USE OF URIDINE TRIPHOSPHATE RELATED COMPOUNDS FOR THE PREVENTION AND TREATMENT OF PNEUMONIA IN IMMOBILIZED PATIENTS

VERWENDUNG VON URIDIN-TRIPHOSPHAT VERWANDTE VERBINDUNGEN ZUR PRÄVENTION UND BEHANDLUNG VON PNEUMONIE IN IMMOBILISIERTEN PATIENTEN

UTILISATION DE COMPOSÉS APPARENTES À L’URIDINE TRIPHOSPHATE POUR PRÉVENIR ET TRAITER LA PNEUMONIE CHEZ DES PATIENTS IMMOBILISÉS

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WO-A-92/11016
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• R.E. WOOD ET AL.: "Recent advances in aerosol therapy." J. AEROSOL MED., vol. 7, no. 1, 1994, pages 1-11, XP002046473


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Description

Technical Field

[0001] This invention relates to the use of certain nucleoside phosphates for preparing pharmaceutical preparations for use in a method of removing or preventing the accumulation of retained mucous secretions from the lungs and bronchi of immobilized or bedridden patients, including those whose breathing is assisted by mechanical ventilation.

Background of the Invention

[0002] Bedrest or immobility can result from a variety of health problems, both acute and chronic in nature. A primary concern in caring for persons who are immobilized or placed on bedrest is that of prevention of pneumonia and other respiratory problems. Once pneumonia develops in these patients, morbidity and mortality can be significant. Because of the immobility it may be difficult for patients to cough and mobilize secretions. Immobile patients include patients confined to either beds or wheelchairs. In addition to complications arising from the immobility, the underlying health problem may place patients at increased risk for infection. Factors or disease states which predispose for high risk for pneumonia development include: altered conciousness (from head injury, anesthesia, drug overdose or other serious illness), tracheal intubation (via endotracheal, nasotracheal, or tracheostomy tubes), mechanical ventilation, and other procedures or treatments including intra-aortic balloon pump, hemo- or ultrafiltration, chronic disease states such as cancer, progressive neuromuscular disorders (multiple sclerosis, amytropic lateral sclerosis, etc.); heart disease, diabetes mellitus, acute neurological disorders (stroke, seizures, Guillain-Barre' syndrome, spinal cord injury), and rehabilitation from injuries or surgeries (bedrest, traction, etc.). (p. 502 "Medical-Surgical Nursing: Assessment and Management of Clinical Problems" by S. Lewis and I. Collier, 2nd ed. 1987, McGraw-Hill, New York).

[0003] Mechanical ventilation is indicated for respiratory failure or compromise resulting from a variety of pulmonary disorders and complications. It has been estimated that over 100,000 patients require mechanical ventilation in the U.S. every year (I. Kappstein, et al., Eur. J. Clin. Microbiol. Infect. Dis. 11(6), 504-8 (1992)). Morbidity and mortality from the underlying disorders can be high, and the addition of mechanical ventilation further increases risk. Complications resulting from mechanical ventilation may include: ventilator-associated pneumonia (VAP), pneumothorax, pulmonary embolus, right mainstem bronchus intubation, accidental exubration, aspiration of gastric contents, sepsis, fluid overload/heart failure, hypotension, and death (B. deBoisblanc, et al., Chest 103, 1543-7 (1993)). One of the most common complications is VAP, with an incidence conservatively estimated at 25%, with greater than 12,000 deaths per year due to VAP (D. Craven, et al., Am. Rev. Respir. Dis. 133, 792-6 (1986). Increased vigilance by nursing or other health care professionals, invasive monitoring, use of vasoactive medications, and frequent overall assessments greatly increase the cost of care for mechanically ventilated patients. A conservative estimate for total cost of these mechanically ventilated patients approaches $1.5 billion per year in the U.S. alone (I. Kappstein, supra).

[0004] Patients who are intubated and on mechanical ventilation are at several-fold higher risk for developing pneumonia and other pulmonary complications than non-intubated patients, due to the impairment or absence of several aspects of the normal pulmonary defense mechanisms (T. Inglis, J. Hosp. Infect. 30, 409-13 (1995)). Normal defense mechanisms consist of: 1) filtration, warming, and humidification of air; 2) epiglottis closure over the trachea; 3) cough reflex; 4) mucociliary escalator system; 5) immunoglobulins A and G; and 6) activity of alveolar macrophages. Airways distal to the larynx are normally sterile, but with intubation, the cough reflex is impaired and closure of the epiglottis cannot occur, allowing contamination of the lower airways. Because clinical practice guidelines generally do not advocate the maintenance of a complete airway seal in the trachea by the endotracheal cuff, some leakage of nasopharyngeal secretions below the epiglottis may occur, therefore increasing risk for infection in the lower airways (P. Mahul, et al., Intensive Care Med. 18, 20-5 (1992)).

