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(54) Title: BISMUTH SALTS OF ANTI-OXIDANTS AND RADICAL SCAVENGERS FOR PREVENTION AND TREATMENT OF MUCOUS MEMBRANE ULCERS

(57) Abstract: Disclosed is a method of treating and/or preventing oral mucositis in a mammal. The method comprises the step of administering an effective amount of a bismuth salt of an antioxidant or a bismuth salt of a free radical scavenger to the mammal.

BISMUTH SALTS OF ANTI-OXIDANTS AND RADICAL SCAVENGERS FOR PREVENTION AND TREATMENT OF MUCOUS MEMBRANE ULCERS

RELATED APPLICATION(S)

This application claims the benefit of U.S. Provisional Application No. 60/296,984, filed June 8, 2001. The entire teachings of the above application(s) are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Oral ulcerative mucositis is a common, painful, dose-limiting toxicity of drug and radiation therapy for cancer. The disorder is characterized by breakdown of the oral mucosa, which results in the formation of ulcerative lesions. In granulocytopenic patients, the ulcerations that accompany mucositis are frequent portals of entry for indigenous oral bacteria often leading to sepsis or bacteremia. Mucositis occurs to some degree in more than one third of all patients receiving anti-neoplastic drug therapy, and there are about one million occurrences of oral mucositis annually in the United States. The frequency and severity are significantly greater among patients who are treated with induction therapy for leukemia or with many of the conditioning regimens for bone marrow transplant. Among these individuals, moderate to severe mucositis (ulceration) is not unusual in more than three-quarters of patients. The incidence of mucositis is even higher in younger patients. Moderate to severe mucositis occurs in virtually all patients who receive radiation therapy for tumors of the head and neck and typically begins with cumulative exposures of 15 Gy and then worsens as total doses of 60 Gy or more are reached.

Clinically mucositis progresses through four stages: (1) An initial stage that is characterized by inflammatory changes of erythema and edema. Localized islands of hyperkeratosis may also been seen. This stage is symptomatically mild and may be successfully palliated by topical anesthetics. (2) Subsequently the mucosa breaks

down and becomes eroded and atrophic with increasingly significant inflammatory changes. This stage is increasingly painful and may require systemic analgesic therapy in the form of NSAIDs or oral narcotics for adequate palliation. (3) The third stage of mucositis is the most symptomatic. Full thickness ulcers of the mucosa cause severe discomfort necessitating parenteral narcotic therapy. In addition, in the myelosuppressive patient, these ulcerations provide a systemic portal of entry for the oral microflora often leading to bacteremia and sepsis. Antimicrobial intervention is required. (4) Finally, spontaneous healing occurs about 2-3 weeks after cessation of anti-neoplastic therapy.

The complexity of mucositis as a biological process has only been recently appreciated. The condition appears to represent a sequential interaction of oral mucosal cells and tissues including connective tissue, endothelium, epithelium and inflammatory cells, pro-inflammatory cytokines and local environmental factors such as bacteria and saliva. Damage to epithelial and connective tissue induces release of inflammatory cytokines leading to mucosal damage. Additionally, both direct and indirect effects to epithelial cells result in either apoptotic or necrotic changes in the basal layer; differentiation into new epithelial cells is halted. The arrest of epithelial cell renewal leads to atrophy followed by ulceration.

Standard therapy for mucositis is predominantly palliative, including application of topical analgesics such as lidocaine and/or systemic administration of narcotics and antibiotics. No standard curative treatment for mucositis exists. Thus, there is a need for new treatments which inhibit, prevent, reduce the severity, and/or promote the healing of mucositis.

SUMMARY OF THE INVENTION

It has now been found that bismuth salts of anti-oxidants and free radical scavengers are even more effective in treating/preventing oral mucositis than other bismuth-containing compounds. For example, bismuth ascorbate was effective in treating mucositis in radiation treated hamsters when administered at concentrations as low as 1.75 mg/ml (see Example 5). Based on this discovery, methods of treating and/or preventing oral mucositis in a mammal are disclosed.

