MATERIALS AND METHODS FOR TREATING INFLUENZA VIRAL INFECTIONS WITH A CYSTEAMINE COMPOUND

Material und Verfahren zur Behandlung von influenza virusinfektionen mit einer cysteamin-verbindung

Substances et méthodes de traitement d’infections virales d’influenza par un composé de cysteamine

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A virus is a small parasite consisting of nucleic acid (RNA or DNA) enclosed in a protein coat. Viruses can only replicate by infecting a susceptible host cell and directing the host cell machinery to produce more viruses. Glycoproteins (located in the protein coat) mediate the adsorption to, and the penetration of, the virus into susceptible host cells.

Most viruses are classified into broad categories based on the types of nucleic acids formed during replication and the pathway by which mRNA is produced. In general, viruses have either RNA or DNA as their genetic material, wherein the nucleic acid can be single- or double-stranded.

Virus families typically classified as the RNA type (also classified as Classes III- VI - See Molecular Cell Biology) include birnaviridae, reoviridae, astoviridae, arterivirus, caliciviridae, tobamoviridae, papovaviridae, densovirusinae, and parvovirinae. Important virus families of the DNA type (also classified as Classes I and II viruses - See Harvey, L. et al, Molecular Cell Biology, Fourth Edition, W.H. Freeman and Company (2000)) include adenoviridae, herpesviridae, poxviridae, papovaviridae, densovirinae, and parvovirinae. Virus families typically classified of the RNA type (also classified as Classes III- VI, See Molecular Cell Biology) include birnaviridae, reoviridae, astoviridae, arterivirus, caliciviridae, coronaviridae, flaviviridae, picornaviridae, togaviridae, bornaviridae, filoviridae, paramyxovirinae, pneumovirinae, rhabdoviridae, bunyaviridae, and orthomyxoviridae.

Influenza, commonly known as the "flu," is a contagious disease that is caused by the influenza virus, classified in the orthomyxoviridae family. There are three known influenza-type viruses which affect human beings: Influenza A, B and C. Influenza A viruses have been isolated from many animal species in addition to humans, while the influenza B and C viruses have been found to infect mainly humans.

Influenza viruses are enveloped viruses containing negative single-stranded RNAs which are segmented and encapsidated. The influenza virus envelope is characterized by the presence of two surface glycoproteins: hemagglutinin and neuraminidase. The influenza A and B virions are pleomorphic and are usually 80-120 nm in diameter. The influenza C virion has many distinctive properties and is thus distinguished from the closely related A and B virions.

Influenza viruses attack the respiratory tract in humans (i.e., nose, throat, and lungs). For example, infection with influenza A or B often can cause a highly contagious, acute respiratory illness. Influenza infection usually includes the following symptoms: fever, headache, tiredness (can be extreme), dry cough, sore throat, nasal congestion, and body aches.

It is estimated that millions of people in the United States - about 10% to 20% of U.S. residents - get influenza each year. The majority of this population generally recovers in one to two weeks. In some cases, however, complications can arise from an influenza infection. Those persons at highest risk for contracting complications from the flu include: persons over 50 years of age, children aged 6 to 23 months, women more than 3 months pregnant, persons living in a long-term care facility or institution, persons with chronic heart, lung, or kidney conditions, diabetes, or weakened immune system. Pneumonia, bronchitis, encephalitis, otitis media, rhinitis, and sinusitis are only a few examples of complications that result from an influenza infection. Moreover, the flu can make chronic health problems worse. For example, people with asthma may experience asthma attacks while they have the flu, and people with chronic congestive heart failure may have worsening of this condition that is triggered by the flu.

An average of about 36,000 people per year in the United States die from influenza, and 114,000 per year have to be admitted to the hospital as a result of the infection. Thus, influenza viruses have a major impact on morbidity leading to increases in hospitalization and in visits to health care providers. For example, high rates of hospitalization are often observed for subjects over 65 years of age and also for children less than 5 years of age.

Furthermore, the spread of influenza virus through a population can result in epidemics, which have considerable economic impact. High rates of mortality were observed due to influenza infection during the influenza epidemics of 1957, 1968 and 1977 (Fields Virology, Second Edition, Volume 1, pp. 1075-1152 (1990)). Periodically, the influenza virus causes a worldwide epidemic. For example, the influenza pandemic of 1918 reportedly caused about 20 million deaths worldwide and about 500,000 deaths in the United States (Medical Microbiology, Fourth Edition, University of Texas Medical Branch at Galveston (1996)).

Influenza viruses are predominantly transmitted from person to person via respiratory droplets (also known as droplet spread) that are released when coughing and/or sneezing. The influenza virus can remain suspended in the air in respiratory droplets for as long as 3 hours; but are sensitive to heat and are rapidly inactivated at temperatures above 50°C. The virus can survive for 24-48 hours on hard, non-porous surfaces (i.e., telephone receivers, computer keyboard, doorknob, kitchen countertop, toys); 8 hours on cloth, paper and tissue; and five minutes on hands (see Muir, P, "Treatment of Influenza. Essential CPE. Continuing Education from the Pharmaceutical Society of Australia," Paragon Printers, Australasia, ACT (2002)). Typical methods of transmittal include mucous membrane contact with infected airborne respiratory droplets, person-to-person contact, contact with contaminated items (i.e., tissues soiled by infected nose and throat discharges).

Transmittal of influenza virus via respiratory droplets can occur as early as one day before a person experiences influenza-related symptoms. Adults can continue to transmit the virus to others for another three to seven days after the initial appearance of symptoms. Unlike adults, children have the ability to transmit the virus for longer than seven days. Symptoms are generally presented one to four days after the virus enters the body. In certain cases, a person can be...
infected with the flu virus but demonstrate no symptoms. During this time, those persons can still transmit the virus to others.  

[0012] Few methods are available for preventing an influenza infection and a cure has yet to be developed. Methods for preventing an influenza infection include vaccination and antiviral medications. Three antiviral drugs (amantadine, rimantadine, and oseltamivir) have been approved in the United States and are commercially available for use in preventing or treating influenza virus disease. These compounds, however, are most effective when used prophylactically, which may allow influenza viruses to develop resistance to both compounds rapidly. See U.S. Patent Nos. 3,352,912 and 3,152,180. Other compounds reported to have activity against influenza viruses have been disclosed in U.S. Patent Nos. 6,271,373; 5,935,957; 5,821,243; 5,684,024; 3,592,934; 3,538,160; 3,534,084; 3,496,228; and 3,483,254.  