[0005] The leading cause of VAP is thought to be aspiration of colonized gastric secretions via the incompletely closed glottis (P. Mahul, et al., supra). Colonization of the lower respiratory tract, especially with gram-negative bacteria is an early stage in the development of VAP. In addition, the use of suction catheters via the endotracheal tube to clear lower airway secretions, as well as other manipulations of the ventilatory system, significantly increase the chance for nosocomial infection, especially pneumonia. The normal warming, humidification, and filtration mechanisms for distal airways are non-functional for intubated patients, and the underlying conditions of the patient, i.e., malnutrition, fluid and/or electrolyte imbalance, and infections, may further complicate a patient's prognosis.

[0006] Mucociliary transport velocity has been shown to be impaired in patients who are intubated and receiving mechanical ventilation (F. Konrad, et al., Intensive Care Med. 21, 482-89 (1995); F. Konrad, et al., Chest 105(1), 237-41 (1994); F. Konrad, et al., Chest 102(5), 1377-83 (1992)). Because movement and clearance of secretions is an important lung defense mechanism, any impairment of this function, in addition to the introduction of artificial airways, mechanical ventilation, and the underlying disease state, can severely compromise the pulmonary host defense mechanisms.

[0007] Agents that can obviate the need for intubation and mechanical ventilation, or reduce time on mechanical
ventilation, thereby decreasing the incidence of complications such as VAP, would certainly have a significant impact in the critical care setting, both in terms of the health of the patient and the costs associated with treatment. Applicants have discovered that uridine 5’-triphosphate (UTP) and related nucleotide compounds modulate specific activities of human airway epithelial cells that are components of the mucociliary escalator. Transport of foreign particles out of the lungs via the mucociliary escalator relies on the integrated action of: 1) mucus secretion by goblet cells and submucosal glands which traps foreign particles; 2) cilia to propel the mucus out of the lungs; and 3) epithelial ion transport systems which maintain the ionic milieu of, and hence the viscosity of, airway surface liquid to allow effective ciliary beating. Application of extracellular UTP to the apical surface of normal human nasal epithelial cells in primary culture causes increased Cl- secretion in a concentration-dependent manner (S. Mason, et al., Br. J. Pharmacol. 103, 1649-56 (1991)).

M. Knowles, et al., N. Engl. J. Med. 325, 533-8 (1991)). This response was also observed in cultured nasal epithelial cells from cystic fibrosis (CF) patients (R. Benali, et al., Am. J. Respir. Cell Mol. Biol. 10, 363-8 (1994)). This increased Cl- transport has been associated with increased fluid transport across the epithelium (C. Jiang, et al., Science 262, 424-7 (1993)). In addition to these effects on Cl- and fluid transport, UTP has been shown to produce an increase in cilia beat frequency in cultured human epithelial cells from normal adult humans and CF patients (D. Drutz, et al., Drug Dev Research 1996; 37(3):185 "Uridine 5’ Triphosphate (UTP) Regulates Mucociliary Clearance Via Purinergic Receptor Activation", presented at "Purines ’96" conference held in Milan, Italy, July 6-9, 1996). These actions of UTP have been associated with an increase in intracellular calcium ion (Ca++) due to stimulation of phospholipase C by the P2Y2 receptor (H. Brown, et al., Mol. Pharmacol. 40, 648-55 (1991)). UTP has also been shown to increase the rate and total amount of mucin secretion by goblet cells in human airway epithelial explants (M. Lethem, et al., Am. J. Respir. Cell Mol. Biol. 9, 315-22 (1993)). These effects were observed in tissues from both healthy individuals and patients with CF.

As for secondary pharmacological effects, aerosol administration of UTP (10-2 M and 10-1 M in nebulizer) to anesthetized and ventilated dogs had no significant effects on peak inspiratory airway pressure, mean pulmonary artery pressure, heart rate, cardiac output, thoracic aortic pressure, electrocardiogram, or arterial blood gases (S. Mason, et al., Am. Rev. Respir. Dis. 147, A27 (1993)). To test the effect of intravenous administration, sequential doses of intravenous UTP (0.1, 1, 3 and 5 mmoles/kg) were infused into anesthetized, ventilated dogs over 10 minutes produced no significant changes in mean pulmonary artery pressure, heart rate, cardiac output, or mean arterial pressure. Id.