One embodiment of the present invention is a method of treating oral mucositis in a mammal. The method comprises the step of administering an effective amount of a bismuth salt of an antioxidant or a bismuth salt of a free radical scavenger to the mammal. Suitable antioxidants and free radical scavengers typically have at least one acidic functional group, such as a carboxylic acid, sulfonic acid, phosphoric acid, sulfinic acid, phenol or thiol functional group, so that the antioxidant or free radical scavenger can readily form an anion and bond ionically with bismuth. In a preferred embodiment, the antioxidant or free radical additionally comprise a phenol, a thiol, a phosphorothioate, or one or more double bonds which readily oxidize or readily react with free radicals. Examples of suitable phenol-containing compounds include 2,6-di-*tert*-butyl-4-methoxy phenol, 2,6-di-*tert*-butyl-4-methyl phenol, α-tocopherol, retinoic acid and catechol; examples of suitable thiol-containing compounds include *N*-acetylcysteine, mercaptoethylamine and glutathione; examples of suitable phosphorothioates include amifostine; and examples of suitable double bond-containing compounds include ascorbic acid and dehydroascorbic acid.

Another embodiment of the present invention is the described bismuth salts for use in the manufacture of a medicament for the treatment or prevention of oral mucositis.

Another embodiment of the present invention is the bismuth salt of an anti-oxidant or free radical scavenger. Examples of suitable anitoxidants and free radical scavengers are provided above. Preferably, the bismuth salt is bismuth ascorbate or bismuth glutathione.

Yet another embodiment of the present invention is a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and the bismuth salt of an anti-oxidant or free radical scavenger. Examples of suitable anitoxidants are provided above. Preferably, the bismuth salt is bismuth ascorbate or bismuth glutathione.

DETAILED DESCRIPTION OF THE INVENTION

As stated above, the invention is based on the unexpected discovery that bismuth salts of anti-oxidants and free radical scavengers are effective in treating and/or preventing oral mucositis. Oral mucositis is defined herein as inflammation of a mucous membrane of the oral cavity or lips. Oral mucositis is characterized by inflammation of a mucous membrane of the oral cavity or lips and is typically accompanied by redness, swelling, and/or ulcerations of the mouth. Included in this description is oral mucositis that is a side-effect of anti-cancer therapies such as chemotherapy and radiotherapy, and oral mucositis that is a side effect of bone marrow transplantation or stem cell transplant or ablation. Mucositis also includes mucositis that develops spontaneously in a healthy patient not receiving anti-cancer therapy, as in the case of a canker sore or mouth ulcer.

The oxidation state of bismuth in the salts used in the method of the present invention is preferably +3, but can also be +5. The counteranions can be the same or different (i.e., "mixed"). Examples of bismuth salts in which the counteranions are all the same include Bi(ascorbate)$_3$, Bi(dehydroascorbate)$_3$, Bi(glutathione)$_3$, Bi(*N*-acetylcysteine)$_3$ and Bi(mercaptoethylamine)$_3$. Mixed bismuth salts can contain more than one type of antioxidant or free radical scavenger. Examples include salts containing two molecules ascorbate and one molecule of glutathione for each bismuth atom [Bi(ascorbate)$_2$(glutathione)] and salts containing one molecule of ascorbate and two molecules of glutathione for each bismuth atom [Bi(ascorbate)(glutathione)$_2$]. Alternatively, a mixed bismuth salt contains one or two counteranions that are not an antioxidant or free radical scavenger, e.g., Bi(ascorbate)$_2$R, Bi(glutathione)$_2$R, Bi(dehydroascorbate)$_2$R, Bi(*N*-acetylcysteine)$_2$ R, Bi(mercaptoethylamine)$_2$R, Bi(ascorbate)R$_2$, Bi(glutathione)R$_2$, Bi(dehydroascorbate)R$_2$, Bi(*N*-acetylcysteine)R$_2$ and Bi(mercaptoethylamine)R$_2$. R is a counteranion that is not an antioxidant or free radical scavenger. Examples include acetate, propionate, butyrate, formate, salicylate, subsalicylate, subgallate, aluminate, citrate, subcitrate, carbonate, subcarbonate, tripotassium dicitrato, nitrate, subnitrate, tartrate. Acetate, salicylate and subsalicylate are preferred examples.