[0014] There is a great need for new therapies for the treatment of viral diseases. Whereas there has been great progress in developing a variety of therapies for the treatment of bacterial infections, there are few viable therapies for the treatment of viruses. As described above, antiviral drugs and vaccines are primary methods used in the prevention and/or treatment of influenza infections. Ganciclovir, acyclovir and foscarnet are currently utilized for the treatment of herpes virus infections. However, these therapies can have substantial side effects based on their deleterious effects on host cell DNA replication or their effect on a limited number of viral infections. In addition, as noted above, viruses are known to develop resistance to therapies, which causes a progressive decline in efficacy.  

[0015] Insofar as is known, cysteamine compounds have not been previously reported as being useful for the treatment of viral infections.  

Brief Summary of the Invention  

[0016] The subject invention provides materials for treating subjects diagnosed with viral influenza infections as well as preventing the onset of viral influenza infections.  


[0018] In a second aspect the present invention provides a cysteamine, or salt thereof, according to any of claims 1 to 7, for use in reducing the severity, intensity, or duration of complications associated with a viral influenza infection.  

[0019] In a third aspect the present invention provides cysteamine, or salt thereof, according to any of claims 1 to 7, for use in treating symptoms associated with a viral influenza infection.  

[0020] In a fourth aspect the present invention provides a cysteamine, or salt thereof, according to any of claims 1 to 7, for use in preventing the development of a viral influenza infection-related complication.  

[0021] In a fifth aspect the present invention provides a composition for use in preventing a viral influenza infection comprising an effective amount of a cysteamine, or salt thereof, and an antiviral drug.  

[0022] In a sixth aspect the present invention provides a composition comprising an effective amount of a cysteamine, or salt thereof, for use in preventing a viral influenza infection and a pharmaceutical material for use in treating symptoms associated with an influenza infection.  

[0023] In a seventh aspect the present invention provides a cysteamine, or salt thereof, and an antiviral drug as a preparation for concurrent use in treating a viral influenza infection.  

[0024] The subject invention is particularly applicable to both human and animal health, especially to animals infected by influenza viruses.  

[0025] Specifically exemplified herein is the use of a cysteamine compound to treat and/or prevent an influenza virus infection. Administration of a cysteamine compound to a subject prior to acquiring the influenza virus can help protect the subject from influenza infection, or at least ensure that symptoms related to influenza virus disease develop to a lesser extent than would be observed in the absence of the cysteamine compound.  

[0026] In another embodiment, a cysteamine compound may be used to prevent and/or delay the development of influenza-related complications in subjects who are at an increased risk of contracting those complications. For example, influenza-related complications such as encephalitis, bronchitis, tracheitis, myositis rhinitis, sinusitis, asthma, bacterial infections (i.e., streptococcus aureus bacterial infection, haemophilus influenzae bacterial infection, staphylococcal pneumonia bacterial infection), cardiac complications (i.e., atrial fibrillation, myocarditis, pericarditis), Reye’s syndrome, neurologic complications (i.e., confusion, convulsions, psychosis, neuritis, Guillain-Barre syndrome, coma, transverse myelitis, encephalitis, encephalomyelitis), toxic shock syndrome, myositis, myoglobulinuria, and renal failure, croup, otitis media, viral infections (i.e., viral pneumonia), pulmonary fibrosis, obliterator bronchiolitis, bronchiectasis, exacerbations of asthma, exacerbations of chronic obstructive pulmonary disease, lung abscess, empyema, pulmonary aspergillosis, myositis and myoglobinaemia, heart failure, early and late fetal deaths in pregnant women, increased perinatal mortality in pregnant women, congenital abnormalities in birth, can be reduced through consumption of a cysteamine compound.  

[0027] In another embodiment of the invention, a cysteamine compound may be used to alleviate influenza-related
symptoms in a subject diagnosed with an influenza infection. A cysteamine compound can be for use alone or concurrently with other known agents that are used to treat/prevent the influenza virus disease (i.e., vaccinations, antiviral drugs) or to treat influenza-related symptoms (i.e., antitussives, mucolytics, and/or expectorants; antipyretics and analgesics; nasal decongestants).

[0028] In one embodiment, a cysteamine compound is for use alone or concurrently with other known agents that are used to treat/prevent an influenza viral infection. Preferably, a cysteamine compound of the invention is for use prior to, during, or after a exposure of a subject to an influenza virus concurrently with known agents that are used to treat/prevent the influenza virus disease (i.e., vaccinations, antiviral drugs) or to treat influenza-related symptoms (i.e., antitussives, mucolytics, and/or expectorants; antipyretics and analgesics; nasal decongestants).

[0029] In a related embodiment, a cysteamine compound is for use alone or concurrently with other known agents that used are to treat and/or prevent an avian influenza viral (AFV) infection. According to the present invention, the cysteamine compound can be for use via injection or oral administration to treat and/or prevent an ATV infection.

[0030] Preferably, a cysteamine compound is for use alone or concurrently with other known agents useful in the treatment and/or prevention of the various subtypes of avian influenza virus. More preferably, a cysteamine compound of the invention is for use alone or concurrently with other known agents useful in the treatment and/or prevention of H5N1 AIV. A dosage of at least 0.1 mg/mL of cysteamine hydrochloride, more preferably at least 1 mg/mL of cysteamine hydrochloride, and even more preferably at least 2 mg/mL of cysteamine hydrochloride, can be administered to a subject to treat and/or prevent any of the AIV subtypes listed above, preferably an H5N1 AIV infection.

[0031] In certain preferred embodiments, the dosage of cysteamine hydrochloride administered in the treatment and/or prevention of a H5N1 AIV infection correlates to the concentration of virus present in the subject. More preferably, the dosage of cysteamine hydrochloride administered in the treatment and/or prevention of H5N1 AIV infection correlates to an initial concentration of about LD50.

[0032] In accordance with the subject invention, the daily dosage amount of a cysteamine compound administered to a subject prior to influenza viral infection to protect the subject from viral infection can be about 10 mg to 3,000 mg. Preferably, a cysteamine compound is administered at about 50 mg to 1,500 mg per day. In a more preferred embodiment, about 200 mg to 900 mg of cysteamine hydrochloride is administered daily to a subject to prevent/treat the onset of an influenza (such as avian influenza virus, influenza A, influenza B, and influenza C or any mutants thereof) virus disease.