Because UTP has been shown to acutely improve mucociliary clearance (MCC) by 2.5-fold in normal volunteers without significant effects (D. Drutz, supra), it is thought that MCC improvement in mechanically ventilated patients would prevent the pooling of secretions, the plugging of mucus, and the resulting infections and atelectasis. In addition, removal of pulmonary secretions by coughing or suctioning may be enhanced by hydrating and thinning mucus secretions. UTP may, therefore, provide a safe adjunct or alternative to beta-adrenergic agonists for enhancing the removal of lung secretions in mechanically ventilated patients. Additionally, the improvement in MCC will enhance the patient’s pulmonary host defense mechanisms, thus preventing ventilator-associated pneumonia (VAP) and other pulmonary complications, such as atelectasis. In addition, by acting on receptors in Type II alveolar cells, UTP may enhance surfactant production and therefore help maintain optimal gas exchange and airway epithelium function in terminal small airways.


Applicant postulates that MCC in mechanically-ventilated patients can be improved by administering nucleoside phosphates such as: P1,P4-di(uridine-5’)tetraphosphate (U2P4). U2P4 is the preferred embodiment of the present invention. By administering U2P4 prior to or soon after intubation, VAP and other associated complications of mechanical ventilation may be avoided. The present invention may also be used to treat chronic bronchitis patients who develop respiratory distress that requires intubation. Finally, the present invention may also be used to promote the drainage of retained mucous secretions in immobilized or bedridden patients.

Summary of the Invention

A method of preventing or treating pneumonia, including ventilator-associated pneumonia (VAP), in a subject in need of such treatment is disclosed. The present invention may be used to promote the drainage and clearance of retained mucous secretions in immobilized or bedridden patients to prevent pneumonia. This is achieved by administering to the patient a compound of Formula II, or a pharmaceutically acceptable salt thereof, in an amount effective to hydrate mucous secretions and stimulate ciliary beat frequency in the luminal epithelial cells of the airway passages:
wherein:

B is uracil

[0016] P1,P4-di(uridine-5') tetraphosphate [U2P4] is a preferred embodiment of the invention.

[0017] A pharmaceutical formulation containing the compound of Formula II, in a sufficient amount is effective to promote or enhance clearance of secretions, hydrate mucous secretions and stimulate ciliary beat frequency in the luminal epithelial cells of the airway passages in a patient in need of such treatment.

[0018] In a further aspect, the present invention is useful in the stimulation of surfactant production in Type II alveolar cells.

[0019] A further aspect of the present invention is the use of the active compounds disclosed herein for the manufacture of a medicament for the therapeutic hydration of mucous secretions and stimulation of ciliary beat frequency in the luminal epithelial cells of the airway passages in a patient in need of such treatment.

Brief Description of the Drawings

Figure 1 represents the results of the studies described in Example 2 showing the effects of UTP on trachael mucous velocity.

Figure 2 represents the results of the studies described in Example 2 showing the effects of U2P4 on tracheal mucous velocity.

Figure 3 represents the results of studies described in Example 2 showing a bar graph of the TMV post dose for varying concentrations of UTP and U2P4.

Figure 4 represents the results of the studies described in Example 3 showing the effects of UTP and U2P4 in mucociliary clearance of adult ewes.

Description of the Specific Embodiments

[0021] The present invention may be used to prevent or treat pneumonia, including ventilator-associated pneumonia (VAP), by hydrating retained mucous secretions, stimulating ciliary beat frequency and promoting clearing of mucous in the airways of a subject in need of such treatment. The present invention may also be used to prevent or treat sinusitis in nasally intubated patients, and to improve mucociliary clearance (MCC) thereby preventing pneumonia in chronically immobilized or bedridden patients. The present invention increases mucociliary clearance (MCC) in three
This compound can be made in accordance with known procedures, or variations thereof. For example, \( \text{U}_2\text{P}_4 \) can be displacement process \( \text{P}_2\text{P}_3\text{-dioxo-P'}\text{5'-nucleosidylcyclo triphophite} \). Oxidation with sulfur forms a nucleoside group of a nucleoside to form an intermediate, which on a subsequent reaction with pyrophosphate forms, in a double the following methods: 2-Chloro-4H-1,3,2-benzodioxaphosphorin-4-one can be used to phosphitylate the 5'-hydroxy (0.35 mmol) in a medium of anhydrous pyridine (10 ml). C. Vallejo, et al., Biochem. Biophys. Acta 438, 304-09 synthesized through the reaction of uridine 5'-phosphoromorpholidate (0.54 mmol) with triethylamine salt of pyrophosphate (0.35 mmol) in a medium of anhydrous pyridine (10 ml). C. Vallejo, et al., Biochem. Biophys. Acta 438, 304-09 (1976).

The present invention also encompasses compounds in the L-configuration, and mixtures of compounds in the D- and L- configurations, unless otherwise specified. The naturally occurring D-configuration is preferred.

