regions of the respiratory system.

[021] A further object of the invention is to provide the combination of a device and an inhalable glucocorticoid composition which provides for the efficient delivery of a glucocorticoid to the lower lungs while minimizing its deposition in other regions of the respiratory system.

[022] Further objects of the invention will become apparent on the basis of the description and patent claims.

SUMMARY OF THE INVENTION

[0022a] In a first aspect, the present invention provides the use of an inhalable corticosteroid selected from the group consisting of fluticasone, beclomethasone dipropionate, budesonide, mometasone furoate, ciclesonide, flunisolide and triamcinolone acetonide as an aerosol comprising said

corticosteroid in amount from 400 to 4000 micrograms in the manufacture of a medicament for treatment of a patient having severe and uncontrollable asthma requiring a concurrent treatment with oral corticosteroids, wherein said medicament is to be administered

using a nebulizer device able to administer an aerosolized corticosteroid into lower lungs with overpressure of 40 mbar or less,

wherein said overpressure results in a larger than 200 micrograms deposition of said corticosteroid into the lower lungs, and

wherein said medicament results in reduction of 30% or more of oral steroids requirement and reduction of oropharyngeal side effects.

[0022b] In another aspect, the present invention provides the use of an inhalable corticosteroid selected from the group consisting of fluticasone, beclomethasone dipropionate, budesonide, mometasone furoate, ciclesonide, flunisolide and triamcinolone acetonide as an aerosol comprising said corticosteroid in amount from 400 to 4000 micrograms in the manufacture of a medicament for treatment of a patient having severe and uncontrollable asthma requiring a concurrent treatment with oral corticosteroids, wherein said medicament is to be administered

during an inspiration time comprising three predefined periods,

wherein in the first period lasting from 1 millisecond to 1 second, an aerosolized particle-free air is to be administered at a preset flow rate and at a preset volume;

wherein in the second period lasting from 0.1 to 5 seconds, an aerosolized corticosteroid is to be administered at a preset flow rate and at a preset volume;

wherein in the third period, lasting from 1 millisecond to 10 seconds, an aerosolized particle-free air is to be administered at a preset flow rate and at a preset volume;

wherein after the third period, the patient is instructed to stop inhaling and exhale;

wherein said protocol is repeated for 6 to 10 minutes or less; and

wherein said medicament results in a larger than 200 micrograms deposition of said corticosteroid into the lower lungs.

[0022c] In yet another aspect, the present invention provides the use of an inhalable glucocorticoid composition in the manufacture of a medicament for the therapy of a patient suffering from severe and uncontrolled asthma, wherein said composition is to be administered as a nebulised aerosol generated by an inhalation device, said device being adapted to

(a) emit the nebulised aerosol during the inhalation phase of the patient at a rate of not more than 20 liters per minute;

(b) emit, per inhalation phase, a total volume of 0.4 or more liters of gas phase, said gas phase including nebulised aerosol and optionally aerosol-free air; and

(c) emit, per inhalation phase, not more than 150 milliliters of aerosol-free air before emitting nebulised aerosol,

wherein said therapy further includes the oral administration of a glucocorticoid at a daily dose which is not higher than 40 milligrams of prednisolone or an equipotent dose of another glucocorticoid.

[023] Also disclosed is~~In a first aspect, the invention provides~~ an inhalable glucocorticoid composition for use in the therapy of a patient suffering from severe and uncontrolled asthma and an inhalation device by which the composition is administered as a nebulised aerosol. The device is adapted for emitting the nebulised aerosol during the inhalation phase of the patient at a rate of not more

than about 20 liters per minute. Moreover, it is adapted for emitting, per inhalation phase, a total volume of at least 0.4 liters and preferably in the range from about 0.4 to about 2 liters of gas phase, said gas phase including the nebulised aerosol and optionally aerosol-free air. It is further adapted to emit, per inhalation phase, not more than about 150 milliliters of aerosol-free air before emitting nebulised aerosol. According to this first aspect, the invention further provides that the therapy includes the oral administration of a glucocorticoid at a daily dose which is not higher than about 40 milligrams of prednisolone or an equipotent dose, which daily dose is herein understood such as to include zero milligrams, i.e. no concurrent oral glucocorticoid therapy.

[024] Also disclosed~~A further aspect of the current invention~~ is a method for the treatment of severe and uncontrolled asthma by providing means for increasing efficacy of an inhalable corticosteroid delivery by delivering large dosages of such inhalable corticosteroid selectively to alveoli and bronchiole of the lower lungs of a patient without causing adverse side effects and secondary symptoms by incidental delivery of these corticosteroid to the oral cavity, throat and upper lungs.