[0033] In accordance with the subject invention, the daily dosage amount of a cysteamine compound administered to a subject once symptoms associated with an influenza viral infection have been presented is about 10mg to 3,000mg. Preferably, a cysteamine compound is administered at about 200mg to 1,500mg per day. In a more preferred embodiment, about 450 mg to 900 mg of cysteamine hydrochloride is administered daily to a subject to treat and/or prevent the onset of an H5N1 AIV infection. A dosage of at least 0.1 mg/mL of cysteamine hydrochloride, more preferably at least 1 mg/mL of cysteamine hydrochloride, and even more preferably at least 2 mg/mL of cysteamine hydrochloride, can be administered to a subject prior to influenza viral infection to protect the subject from viral infection can be about 10 mg to 3,000 mg. Preferably, a cysteamine compound is administered at about 50 mg to 1,500 mg per day. In a more preferred embodiment, about 200 mg to 900 mg of cysteamine hydrochloride is administered daily to a subject to prevent/treat the onset of an influenza (such as avian influenza virus, influenza A, influenza B, and influenza C or any mutants thereof) virus disease.

[0034] In accordance with the subject invention, the daily dosage amount of a cysteamine compound administered to a subject at risk for contracting complications associated with an influenza virus infection is about 10mg to 3,000mg. Preferably, a cysteamine compound is administered at about 200mg to 1,500mg per day. In a more preferred embodiment, about 450 mg to 900 mg of cysteamine hydrochloride is administered daily to a subject to treat and/or delay the onset of complications associated with influenza (such as avian influenza virus, influenza A, influenza B, and influenza C or any mutants thereof) virus disease.

Brief Description of Drawings

[0035] Figure 1 shows cysteamine as a constituent of co-enzyme A.

Figure 2 shows a metabolic pathway of cysteamine.

Detailed Disclosure of the Invention

[0036] The subject invention provides materials for treating viral influenza infections treating/ameliorating symptoms associated with viral influenza infections; and/or preventing/delaying the onset of complications associated with influenza viral infections.

[0037] The term “symptom(s)” as used herein, refers to common signs or indications that a subject is suffering from a specific condition or disease. For example, symptoms associated with an influenza viral infection, as used herein, refer to common signs or indications that a subject is infected with an influenza virus. Influenza-related symptoms contemplated herein include, but are not limited to, fever, headache, exhaustion/fatigue, muscular aches, sore joints, irritated watering eyes, malaise, nausea and/or vomiting, shaking chills, chest pain, sneezing and respiratory symptoms (i.e., inflamed respiratory mucous membranes, substernal burning, nasal discharge, scratchy/sore throat, dry cough, loss of smell).
According to the subject invention, symptoms associated with an influenza virus infection can start within 24 to 48 hours after infection and can begin suddenly. Chills or a chilly sensation are often the first indication of influenza. Fever is common during the first few days, and the temperature may rise to 102°F to 103°F. In many instances, subjects feel sufficiently ill to remain in bed for days; subjects often experience aches and pains throughout the body, most pronounced in the back and legs.

As used herein, the term "complication(s)" refers to a pathological process or event occurring during a disease or condition that is not an essential part of the disease or condition; where it may result from the disease/condition or from independent causes. Accordingly, the term complication(s) refers to medical/clinical problems that are observed in subjects diagnosed with an influenza virus infection.

One complication of an influenza virus infection is that the influenza virus infection can make chronic health problems worse. For example, complications associated with a viral infection include, without limitation, encephalitis, bronchitis, tracheitis, myositis rhinitis, sinusitis, asthma, bacterial infections (i.e., streptococcus aureus bacterial infection, haemophilus influenzae bacterial infection, staphylococcal pneumonia bacterial infection), cardiac complications (i.e., atrial fibrillation, myocarditis, pericarditis), Reye’s syndrome, neurologic complications (i.e., confusion, convulsions, psychosis, neuritis, Guillain-Barre syndrome, coma, transverse myelitis, encephalitis, encephalomyelitis), toxic shock syndrome, myositis, myoglobinuria, and renal failure, croup, otitis media, viral infections (i.e., viral pneumonia), pulmonary fibrosis, obliterate bronchiolitis, bronchiectasis, exacerbations of asthma, exacerbations of chronic obstructive pulmonary disease, lung abscess, empyema, pulmonary aspergillosis, myositis and myoglobinemia, heart failure, early and late fetal deaths in pregnant women, increased perinatal mortality in pregnant women, and congenital abnormalities in birth.

The terms "influenza," "influenza virus," or "flu," as used herein, refer to an RNA virus of the Orthomyxoviridae family, including influenza A, influenza B, and influenza C, and mutants thereof. Influenza viruses contemplated herein include those viruses that have two antigenic glycosylated enzymes on their surface: neuraminidase and hemagglutinin. Various subtypes of influenza virus that can be treated using the materials and methods of the invention include, but are not limited to, the H1N1, H1N2, H2N2, H3N2, H3N8, H5N1, H5N3, H5N8, H5N9, H7N1, H7N2, H7N3, H7N4, H7N7, H9N2, and H10N7 subtypes including the following subtypes commonly known as the "Spanish Flu," "Asian Flu," "Hong Kong Flu," "Avian Flu," "Swine Flu," "Horse Flu," and "Dog Flu."

The term "subject," as used herein, describes an organism, including humans and mammals, to which treatment with the compositions according to the invention is provided. Mammalian species that benefit from the present invention include but are not limited to, apes, chimpanzees, orangutans, humans, monkeys; and domesticated animals (i.e., pets) such as dogs, cats, mice, rats, guinea pigs, and hamsters.

"Concurrent administration" and "concurrently administering," as used herein, includes administering a compound or therapeutic method suitable for use with the composition of the invention (a cysteamine compound) in the treatment of an influenza viral infection or for the treatment of an influenza viral infection-related symptoms/complications.

For a subject diagnosed with an influenza infection, a cysteamine compound can be concurrently administered with vaccinations, antiviral drugs, antitussives, mucolytics, and/or expectorants; antipyretics and analgesics; nasal decongestants. By way of example, a compound can be provided in admixture with a cysteamine compound, such as in a pharmaceutical composition; or the compound and cysteamine can be provided as separate compounds, such as, for example, separate pharmaceutical compositions administered consecutively, simultaneously, or at different times. Preferably, if the cysteamine compound and the known agent for treating/preventing influenza infection and/or treating influenza-related symptoms/complications are administered separately, they are not administered so distant in time from each other that the cysteamine compound and the known agent cannot interact.

In certain embodiments of the invention, a cysteamine compound can be administered concurrently with, but not limited to, vaccination, antiviral medications such as amantadine, rimantadine, ribavirin, idoxuridine, trifluridine, vidarabine, acyclovir, ganciclovir, foscarin, zidovudine, didanosine, zalcitabine, stavudine, famciclovir, oseltamivir, and valaciclovir (materials and/or methods used to treat an influenza viral infection); or antitussives, mucolytics, and/or expectorants; antipyretics and analgesics; nasal decongestants (materials used to treat symptoms associated with an influenza infection).