A compound illustrative of the compounds of Formula II includes \( \text{P}_1\text{P}_4\text{-di(urdine-5') tetraphosphate (U}_2\text{P}_4 \) . This compound can be made in accordance with known procedures, or variations thereof. For example, \( \text{U}_2\text{P}_4 \) can be synthesized through the reaction of uridine 5'-phosphoromorpholidate (0.54 mmol) with triethylamine salt of pyrophosphate (0.35 mmol) in a medium of anhydrous pyridine (10 ml). C. Vallejo, et al., Biochem. Biophys. Acta 438, 304-09 (1976).

Derivatives with alpha, beta and gamma thiophosphorus groups can be derived by the following or by adapting the following methods: 2-Chloro-4H-1,3,2-benzodioxaphosphorin-4-one can be used to phosphitylate the 5'-hydroxy group of a nucleoside to form an intermediate, which on a subsequent reaction with pyrophosphate forms, in a double displacement process a \( \text{P}_2\text{P}_3\text{-dioxo-P'}\text{-5'-nucleosidylcyclo triphophite} \). Oxidation with sulfur forms a nucleoside 5'-1-thiocyclotri phosphophite, which is hydrolyzed to the diastereomeric mixture of a nucleoside 5'-O-(1-thiotriphosphate). Alternatively, \( \text{P}_2\text{P}_3\text{-dioxo-P'}\text{-5'-nucleosidylcyclo triphophite} \) can be oxidized with iodine/water to yield nucleoside 5'-triphosphates. This reagent can also be used for the synthesis of nucleoside 2',3'-cyclic phosphorothioates. J. Ludwig and F. Eckstein, J. Org. Chem. 54, 631-35 (1989).

Derivatives with alpha, beta and gamma thiophosphorus groups can also be made by following the protocol recited in F. Eckstein and R. Goody, Biochemistry 15, 1685 (1976).

The active compounds of Formula II may be administered by themselves or in the form of their pharmaceutically acceptable salts, e.g., an alkali metal salt such as sodium or potassium, an alkaline earth salt, or an ammonium and tetraalkyl ammonium salts, \( \text{NX}_4^+ \) (wherein \( \text{X} = \text{C}_1\text{-4} \) ). Pharmacologically acceptable salts are salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects.

The active compounds disclosed herein may be administered to the lungs, sinuses, ears or eyes by a variety of suitable means, but are preferably administered by administering a liquid/liquid suspension (either a nasal spray of respirable particles which is either inhaled by the subject or administered to the subject by means of nebulization through the mechanical ventilation system, or nasal drops of a liquid formulation, or eye drops of a liquid formulation) comprised of the active compound. Liquid pharmaceutical compositions of the active compound for producing a nasal spray or nasal powder, nasal or eye drops, or a liquid nebulized preparation may be prepared by combining the active compound with a suitable vehicle, such as sterile pyrogen free water or sterile saline by techniques known to those skilled in the art. Further, other methods of administration could be used including, systemic administration and oral forms (liquid or pill), powder inhalation, topical, injectable, infra-operative instillation of a gel, cream, powder, foam, crystals or liquid suspension or suppository form.

The methods described herein are also applicable to veterinary use.

EXPERIMENTAL

Example 1

Treatment of Patients At Risk For Ventilator-Associated Pneumonia (VAP)

Uridine 5'-triphosphate (UTP) or \( \text{P}_1\text{P}_4 \text{di(urdine-5')-tetraphosphate (U}_2\text{P}_4 \) is administered to adult patients with acute neurological impairment requiring intubation and mechanical ventilation. UTP is administered in an aerosolized form via an in-line nebulizer, 2-3 times per day, for a total of 5 days. The concentration of UTP is in the range of 10-7 to 10-1 moles/liter. Treatment with UTP begins within 12 hours of intubation/mechanical ventilation. The length of treatment for each patient is 5 days.

The safety of UTP to prevent or treat VAP is assessed by standard safety measures of vital signs--heart rate, respiratory rate, blood pressure, electrocardiogram and laboratory blood tests (e.g., blood chemistries, complete blood count, hematology), as well as any adverse events observed.

The effectiveness of UTP in preventing VAP is measured by a diminution of symptoms of VAP as determined by periodic physical examinations, and by laboratory and bacteriology evaluations. Another means of measuring effectiveness is a decrease in the total number of days on mechanical ventilation--this is because an improvement in
mucociliary clearance would decrease airway ventilating pressures and the need for assisted ventilation.

Example 2

**Tracheal Mucus Study**

[0032] The effects of UTP and U₂P₄ on tracheal mucus velocity (TMV) were studied using the following procedures: The nasal passages of conscious adult ewes were anesthetized with a 2% lidocaine solution. After local anesthesia was produced, a modified endotracheal tube 7.5 mm was placed such that the cuff was just below the vocal cords (verified by fluoroscopy). Inspired air was warmed and humidified. The cuff of the endotracheal tube was inflated only during administration of the test compound to minimize possible impairment of TMV by the cuff. Test compounds were administered by nebulization in a volume of 4 mL over a period of 10-12 min.