The terms "bismuth *N*-acetylcysteine", "bismuth mercaptoethylamine" "bismuth dehydroascorbic acid", "bismuth ascorbate" and "bismuth glutathione" refer to a salt which contains one, two or three molecules of *N*-acetylcysteine, mercaptoethylamine dehydroascorbic acid, ascorbate or glutathione, respectively, per atom of bismuth.

The bismuth salt is generally locally administered to the lesion in the mouth. This can be accomplished by administering an aqueous suspension of the compound or by administering a powder or tablet which is then masticated. The composition can be applied directly to the lesion, e.g., by a swab, or by other means, such as in a mouthwash or rinse. Preferably, the compound is administered as a suspension, either by a swab or by a rinse.

An "effective amount" of the compound or composition is the quantity which results in a desired therapeutic or prophylactic effect with respect to oral mucositis. "A desired therapeutic effect" includes an amelioration of the discomfort associated with the oral mucositis and/or an increase in the rate of healing of lesions associated with the condition. A "desired prophylactic effect" includes a reduced number of lesions and/or reduced size mucositis lesions compared with, for example, what is normally experienced by a mammal undergoing cancer therapy. Typically, an "effective amount" is between about 0.1 mg/day to about 10 grams/day applied to or contacted with the lesion or oral mucosal surface, and preferably between about 1.0 mg/day to about 1 gram/day and more preferably between about 10 mg/day to about 500 mg/day.

Typically, a pharmaceutical composition comprises an effective concentration of the bismuth salt. An "effective concentration" means that concentration of the bismuth salt in the solution or mixture (liquid or solid mixture) is such that a desirable therapeutic or prophylactic effective is achieved when a lesion or the mucosal surface is treated with the pharmaceutical composition. Typical concentrations of the bismuth salt in the pharmaceutical composition are from about 1 μg/ml to about 500 mg/ml, more typically from about 0.1 mg/ml to about 100 mg/ml and preferably from about 1 mg/ml to about 50 mg/ml.

The composition can be administered to the patient as needed to provide amelioration or prevention (inhibition) of the symptoms. For example, the composition can be administered one, two, three, four or more times daily. In another embodiment, the composition is administered following meals and/or other fluid intake and/or as the saliva dissolves or removes the composition from the lesions.

Preferred suspensions of the bismuth-containing compound include aqueous suspensions further comprising an anionic or a non-ionic cellulose ether. Examples of nonionic cellulose ethers include alkyl-celluloses (e.g., methylcellulose), hydroxyalkylalkylcelluloses (e.g., hydrocyclopropylmethylcellulose; hydroxybutylmethylcellulose; hydroxyethylmethylcellulose; ethylhydroxyethylcellulose), hydroxyalkylcelluloses (e.g., hydroxyethylcellulose; hydroxypropylcellulose), and mixtures thereof. Most preferred are alkylcelluloses, especially methylcellulose. Pharmaceutically-acceptable non-ionic cellulose ether polymers are well known in the art, and are described in more detail in "Handbook of Water-Soluble Gums and Resins" (McGraw-Hill Book Company, New York; 1980; Davidson, editor), chapters 3, 12, and 13, the disclosures of which are incorporated herein by reference in their entirety. An anionic cellulose ether includes carboxymethyl cellulose.