By way of example, a compound for use with a cysteamine compound of the invention can be provided in admixture with the cysteamine compound, such as in a pharmaceutical composition. Alternatively, the compound and cysteamine can be provided as separate compounds, such as, for example, separate pharmaceutical compositions administered consecutively, simultaneously, or at different times. Preferably, if the cysteamine compound and the known agent for treating/preventing influenza infection and/or treating influenza-related symptoms/complications are administered separately, they are not administered so distant in time from each other that the cysteamine compound and the known agent cannot interact.

As used herein, reference to a "cysteamine compound" includes cysteamine, the various cysteamine salts, which include pharmaceutically acceptable salts of a cysteamine compound.

The term "pharmaceutically acceptable salt," as used herein, refers to any salt of a cysteamine compound that is pharmaceutically acceptable.
is pharmaceutically acceptable and does not greatly reduce or inhibit the activity of the cysteamine compound. Suitable examples include acid addition salts, with an organic or inorganic acid such as acetate, tartrate, trifluoroacetic, lactate, maleate, fumarate, citrate, methane, sulfonate, sulfate, phosphate, nitrate, or chloride.

Accordingly, in one embodiment of the subject invention, the advantages of cysteamine, as set forth herein, can be achieved by promoting the endogenous production of cysteamine through natural metabolic process such as through the action of co-enzyme A or as a precursor and/or metabolite of cysteine (see Figures 1 and 2). This can be achieved by, for example, the administration of pantothentic acid.

The term “effective amount,” as used herein, refers to the amount necessary to elicit the desired biological response, hi accordance with the subject invention, the effective amount of a cysteamine compound is the amount necessary to treat/prevent an influenza viral infection; treat/ameliorate symptoms associated with influenza viral infections; and/or prevent/delay/ameliorate the onset of complications associated with influenza viral infections, hi a preferred embodiment, the effective amount of a cysteamine compound is the amount necessary to treat/prevent an influenza infection; treat/ameliorate symptoms associated with influenza infection; and/or prevent/delay/ameliorate the onset of complications in patients with increased risk for contracting complications associated with influenza infection. The amelioration in symptom and/or complication severity may be a 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or 99% decrease in severity.

The present invention is particularly applicable to non-human subject health, especially to non-human subjects infected with an influenza virus.

With regard to human subjects, the present invention is particularly applicable to the treatment and/or prevention of influenza virus infections, especially avian influenza virus infections. According to the subject invention, a cysteamine compound is useful in the treatment and/or prevention of various avian influenza strains, including viruses of subtype H1N1, H1N2, H2N2, H3N2, H3N8, H5N1, H5N2, H5N3, H5N8, H5N9, H7N1, H7N2, H7N3, H7N4, H7N7, H9N2, and H10N7. In one embodiment of the invention, the cysteamine hydrochloride is used to treat and/or prevent a H5N1 avian influenza virus infection in humans or animals. The cysteamine hydrochloride can be administered alone or concurrently with other known agents known to be effective in treating and/or preventing an influenza infection.

In a related embodiment, a cysteamine compound (such as cysteamine hydrochloride) is administered alone or concurrently with other known agents that are used to treat and/or prevent an avian influenza viral (AIV) infection. The cysteamine compound can be administered to a subject via injection or oral administration.

Preferably, a dosage of at least 0.1 mg/mL of cysteamine hydrochloride, more preferably at least 1 mg/mL of cysteamine hydrochloride, and even more preferably at least 2 mg/mL of cysteamine hydrochloride, can be administered to a subject to treat and/or prevent a H5N1 ATV infection.

In certain preferred embodiments, the dosage of cysteamine hydrochloride administered in the treatment and/or prevention of an AIV infection (including viruses of subtype H1N1, H1N2, H2N2, H3N2, H3N8, H5N1, H5N2, H5N3, H5N8, H5N9, H7N1, H7N2, H7N3, H7N4, H7N7, H9N2, and H10N7) correlates to the concentration of virus present in the subject. More preferably, the dosage of cysteamine hydrochloride administered in the treatment and/or prevention of a H5N1 AIV infection correlates to a concentration of about LD50 of virus present in the subject.

The compositions of the invention can be used in a variety of routes of administration, including, for example, orally-administrable forms such as tablets, capsules or the like, or via parenteral, intravenous, intramuscular, transdermal, buccal, subcutaneous, suppository, or other route. Such compositions are referred to herein generically as “pharmaceutical compositions.” Typically, they can be in unit dosage form, namely, in physically discrete units suitable as unitary or concurrently with other known agents that are used to treat and/or prevent an avian influenza viral (AIV) infection.

The compositions of the invention can be used in a variety of routes of administration, including, for example, orally-administrable forms such as tablets, capsules or the like, or via parenteral, intravenous, intramuscular, transdermal, buccal, subcutaneous, suppository, or other route. Such compositions are referred to herein generically as “pharmaceutical compositions.” Typically, they can be in unit dosage form, namely, in physically discrete units suitable as unitary or concurrently with other known agents that are used to treat and/or prevent an avian influenza viral (AIV) infection.

The cysteamine compounds of the subject invention can be formulated according to known methods for preparing pharmaceutically useful compositions. Formulations are described in a number of sources, which are well known and readily available to those skilled in the art. For example, Remington’s Pharmaceutical Science (Martin EW [1995] Easton Pennsylvania, Mack Publishing Company, 19th ed.) describes formulations that can be used in connection with the subject invention. Formulations suitable for parenteral administration include, for example, aqueous sterile injection solutions, which may contain antioxidants, buffers, bacteriostats, and solutes, which render the formulation isotonic with the blood of the intended recipient; and aqueous and nonaqueous sterile suspensions, which may include suspending agents and thickening agents. The formulations may be prepared in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the condition of the sterile liquid carrier, for example, water for injections, prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powder, granules, tablets, etc. It should be understood that in addition to the ingredients particularly mentioned above, the formulations of the subject invention can include other agents conventional in the art having regard to the type of formulation in question.

The formulations comprising a cysteamine compound include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal, parenteral (including subcutaneous, intramuscular, intravenous, intradermal,
intrathecal and epidural) administration as well as administration to the eye. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the cysteamine compound with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the cysteamine compound with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product. In certain embodiments, the cysteamine compound can be provided in a formulation for use in a skin patch.

[0059] Administration of a cysteamine compound, in accordance with the subject invention, can be accomplished by any suitable method and technique presently or prospectively known to those skilled in the art. In a preferred embodiment, a cysteamine compound is formulated in a patentable and easily consumed oral formulation such as a pill, lozenge, tablet, gum, beverage, etc. The consumption is then taken at, prior to, or after, experiencing a stressful event and/or when needed to augment immune activity (i.e., after diagnosis with an influenza infection).