[025] Also disclosed~~Another aspect of the current invention~~ is a method for treatment of severe uncontrollable asthma by providing means for delivering a larger percentage of dosages of a corticosteroid selectively to the lower lungs of a patient suffering from severe uncontrollable asthma and thereby eliminating or significantly reducing a need for concurrently administered corticosteroids orally or systemically.

[026] Also disclosed~~Still another aspect of the current invention~~ is a method for treatment of severe uncontrollable asthma with completely eliminated or with at least 30% reduced dose of orally delivered corticosteroid by providing means for treating such severe and uncontrollable asthma with a high dosage of a corticosteroid delivered as an aerosol having particle sizes predominantly from about 2 to about 6 μm, by nebulization using a nebulizing system that applies, during delivery into a patient's lungs, an overpressure enabling such delivery in

less than 6-10 minutes and further resulting in selective delivery and homogeneous distribution of the corticosteroid in the lower lungs, wherein said nebulizing system is equipped to have a controlled airflow, and defined volume.

[027] Also disclosed~~Yet another aspect of the current invention~~ is a method for treatment of severe uncontrolled asthma with nebulized fluticasone, budesonide, beclomethasone dipropionate, budesonide, mometasone furoate, ciclesonide, flunisolide or triamcinolone acetonide wherein the clinical effect is reached without increasing systemic and local extrathoracic or oropharyngeal side effects.

[028] Also disclosed~~Yet another aspect of the current invention~~ is a method for treatment of severe uncontrolled asthma by inhalation of nebulized fluticasone as a representative corticosteroid administered into lungs via nebulizer with concentration of fluticasone in the nebulizer being higher than 200 μg/ml, preferably 0.5 – 2 mg/mL, formulated as a suspension and with total filling dose of fluticasone not exceeding about 4000 μg, using a nebulizing system that applies overpressure during inhalation and thus assures selective deposition of more than 200 μg of said corticosteroid into the lower lungs in less than 6-10 minutes.

[029] Also disclosed~~Yet another aspect of the current invention~~ is a nebulizing system comprising a device able to provide an overpressure as well as a controlled air flow during a patient's inspiration time to reduce patient breathing effort with pressure at the nebulizer mouthpiece up to a positive pressure of between 0-40 mbar.

[030] Also disclosed~~Another aspect of the current invention~~ is a method for treatment of severe uncontrollable asthma by providing a nebulization protocol wherein, during one inspiration time and under the mean inspiratory flow rate equal to or below 20 l/min, the patient is subjected to a first volume of 150 ml or less of particle-free air in a predetermined time of less than 0.5 sec, followed by a second volume of between about 200 and about 3000 ml of an aerosol containing an inhalable corticosteroid administered in a predetermined time from about 1 to about 10 seconds, said aerosol preferably administered within less than 0.2 sec after the

start of inspiration, followed by a third volume of between about 100 to about 500 ml of particle-free air, and wherein such protocol results in forcing said inhalable corticosteroid from the extrathoracic and tracheal airways to be deposited more selectively into the lower airways.

[031] Also disclosed~~Yet another aspect of the current invention~~ is a method for treatment of severe uncontrolled asthma by inhalation of nebulized corticosteroid in an aerosol having particle sizes predominantly in the range from about 2 to about 6 μm, preferably from about 3 to about 5 μm.

[032] Also disclosed~~Another aspect of the current invention~~ is a method for treatment of severe uncontrollable asthma by providing means for delivering larger dosages of a corticosteroid once a day selectively to the lower lungs of a patient thereby eliminate or significantly reduce a need for concurrently administered corticosteroid orally or systemically wherein asthma is improved without loss of FEV1 and with diminished adverse side effects.

[033] Also disclosed~~Still another aspect of the current invention~~ is a method for treatment of severe uncontrollable asthma by providing a nebulization system for individualization of the treatment wherein said nebulization system comprises a pre-programmable volume for drug delivery, a pre-programmable air flow delivery, a preprogrammable overpressure, and may further comprise a compliance monitoring system which allows the patient and the doctor to see and control frequency of the corticosteroid delivery, such means being any storage media, a smart card, a chip or a wireless communication connection that permits evaluation of the treatment during and after the end of a treatment period and determination of frequency of the corticosteroid administration.

DEFINITIONS

[034] "Glucocorticoid" means a pharmaceutically acceptable glucocorticoid compound useful for oral and/or inhalable therapy. As used herein, such compound may also be referred to as "steroid" or "corticosteroid".