[0033] TMV was measured by fluoroscopy. Ten to twenty radiopaque disks (Teflon®/bismuth trioxide; 1mm diameter, 0.8 mm thick, weighing 1.8 mg) were introduced into the trachea through a modified suction catheter with a puff of compressed air (3-4 L/min). Velocities of the individual disks were recorded on videotape from a portable image intensifier unit. Individual disk velocities were calculated by measuring the distance traveled by each disk during a 1 min observation period. Values reported are the means of the individual disk velocities. A collar was worn by the sheep which was used as a standard to correct for magnification errors inherent in the fluoroscope.

[0034] Both UTP and U₂P₄ produced significant dose-related effects on tracheal mucus velocity. The doses ranged from 4 to 400 µmole. Both compounds had their maximal effects at a dose of 400 µmole (4 ml of 10⁻¹ M). UTP produced a maximal effect of 125 ± 7 % of baseline (mean ± standard error, n=6). U₂P₄ produced a maximal effect of 144 ± 9 % of baseline (n=6). Both compounds produced their maximal effects 15 min after administration. The highest dose of UTP produced significant effects on TMV up to 4 h after administration. The effects of U₂P₄ were significant out to 2 h after administration. Results are shown in Figures 1-3.

Example 3

**Mucociliary Clearance Study**

[0035] In this study healthy adult ewes were given 99 mTc-labeled human serum albumin (99mTc-HSA) via a nebulized aerosol. The 99 mTc-HSA (20mCi) was administered over 5 min through a nasotracheal tube introduced under local anesthesia with 2% lidocaine. After administration of the 99mTc-HSA, the animals were given a test compound: either UTP or U₂P₄. Test compounds were administered by nebulization in a volume of 4 mL over a period of 10-12 min. The test compounds were given at a dose of 400 µmole. After the administration of the test compound, the animals were extubated. Clearance of the radiolabeled particles was monitored with a gamma camera. Measurements were made at 0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 75, 90, 105 and 120 min. Initial results (n=2) have shown that both test compounds promote clearance of the radiolabeled particles (compared to the saline control). Results are shown in Figure 4.

[0036] The results of the studies in sheep on tracheal mucus velocity (TMV) and whole lung mucociliary clearance (WLC) demonstrated that UTP and U₂P₄ can enhance mucociliary clearance in intubated animals. Intubation is known to have detrimental effects on mucociliary clearance. This was shown in the TMV study by the decline in TMV over the study period in the saline treated animals. Despite this declining baseline, UTP and U₂P₄ were able to produce an enhancement of TMV. Although the intubation period was brief in the WLC study (only during administration of the test compound), impairment of mucociliary clearance is a realistic possibility. UTP and U₂P₄ produced enhanced clearance under these conditions as well. These data strongly suggest that these agents will enhance mucociliary clearance in intubated patients, which may be therapeutically useful in the prevention or treatment of VAP and subjects at risk.

[0037] The subject methods and compounds described herein provide a means for preventing or treating ventilator-associated pneumonia in the intensive care unit setting. The method comprises administering to the airways of the subject a uridine triphosphate such as uridine 5'-triphosphate (UTP) or any analog of UTP, for example U₂P₄, in an amount effective to hydrate mucous secretions to promote or enhance clearance, or to stimulate ciliary beat frequency in the lungs.

Claims

1. Use of a compound of Formula II, or a pharmaceutical acceptable salt thereof, in a pharmaceutical carrier having an amount of said compound effective to promote clearance from the airways:
wherein:

B is uracil

for preparing a pharmaceutical composition for use in a method of preventing or treating pneumonia, including ventilator-associated pneumonia, in a bedridden or immobilized subject in need of such treatment.

2. The use according to claim 1, wherein said compound is delivered by administering a liquid/liquid suspension, including eye drops of said compound to the eyes, or nasal drops, or spray, of said compound to the nasopharyngeal airways, nasotracheal tube, endotracheal tube, or tracheostomy of said subject, such that a therapeutically effective amount of said compound contacts the airways of said subject either directly or via systemic absorption and circulation.

3. The use according to claim 1, wherein said compound is delivered by administering an oral form of said compound, such that a therapeutically effective amount of said compound contacts the airways of said subject via systemic absorption and circulation.

4. The use according to claim 1, wherein said compound is delivered by administering a nebulized aerosol or suspension of said compound to the nasopharyngeal airways, nasotracheal tube, endotracheal tube, or tracheostomy of said subject, such that a therapeutically effective amount of said compound contacts the airways of said subject either directly or via systemic absorption and circulation.