[0060] In accordance with the invention, compositions comprising, as an active ingredient, an effective amount of the cysteamine for use in treating a viral influenza infection may further comprise one or more non-toxic, pharmaceutically acceptable carrier or diluent. Examples of such carriers for use in the invention include ethanol, dimethyl sulfoxide, glycerol, silica, alumina, starch, sorbitol, inositol, xylitol, D-xylene, mannitol, powdered cellulose, microcrystalline cellulose, talc, colloidal silicon dioxide, calcium carbonate, magnesium carbonate, calcium phosphate, calcium sulphate, calcium aluminium silicate, aluminium hydroxide, sodium starch phosphate, lecithin, and equivalent carriers and diluents.

[0061] To provide for the administration of such dosages for the desired therapeutic treatment, compositions of the invention will typically comprise between about 0.1% and 95%, of the total composition including carrier or diluent. The dosage used can be varied based upon the age, weight, health, or the gender of the individual to be treated.

[0062] In one embodiment, the dosage of cysteamine administered to a patient to elicit a desired response is about 10 mg to about 3,000 mg per day. The desired response can include (1) prevention of influenza viral infections; (2) a reduction in the severity, duration, or intensity of symptoms associated with influenza viral infections; and (3) prevention, delay, or reduction in the severity, duration, or intensity of complications related to an influenza viral infections. Preferably, cysteamine hydrochloride is administered daily at about 50 mg to 1,000 mg to elicit a desired response. In a more preferred embodiment, the dosage of cysteamine hydrochloride administered to a patient to elicit a desired response is about 200 mg to 900 mg per day.

[0063] Following are examples that illustrate procedures for practicing the invention. These examples should not be construed as limiting. All percentages are by weight and all solvent mixture proportions are by volume unless otherwise noted.

**Example 1 - Treatment of Influenza-Related Symptoms**

[0064] A male subject infected with an influenza virus, demonstrating symptoms (nasal discharge, fever, exhaustion) associated with an influenza infection, was initially treated with over-the-counter nasal decongestant and mucolytic medications. The over-the-counter medications were ineffective in treating the influenza-related symptoms within 24 hours.

[0065] After the over-the-counter medications proved ineffective, the subject was administered orally a dose of about 700 mg of cysteamine hydrochloride. Within 24 hours, symptoms associated with the influenza infection had disappeared. The subject expressed general feelings of health.

**Example 2 - Study of Antiviral Activity of Cysteamine against H5N1 Avian Influenza Virus: In-vitro and In-vivo Studies Using Oseltamivir Phosphate as Control**

[0066] According to one embodiment of the invention, cysteamine demonstrates antiviral activity against H5N1 avian influenza virus. The subject matter of the present invention is particularly advantageous due to its unexpected results with avian influenza virus. For example, as described below, cysteamine is particularly efficacious in treating H5N1 avian influenza virus, more so than even oseltamivir phosphate (whose generic name is TAMIFLU®), which is a licensed drug against avian influenza virus.

**Materials and Method**

[0067] Cysteamine (hereinafter referred to as TG21™; comprising 99% cysteamine) was supplied by Omega Bio-Pharma (H.K.) Limited. Embryonated eggs from specific-pathogen-free (SPF) hens (Beijing, China) were used in this experiment. H5N1 avian influenza viruses CV strain was isolated from infected chickens. Roman chickens were purchased from Hebei without immunization with avian influenza vaccine. TAMIFLU® (Roche (China) Ltd., Shanghai, China) was used as described herein.
Evaluation of TG21 Toxicity in Embryonated Hen Eggs

[0068] One gram of TG21 was dissolved in 10 mL (1:10) 0.01mol/L, in pH7.2 PBS (1:10, 10mg/mL), and then diluted in 2-fold serials from 1:10 to 1:5120. The diluted drug (test group) or PBS buffer (control group) was injected into chorio allantoic cavities of 10-day-old embryonated hen eggs, 5 eggs each dilution. The eggs were hatched at 37°C and monitored twice a day for 5 days to observe embryo survival and to calculate LD50 (50% Lethal Dose of virus).

Evaluation of EID50 of H5N1 Avian Influenza in Embryonated Hen Eggs

[0069] Original stock of avian influenza viruses CV strain was diluted 10-fold series with 0.01M pH7.2 PBS from $10^{-1}$ to $10^{-10}$. The 0.2 mL diluted virus (test group) or PBS buffer (control group) was inoculated into chorio allantoic cavities of 10-day-old embryonated hen eggs, 5 eggs each dilution. The eggs were hatched at 37°C and monitored twice a day for 5 days to observe embryo survival. EID50 (50% egg infective dose) was calculated based on the Reed-Muench Method.

Evaluation of TG21 Antiviral Effect on Avian Influenza in Embryonated Hen Eggs.

[0070] One gram of TG21 was dissolved in 10 mL 0.01mol/L, in pH7.2 PBS (1:10, 100mg/mL), and then diluted in 2-fold serials from 1:10 to 1:5120. The diluted TG 21 solution was incubated with same volume of 10 or 100 times EID50 H5N1 avian influenza viruses CV strain at room temperature for 30, 60 and 120 minutes, respectively, and then the 0.2 mL virus-drug mixture solution was inoculated into chorio allantoic cavities of 10-day-old embryonated eggs from SPF hens. All of the embryonated eggs were hatched at 37°C and monitored twice a day for 5 days to observe embryo survival. The IC50 was calculated.

[0071] As a positive control, the antiviral effect of TAMIFLU® on avian influenza virus was evaluated under 100 times EID50.

Evaluation of Avian Influenza Viruses LD50 in chicken.

[0072] The original stock of avian influenza viruses CV strain was diluted 10-fold series with 0.01M pH7.2 PBS from $10^{-1}$ to $10^{-9}$, and then was used to infect the chickens by nasal dropping, 10 heads each dilution. The animals were monitored twice a day for 7 days to observe survival. The LD50 of avian influenza viruses to chicken was calculated according to animal survival.

Evaluation of TG21 Efficiency against Avian Influenza in Chicken.

[0073] 4 to 6-week-old Roman chickens were administered TG21 through drinking water, with dosages of 40, 20, 10 mg TG21/head.day$^{-1}$ high for three days, then the chickens were challenged with 2.5, 25, 250 times EID50 by nasal dropping, once a day for three days. The animals continued to accept treatment with same doses of TG21 for five days after challenge. The chickens were monitored twice a day for 7 days. A negative control without treatment was carried out in parallel. Animal survival was recorded and the efficiency of TG21 drug was evaluated in accordance to the following formula: Efficiency = (death date in control group-death rate of treatment group)/ (death rate of control group) x 100%.

Results

1. Toxicity

[0074] 120 hours after TG21 was inoculated into embryonated eggs, some toxicity was detected at a high doses ranging from about 100mg/mL (1:10 dilution) to 25 mg/mL (1:40). The LD50 of TG21 to embryonated hen eggs was 32.1 mg/mL. No side-effect was found when dosed below 12.5mg/mL (1:80).

2. EID50 of H5N1 Avian Influenza in Embryonated Hen Eggs, and LD50 in Chicken.

[0075] When an original stock of virus was diluted more than $10^9$ times (concentration $10^{-9}$), embryonated eggs survived. According to the Reed-Muench Method, EID50 of H5N1 avian influenza in embryonated hen eggs was calculated as $10^{-8.17}$. When virus stock was diluted to $10^{-8}$ or below, the tested virus was not lethiferous. The LD50 of H5N1 avian influenza in chicken was $10^{-5.41}/0.2mL$. 
3. Antiviral Effect of TG21 on H5N1 Avian Influenza Viruses in Embryonated Hen Eggs.

[0076] Prior to inoculation into embryonated hen eggs, the H5N1 avian influenza viruses were treated with different dilutions of TG21 for 30, 60, and 120 minutes. The IC50s of TG21 against H5N1 avian influenza virus were 15.6, 14.9, and 6.8 mg/mL, respectively, with treatment times of 30, 60, and 120 minutes under 10 times EID50 viral challenge dose. The IC50s were 17.5 and 16.1 mg/mL, respectively, when the virus was treated with TG21 for 30 and 120 minutes prior to inoculation under virus doses of 10 times EID50 (see Table 1 below).

[0077] In a positive control group treated with TAMIFLU®, the IC50s of TAMIFLU® against H5N1 avian influenza in embryonated hen eggs were 25.1 and 19.4 mg/mL, respectively, with 30 and 120 minutes treatment times prior to inoculation under a virus dose of 100 times EID50. In a negative control group (no drug administered), all embryonated hen eggs died.

### Table 1—Antiviral effect of TG21 on H5N1 AIV in embryonated hen eggs

<table>
<thead>
<tr>
<th>TG21 Dilutions</th>
<th>10 EID50&lt;sup&gt;a&lt;/sup&gt;</th>
<th>100 EID50</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 Mins&lt;sup&gt;b&lt;/sup&gt;</td>
<td>60 Mins</td>
</tr>
<tr>
<td>1:10&lt;sup&gt;c&lt;/sup&gt;</td>
<td>100% (16/16)</td>
<td>100% (17/17)</td>
</tr>
<tr>
<td>1:20</td>
<td>100% (11/11)</td>
<td>100% (12/12)</td>
</tr>
<tr>
<td>1:40</td>
<td>75% (6/8)</td>
<td>77.8% (7/9)</td>
</tr>
<tr>
<td>1:80</td>
<td>37.5% (3/8)</td>
<td>40% (4/10)</td>
</tr>
<tr>
<td>1:160</td>
<td>10% (1/10)</td>
<td>27% (3/11)</td>
</tr>
<tr>
<td>1:320</td>
<td>0% (0/14)</td>
<td>0% (0/13)</td>
</tr>
<tr>
<td>1:640</td>
<td>0% (0/19)</td>
<td>0% (0/18)</td>
</tr>
<tr>
<td>1:1280</td>
<td>0% (0/24)</td>
<td>0% (0/23)</td>
</tr>
<tr>
<td>1:2560</td>
<td>0% (0/29)</td>
<td>0% (0/28)</td>
</tr>
</tbody>
</table>

| IC50 | 15.6 | 14.9 | 6.8 | 17.5 | 16.1 |
| (mg/mL) | | | | | |

Note: Mins=minutes; <sup>a</sup>EID50: drug dose for 50% egg infection; <sup>b</sup>reaction time of drug-virus prior inoculation; <sup>c</sup>drug initialization concentration is 100mg/mL; <sup>d</sup>survival /total; IC50: the drug concentration required to survive 50% embryo.

Efficiency of TG21 against H5N1 Avian Influenza Viruses in Chickens.

[0078] Four to six-week-old chickens were administered with 10-40 mg/head.day<sup>-1</sup> TG21 through drinking water for three days before and for five days after challenge with high virus dosage (250X LD50), mediate virus dosage (25X LD50), and low virus dosage (2.5X LD50) of infectious H5N1 avian influenza viruses. The results of TG21’s antiviral effect on H5N1 avian influenza virus in the chickens are showed in Table 2 below. All of the tested chickens died within three days under 250 times LD50 viral infectious dosages, including the animals in the TAMIFLU® control group. This
may due to too high A dosage of viral infection such that no medicinal treatment, including TAMIFLU®, can provide effective protection against the viral infection.

The protection of TG21 against H5N1 avian influenza virus in chickens in dosages of 40, 20, 10 mg/head.day⁻¹ was 100%, 62.5%, and 87.5%, respectively, under 2.5 times LD50 viral infectious doses, and 70%, 80%, and 50%, respectively, under 25 times LD50 viral infectious doses. The statistical difference of efficiency of TG21 and of the negative control (no drug) was extremely significant (all p volume <0.01 by Chi-square test). The efficiency of TAMIFLU® (5mg/head.day⁻¹) was 50% under 25 times LD50 viral challenge doses. No significant difference between IC50 of TG21 (10mg/ head.day⁻¹) and TAMIFLU® (5mg/head.day⁻¹) was found (P>0.005) under 25 times LD50 viral challenge doses (Table 2).

### Table 2—Antiviral effect of TG21 on H5N1 avian influenza virus in Chicken

<table>
<thead>
<tr>
<th>Drug and Dose</th>
<th>Viral infectious dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>250 LD50</td>
</tr>
<tr>
<td>40 mg/mL</td>
<td></td>
</tr>
<tr>
<td>20 mg/mL</td>
<td></td>
</tr>
<tr>
<td>10 mg/mL</td>
<td></td>
</tr>
<tr>
<td>Tamiflu (5.4 mg/mL)</td>
<td></td>
</tr>
<tr>
<td>Negative control</td>
<td></td>
</tr>
</tbody>
</table>

Note: ** P<0.01 compare with control group by Chi-square test; a: survival/ total

**Example 3—Antiviral activity of Cysteamine against H5N1 avian influenza virus in mice**

**Materials and Method**

Cysteamine (hereinafter referred to as "TG21"); comprising 99% cysteamine) was supplied by Omega Bio-Pharma (H.K.) Limited. H5N1 avian influenza virus, WV strain, was isolated from infected chickens. TAMIFLU® (Roche (China) Ltd., Shanghai, China) was used as described herein.
Evaluation of 50% lethal dose of H5N1 avian influenza virus in mice (mLD50)

[0082] H5N1 avian influenza (WV strain) stock solution was initially diluted 1:5 and then diluted with PBS in four-fold series for 5 dilutions (1:5 to 1:1280). Six to eight-week old female mice were anesthetized by intramuscularly injection 100µL of 1% sodium barbiturate and then inoculated by dropping 50µL diluted H5N1 avian influenza virus WV strain into each mouse’s nasal cavity (n = 10 mice for each dilution). Animals were monitored daily for 14 days and mLD50 was calculated based on the death of mice with the Reed-Muench Method. The results indicate that the survival of the mice were 0% in the 1:5 virus dilution group, 10% in the 1:20 virus dilution group, 25% in the 1:80 virus dilution group, 80% in the 1:320 virus dilution group, and 90% in the 1:1280 virus dilution group. The mLD50 of H5N1 avian influenza (WV strain) was 10^{-2.1509/0.05mL} or 1:141.5 dilution/0.05mL.