5. The use according to claim 1, wherein said compound is delivered by administering a topical form of said compound to the airways via the nose, eyes, outer ear or nasopharyngeal airways of said subject, such that a therapeutically effective amount of said compound contacts the airways of said subject.

6. The use according to claim 1, wherein said compound is delivered by administering an injected form of said compound, such that a therapeutically effective amount of said compound contacts the airways of said subject either directly or via systemic absorption and circulation.

7. The use according to claim 1, wherein said compound is delivered by administering a suppository form of said compound, such that a therapeutically effective amount of said compound contacts the airways of said subject via systemic absorption and circulation.
8. The use according to claim 1, wherein said compound is delivered by administering an intra-operative instillation of a gel, cream, powder, foam, crystals or liquid suspension form of the active compound such that a therapeutically effective amount of said compound contacts the airways either directly or via systemic absorption and circulation.

9. The use according to claim 1, wherein said compound is delivered by administering a dry-powder aerosolized form of said compound, such that a therapeutically effective amount of said compound contacts the airways of said subject either directly or via systemic absorption and circulation.

10. The use according to claim 1, wherein said compound is administered in an amount sufficient to achieve concentrations thereof on the surfaces of the airways of said subject to increase the ciliary beat frequency of cilia on the surface of luminal epithelia cells, to increase the secretions of mucous by goblet cells, to increase the chloride ion secretion to stimulate surfactant reduction and to promote the clearance of retained secretions.

11. The use according to claim 1, wherein said compound is administered in an amount sufficient to achieve concentrations on the surfaces of the airways of said subject of from about 10⁻⁷ to about 10⁻¹ moles/liter.

12. The use according to claim 1, wherein said compound of Formula II is selected from the group consisting of P1, P4-di(uridine-5')tetraphosphate(U₂P₄) and substituted derivatives and the pharmaceutically acceptable salts thereof.

13. Use of a compound of Formula II, or a pharmaceutically acceptable salt thereof, in a pharmaceutical carrier having an amount of said compound effective to promote mucociliary clearance from the sinuses for preparing a pharmaceutical composition for use in a method of preventing or treating sinusitis in a nasally-intubated patient.

14. Use of a compound of Formula II, or a pharmaceutically acceptable salt thereof, in a pharmaceutical carrier having an amount of said compound effective to promote mucociliary clearance from the airways for preparing a pharmaceutical composition for use in a method of preventing or treating retained mucous secretions in a bedridden or immobilized patient.

15. The use according to claim 14, wherein the subject is placed in a lateral rotation therapeutic bed which rotates the subject to further loosen mucous secretions.

Patentansprüche

1. Verwendung einer Verbindung der Formel II oder eines pharmazeutisch annehmbaren Salzes davon in einem pharmazeutischen Träger mit einer Menge an Verbindung, die dahingehend wirksam ist, dass sie die Freisetzung aus den Luftwegen fördert:

![Formel II](image)

worin:

B Uracil ist
zum Herstellen einer pharmazeutischen Zusammensetzung zur Verwendung bei einem Verfahren zum Verhindern oder Behandeln einer Lungenentzündung, einschließlich einer mit einem Beatmungsgerät in Zusammenhang stehenden Lungenentzündung, bei einer bettlägerigen oder ruhiggestellten Person, die einer solchen Behandlung bedarf.

2. Verwendung nach Anspruch 1, wobei die Verbindung durch Verabreichen einer Flüssig/Flüssig-Suspension, einschließlich Augentropfen der Verbindung an die Augen oder Nasentropfen oder Spray der Verbindung an die nasopharyngealen Luftwege, die nasotracheale Röhre, endotracheale Röhre oder Tracheostomie der Person zugeführt wird, so dass eine therapeutisch wirksame Menge an Verbindung die Luftwege der Person entweder direkt oder über systemische Absorption und Zirkulation kontaktiert.

3. Verwendung nach Anspruch 1, wobei die Verbindung durch Verabreichen einer oralen Form der Verbindung zugeführt wird, so dass eine therapeutisch wirksame Menge an Verbindung die Luftwege der Person über systemische Absorption und Zirkulation kontaktiert.

4. Verwendung nach Anspruch 1, wobei die Verbindung durch Verabreichen eines zerstäubten Aerosols oder Suspension der Verbindung an die nasopharyngealen Luftwege, die nasotracheale Röhre, endotracheale Röhre oder Tracheostomie der Person zugeführt wird, so dass eine therapeutisch wirksame Menge an Verbindung die Luftwege der Person entweder direkt oder über systemische Absorption und Zirkulation kontaktiert.