Therapeutic role of Cysteamine in mice infected with avian influenza virus

[0083] Fifty female mice (6-8 weeks old) were allotted into three treatment groups (T1, T2, and T3), one negative (untreated) control group, and one positive (TAMIFLU®) control group, with 10 mice in each group. After being anesthetized via intramuscular injection of 100µL 1% sodium barbiturate, all of the mice were inoculated intranasally with 10 times mLD50 H5N1 avian influenza virus in 50µL PBS. Within one hour after infection, the animals was treated for 12 days by oral gavage administration with TG21 at a daily dose of 4.8, 2.4, 1.2 mg per mouse in T1-T3 treatment groups respectively, TAMIFLU® 0.3mg per mouse daily in the positive control group and same volume of PBS in the negative group.

[0084] Mice were observed twice a day for 14 days for clinical signs of infection and for survival. The protection rate of TG21 against H5N1 avian influenza was calculated and the significant differences between the groups were compared by Chi-square test. For example, the equation for identifying the protection rate (%) = (death date in control group-death rate of treatment group)/ (death rate of control group) X 100%. Results showed that the protection were 50%, 70% and 10% in TG21 treatment of T1 group (4.8 mg/mouse.day^{-1}), T2 group (2.4 mg/mouse.day^{-1}), and T3 group (1.2 mg/mouse.day^{-1}), respectively; with a 0% protection rate in the negative control group and a 60% protection rate in the positive (TAMIFLU®) control group. The protection rate of TG21 in the T1 group (P<0.05), T2 group (P<0.01), and T3 group (P<0.05) differed significantly from that in the negative control group. These results indicate that TG21 has a strong antiviral activity against H5N1 avian influenza virus as an ideal drug in the treatment of avian influenza viral infections.

Claims

1. A cysteamine, or salt thereof, for use in treating a viral influenza infection in a subject.

2. The cysteamine, or a salt thereof, according to claim 1, wherein the viral infection is selected from the group consisting of avian influenza viruses and influenza A, B, and C viruses.

3. The cysteamine, or salt thereof, according to claim 2, wherein the subject is infected with at least one avian influenza subtype selected from the group consisting of H1N1, H1N2, H2N2, H3N2, H3N8, H5N1, H5N2, H5N3, H5N8, H5N9, H7N1, H7N2, H7N3, H7N4, H7N7, H9N2, and H10N7.

4. The cysteamine, or salt thereof, according to claim 1, which comprises administering at least 0.1 mg of the cysteamine, or salt thereof, to the subject daily.

5. The cysteamine, or salt thereof, according to claim 4, which comprises administering between 2 mg to 3,000 mg of the cysteamine, or salt thereof, daily.

6. The cysteamine, or salt thereof, according to claim 1, wherein said cysteamine salt is cysteamine hydrochloride or cysteamine phosphate.

7. The cysteamine, or salt thereof, according to claim 1, wherein said cysteamine or salt thereof is taken orally, parenterally, intravenously, intramuscularly, transdermally, via buccal route, subcutaneously, or via suppository.

8. A cysteamine, or salt thereof, according to any of claims 1 to 7, for use in reducing the severity, intensity, or duration of complications associated with a viral influenza infection.
9. A cysteamine, or salt thereof, according to any of claims 1 to 7, for use in treating symptoms associated with a viral influenza infection.

10. A cysteamine, or salt thereof, according to any of claims 1 to 7, for use in preventing the development of a viral influenza infection-related complication.

11. A composition for use in preventing a viral influenza infection comprising an effective amount of a cysteamine, or salt thereof, and an antiviral drug.

12. The composition, according to claim 11, wherein the viral influenza infection is an avian influenza virus and wherein the antiviral drug is selected from the group consisting of ganciclovir, acyclovir, foscarnet, amantadine, rimantadine and oseltamivir.

13. A composition comprising an effective amount of a cysteamine, or salt thereof, for use in preventing a viral influenza infection and a pharmaceutical material for use in treating symptoms associated with an influenza infection.

14. The composition according to claim 13, wherein the viral influenza infection is an avian influenza virus and wherein the pharmaceutical material is selected from the group consisting of antitussives, mucolytics, expectorants, antipyretics, analgesics and nasal decongestants.

15. A cysteamine, or salt thereof, and an antiviral drug as a preparation for concurrent use in treating a viral influenza infection.

16. The cysteamine, or salt thereof, and the antiviral drug according to claim 15, wherein the viral influenza infection is selected from the viruses defined in any of claims 2 or 3.

17. The cysteamine, or salt thereof, and the antiviral drug according to claim 15 or claim 16, further comprising any of the features of claims 4 to 7.

Patentansprüche

1. Ein Cysteamin oder Salz desselben zur Anwendung bei der Behandlung einer Grippevirusinfektion bei einem Patienten.

2. Das Cysteamin oder Salz desselben gemäß Anspruch 1, wobei die Virusinfektion aus der Gruppe ausgewählt ist, die Vogelgrippeviren und Grippe-A-, -B- und -C-Viren umfasst.

3. Das Cysteamin oder Salz desselben gemäß Anspruch 2, wobei der Patient mit mindestens einem Vogelgrippe-Subtyp infiziert ist, der aus der Gruppe ausgewählt ist, die H1N1, H1N2, H2N2, H3N2, H3N8, H5N1, H5N2, H5N3, H5N8, H5N9, H7N1, H7N2, H7N3, H7N4, N7N7, H9N2 und H10N7 umfasst.

4. Das Cysteamin oder Salz desselben gemäß Anspruch 1, das die Verabreichung von mindestens 0,1 mg Cysteamin oder Salz desselben täglich an den Patienten umfasst.

5. Das Cysteamin oder Salz desselben gemäß Anspruch 4, das die Verabreichung von zwischen 2 mg bis 3000 mg Cysteamin oder Salz desselben täglich an den Patienten umfasst.