5. Verwendung nach Anspruch 1, wobei die Verbindung durch Verabreichen einer topischen Form der Verbindung an die Luftwege über die Nase, Augen, Außenohr oder nasopharyngealen Luftwege der Person zugeführt wird, so dass eine therapeutisch wirksame Menge an Verbindung die Luftwege der Person kontaktiert.

6. Verwendung nach Anspruch 1, wobei die Verbindung durch Verabreichen einer injizierten Form der Verbindung zugeführt wird, so dass eine therapeutisch wirksame Menge an Verbindung die Luftwege der Person entweder direkt oder über systemische Absorption und Zirkulation kontaktiert.

7. Verwendung nach Anspruch 1, wobei die Verbindung durch Verabreichen einer Suppositoriumsform der Verbindung zugeführt wird, so dass eine therapeutisch wirksame Menge an Verbindung die Luftwege über systemische Absorption und Zirkulation kontaktiert.

8. Verwendung nach Anspruch 1, wobei die Verbindung durch Verabreichen einer intraoperativen Instillation eines Gels, einer Creme, eines Pulvers, eines Schaums, von Kristallen oder einer FlüssigSuspensionsform der aktiven Verbindung zugeführt wird, so dass eine therapeutisch wirksame Menge an Verbindung die Luftwege entweder direkt oder über systemische Absorption und Zirkulation kontaktiert.

9. Verwendung nach Anspruch 1, wobei die Verbindung durch Verabreichen einer aerosolisierten Form eines Trockenpulvers der Verbindung zugeführt wird, so dass eine therapeutisch wirksame Menge an Verbindung die Luftwege der Person entweder direkt oder über systemische Absorption und Zirkulation kontaktiert.

10. Verwendung nach Anspruch 1, wobei die Verbindung in einer Menge verabreicht wird, die ausreicht, um auf den Oberflächen der Luftwege der Person Konzentrationen davon zu erreichen und so die ziliare Bewegungsfrequenz von Zilien auf der Oberfläche von luminalen Epithelzellen zu erhöhen, um die Sekretionen von Schleim durch Becherzellen zu steigern, um die Chloridionensekretion zu erhöhen und so die Surfactant-Reduktion zu stimulieren und die Freisetzung von zurückgebliebenen Sekreten zu fördern.

11. Verwendung nach Anspruch 1, wobei die Verbindung in einer Menge verabreicht wird, die ausreicht, um auf den
Oberflächen der Luftwege der Person Konzentrationen von ungefähr 10^{-7} bis ungefähr 10^{-1} mol/Liter zu erreichen.

12. Verwendung nach Anspruch 1, wobei die Verbindung der Formel II aus der Gruppe bestehend aus P1,P4-Di(uridin-5')-tetraphosphat (U_2P_4) und substituierten Derivaten und den pharmazeutisch annehmbaren Salzen davon ausgewählt ist.

13. Verwendung einer Verbindung der Formel II oder eines pharmazeutisch annehmbaren Salzes davon in einem pharmazeutischen Träger, der eine Menge an Verbindung aufweist, die dahingehend wirksam ist, dass sie die mukoziliare Freisetzung aus den Nebenhöhlen fördert, zum Herstellen einer pharmazeutischen Zusammensetzung zur Verwendung bei einem Verfahren zum Verhindern oder Behandeln von Sinusitis bei einem über die Nase intubierten Patienten.

14. Verwendung einer Verbindung der Formel II oder eines pharmazeutisch annehmbaren Salzes davon in einem pharmazeutischen Träger, der eine Menge an Verbindung aufweist, die dahingehend wirksam ist, dass sie die mukoziliare Freisetzung aus den Luftwegen fördert, zum Herstellen einer pharmazeutischen Zusammensetzung zur Verwendung bei einem Verfahren zum Verhindern oder Behandeln von zurückgebliebenen Schleimsekreten bei einem bettlägerigen oder ruhiggestellten Patienten.

15. Verwendung nach Anspruch 14, wobei die Person in ein laterales therapeutisches Rotationsbett gelegt wird, das die Person dreht, um weitere Schleimsekrete zu lösen.

Revendications

1. Utilisation d’un composé de la formule II, ou son sel acceptable sur le plan pharmaceutique, dans un support pharmaceutique ayant une quantité dudit composé efficace pour promouvoir la clairance des voies aériennes :

Formule II

B est de l’uracile

pour préparer une composition pharmaceutique à utiliser dans une méthode de prévention ou de traitement de la pneumonie, y compris la pneumonie associée à un respirateur, chez un sujet alité ou immobilisé ayant besoin d’un tel traitement.
2. Utilisation selon la revendication 1, dans laquelle ledit composé est délivré en administrant une suspension liquide / liquide, y compris des gouttes oculaires dudit composé dans les yeux, ou des gouttes nasales, ou une vaporisation dudit composé dans les voies aériennes nasopharyngiennes, par sonde nasotrachéale, par sonde endotrachéale, ou par trachéotomie dudit sujet, de sorte qu’une quantité efficace sur le plan thérapeutique dudit composé entre en contact avec les voies aériennes dudit sujet, soit directement, soit par une absorption et une circulation systémiques.

3. Utilisation selon la revendication 1, dans laquelle ledit composé est délivré en administrant une forme orale dudit composé, de sorte qu’une quantité efficace sur le plan thérapeutique dudit composé entre en contact avec les voies aériennes dudit sujet.

4. Utilisation selon la revendication 1, dans laquelle ledit composé est délivré en administrant un aérosol nébulisé ou une suspension dudit composé aux voies aériennes nasopharyngiennes, par sonde nasotrachéale, par sonde endotrachéale, ou par une trachéotomie dudit sujet, de sorte qu’une quantité efficace sur le plan thérapeutique dudit composé entre en contact avec les voies aériennes dudit sujet soit directement, soit par absorption et circulation systémiques.

5. Utilisation selon la revendication 1, dans laquelle ledit composé est délivré en administrant une forme topique dudit composé aux voies aériennes, via le nez, les yeux, l’oreille externe ou les voies aériennes dudit sujet, de sorte qu’une quantité efficace sur le plan thérapeutique dudit composé entre en contact avec les voies aériennes dudit sujet.

6. Utilisation selon la revendication 1, dans laquelle ledit composé est délivré en administrant une forme injectée dudit composé, de sorte qu’une quantité efficace sur le plan thérapeutique dudit composé entre en contact avec les voies aériennes dudit sujet, soit directement, soit par absorption et circulation systémiques.

7. Utilisation selon la revendication 1, dans laquelle ledit composé est délivré en administrant une forme de suppositoire dudit composé, de sorte qu’une quantité efficace sur le plan thérapeutique dudit composé entre en contact avec les voies aériennes dudit sujet, via une absorption et circulation systémiques.

8. Utilisation selon la revendication 1, dans laquelle ledit composé est délivré en administrant une instillation péropéritoire d’un gel, d’une crème, d’une poudre, de cristaux ou d’une suspension liquide du composé actif de sorte qu’une quantité efficace sur le plan thérapeutique dudit composé entre en contact avec les voies aériennes soit directement, soit par absorption et circulation systémiques.

9. Utilisation selon la revendication 1, dans laquelle ledit composé est délivré en administrant une forme d’aérosol en poudre inerte dudit composé, de sorte qu’une quantité efficace sur le plan thérapeutique dudit composé entre en contact avec les voies aériennes dudit sujet soit directement, soit par absorption et circulation systémiques.

10. Utilisation selon la revendication 1, dans laquelle ledit composé est administré dans une quantité suffisante pour atteindre des concentrations sur les surfaces des voies aériennes dudit sujet en mesure d’augmenter la meilleure fréquence ciliaire des cils sur la surface des cellules épithéliales luminales, pour augmenter les sécrétions muqueuses par les cellules caliciformes, afin d’augmenter la sécrétion d’ions de chlorure pour stimuler la réduction des tensioactifs et pour activer la clairance des sécrétions conservées.

11. Utilisation selon la revendication 1, dans laquelle ledit composé est administré dans une quantité suffisante pour atteindre des concentrations sur les surfaces des voies aériennes dudit sujet d’environ 10-7 à environ 10-1 moles/litre.

12. Utilisation selon la revendication 1, dans laquelle ledit composé de la formule II est choisi dans le groupe constitué de P1, P4-di(udrine-5’)térphosphate(U₂P₄) et des dérivés substitués et ses sels acceptables sur le plan pharmaceutique.

13. Utilisation d’un composé de la formule II, ou son sel acceptable sur le plan pharmaceutique, dans un support pharmaceutique ayant une quantité dudit composé efficace pour promouvoir la clairance mucociliaire des sinus afin de préparer une composition pharmaceutique à utiliser dans un procédé de prévention ou de traitement de la sinusite chez un patient intubé par le nez.
14. Utilisation d'un composé de la formule II, ou de son sel acceptable sur le plan pharmaceutique, dans un support pharmaceutique ayant une quantité dudit composé efficace pour activer la clairance mucociliaire des voies aériennes afin de préparer une composition pharmaceutique à utiliser dans un procédé de prévention ou de traitement des sécrétions muqueuses chez un patient allé ou immobilisé.

15. Utilisation selon la revendication 14, dans laquelle le sujet est placé dans un lit thérapeutique à rotation latérale qui tourne le sujet afin de relâcher ultérieurement les sécrétions muqueuses.