6. Das Cysteamin oder Salz desselben gemäß Anspruch 1, wobei das Cysteaminsalz Cysteaminhydrochlorid oder Cysteaminphosphat ist.

7. Das Cysteamin oder Salz desselben gemäß Anspruch 1, wobei das Cysteamin oder Salz desselben oral, parenteral, intravenös, intramuskulär, transdermal, bukkal, subkutan oder mittels Zäpfen angewendet wird.

9. Ein Cysteamin oder Salz desselben gemäß einem beliebigen der Ansprüche 1 bis 7 zur Anwendung bei der Be- 
handlung von Symptomen im Zusammenhang mit einer Grippevirusinfektion.

10. Ein Cysteamin oder Salz desselben gemäß einem beliebigen der Ansprüche 1 bis 7 zur Anwendung bei der Prä-
vention des Eintritts einer Komplikation im Zusammenhang mit einer Grippevirusinfektion.

11. Eine Zusammensetzung zur Anwendung bei der Prämvention einer Grippevirusinfektion, die eine wirksame Menge 
eines Cysteamins oder Salzes desselben und ein antivirales Mittel umfasst.

12. Die Zusammensetzung gemäß Anspruch 11, wobei die Grippevirusinfektion ein Vogelgrippevirus ist und wobei das 
antivirale Mittel aus der Gruppe ausgewählt ist, die Ganciclovir, Acyclovir, Foscartern, Amantadin, Rimantadin und 
Oseltamivir umfasst.

13. Eine Zusammensetzung, die eine wirksame Menge eines Cysteamins oder Salzes desselben zur Anwendung bei 
der Prämvention einer Grippevirusinfektion und ein pharmazeutisches Material zur Anwendung bei der Behandlung 
von Symptomen im Zusammenhang mit einer Grippeinfektion umfasst.

14. Die Zusammensetzung gemäß Anspruch 13, wobei die Grippevirusinfektion ein Volgegrippevirus ist und wobei das 
pharmazeutische Material aus der Gruppe ausgewählt ist, die Antitussiva, Mukolytika, Expektoranzien, Antipyretika, 
Analgéтика и nasale Dekongestiva umfasst.

15. Ein Cysteamin oder Salz desselben und ein antivirales Mittel als Präparat zur gleichzeitigen Verwendung bei der 
Behandlung einer Grippevirusinfektion.

16. Das Cysteamin oder Salz desselben und ein antivirales Mittel gemäß Anspruch 15, wobei die Grippevirusinfektion 
aus den in einem der Ansprüche 2 oder 3 definierten Viren ausgewählt ist.

17. Das Cysteamin oder Salz desselben und ein antivirales Mittel gemäß Anspruch 15 oder Anspruch 16, die weiterhin 
eines der Merkmale von Ansprüchen 4 bis 7 umfassen.

Revendications

1. Cystéamine ou sel de celle-ci, à utiliser dans le traitement d’une infection de grippe virale chez un sujet.

2. Cystéamine ou sel de celle-ci selon la revendication 1, où l’infection virale est sélectionnée parmi le groupe consistant 
en virus influenza aviaires et virus influenza de type A, B et C.

3. Cystéamine ou sel de celle-ci selon la revendication 2, où le sujet est infecté par au moins un sous-type d’influenza 
aviaire sélectionné parmi le groupe consistant en H1N1, H1N2, H2N2, H3N2, H3N8, H5N1, H5N2, H5N3, H5N8, 
H5N9, H7N1, H7N2, H7N3, H7N4, H7N7, H9N2 et H10N7.

4. Cystéamine ou sel de celle-ci selon la revendication 1, ce qui comprend administrer au moins 0,1 mg de la cystéamine 
ou sel de celle-ci tous les jours au sujet.

5. Cystéamine ou sel de celle-ci selon la revendication 4, ce qui comprend administrer entre 2 mg et 3000 mg de la 
cystéamine ou sel de celle-ci tous les jours.

6. Cystéamine ou sel de celle-ci selon la revendication 1, où ledit sel de cystéamine est du chlorhydrate de cystéamine 
ou du phosphate de cystéamine.

7. Cystéamine ou sel de celle-ci selon la revendication 1, où ladite cystéamine ou sel de celle-ci est pris par voie orale, 
parentérale, intraveineuse, intramusculaire, transdermique, par voie buccale, sous-cutanée ou en suppositoire.

8. Cystéamine ou sel de celle-ci selon l’une quelconque des revendications 1 à 7, à utiliser pour réduire la sévérité, 
l’intensité ou la durée de complications associées à une infection de grippe virale.

9. Cystéamine ou sel de celle-ci selon l’une quelconque des revendications 1 à 7, à utiliser pour traiter des symptômes
associés à une infection de grippe virale.

10. Cystéamine ou sel de celle-ci selon l’une quelconque des revendications 1 à 7, à utiliser dans la prévention du développement d’une complication associée à une infection de grippe virale.

11. Composition à utiliser dans la prévention d’une infection de grippe virale, comprenant une quantité efficace d’une cystéamine ou sel de celle-ci et d’un médicament antiviral.

12. Composition selon la revendication 11, où l’infection de grippe virale est un virus influenza aviaire et où le médicament antiviral est sélectionné parmi le groupe consistant en ganciclovir, acyclovir, foscarnet, amantadine, rimantadine et oseltamivir.

13. Composition comprenant une quantité efficace d’une cystéamine ou sel de celle-ci, à utiliser dans la prévention d’une infection de grippe virale, et une substance pharmaceutique à utiliser dans le traitement de symptômes associés à une infection à influenza.

14. Composition selon la revendication 13, où l’infection de grippe virale est un virus influenza aviaire et où la substance pharmaceutique est sélectionnée parmi le groupe consistant en antitussifs, mucolytiques, expectorants, antipyrétiques, analgésiques et décongestionnants nasaux.

15. Cystéamine ou sel de celle-ci et médicament antiviral en tant que préparation pour emploi simultané dans le traitement d’une infection de grippe virale.

16. Cystéamine ou sel de celle-ci et médicament antiviral selon la revendication 15, où l’infection de grippe virale est sélectionnée parmi les virus définis dans l’une quelconque des revendications 2 ou 3.

Cysteine → 4'-Phosphopantothenoyl-L-Cysteine → 4'-phosphopantetheine → Pantetheine → Cysteamine → Hypotaurine → Taurine

Coenzyme A (CoA) → Dephospho-CoA → Lysosomal acid phosphatase

Nuclear or microsomal nucleotide pyrophosphatases

FIG. 2
REFERENCES CITED IN THE DESCRIPTION

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