Representative examples of pharmaceutically-acceptable non-ionic cellulose ether polymers useful in the compositions of the present invention are: Methocel A® (methylcellulose, sold by the Dow Chemical Company); Metolose SM® (methylcellulose, sold by Shin Etsu Chemical Products Ltd.); and Methocel E® (hydroxypropylmethylcellulose, sold by the Dow Chemical Company).

The pharmaceutical compositions of the present invention typically comprise, by weight, from about 0.1% to about 25% or more of a non-ionic cellulose ether polymer, preferably from about 0.1% to about 10%, more preferably from about 0.5% to about 3%, and most preferably from about 0.5% to about 1.5%.

Alternatively or additionally, the composition can contain other high molecular weight polysaccharides, such as a xanthan or guar gum. Xanthan gum is available from a variety of commercial sources, including Rhodigel® (sold by Rhone Poulenc Industries) and Keltrol® (sold by Kelco Division of Merck & Co., Inc.).

Xanthan gum is typically used at a level of from about 0.1% to about 5%, preferably from about 0.1% to about 3%, and more preferably from about 0.5% to about 1.5%.

The suspension further preferably comprises a magnesium aluminum silcate. Magnesiuim aluminum silicate (or aluminum magnesium silicate) is of the formula $Al_2MgO_8Si_2$, occurring naturally in such smectite minerals as colerainite, saponite, and sapphirine. Refined magnesium aluminum silicates useful herein are readily available, such as Veegum®, magnesium aluminum silicate, manufactured by R.T. Vanderbilt Company, Inc.

The pharmaceutical compositions of the present invention typically comprise, by weight, from about 0.1% to about 25% or more of a magnesium aluminum silicate, preferably from about 0.1% to about 10%, more preferably from about 0.1% to about 5%, and most preferably from about 0.1% to about 5%, and most preferably from about 0.5% to about 1.5%.

In addition to the essential components described hereinbefore, the pharmaceutical compositions of the present invention may comprise additional optional components selected as appropriate for the particular orally-administrable dosage form being used. Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules and bulk powders, as well as the preferred aqueous liquid forms. Tablets can be compressed, tablet triturates, sugar-coated, film-coated or multiple compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents.

Liquid oral dosage forms are preferred herein. Compositions herein in the form of a liquid include, for example, aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. They may contain suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, melting agents, coloring agents, and/or flavoring agents. Preferably, these liquid dosage forms comprise water, typically at a level by weight of from about 75% to about 99%, preferably from about 85% to about 98%, and most preferably from about 92% to about 96%.

Some examples of substances which can serve as pharmaceutically-acceptable optional components are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; powdered tragacanth; malt; gelatin; talc; stearic acid; magnesium stearate; calcium sulfate; and polyols such as propylene glycol, glycerine, sorbitol, mannitol, polyethylene glycol, benzoic acid, methylsalicylate, salicylic acid, and salts thereof, sodium saccharin, sorbic acid, aspartame, acesulfome and cyclamate. Wetting agents and lubricants such as sodium lauryl sulfate, as well as coloring agents, flavoring agents, excipients, tableting agents, stabilizers, anti-oxidants (preferably antioxidants which do not have acidic functional groups) and preservatives can also be present.

The choice of pharmaceutically-acceptable optional components to be used in the compositions of the present invention is basically determined by the form and aesthetic properties desired for the composition. Pharmaceutically-acceptable optional components suitable for the preparation of compositions herein for oral administration are well known in the art. Their selection will depend on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of the present invention, and can be made without difficulty by a person skilled in the art.

In yet another embodiment, the composition further comprises an antimicrobial agent (e.g., antibacterial, antiviral and antifungal agents), such as chlorhexidine, triclosan, iodine complexes, tetracyclines, metronidazole, bacitracin, neomycin, polymyxin B, tobramycin, vidariabine, denavir, acyclovir, gancyclovir, foscarnet, famcyclovir, nystatin, emphotericin, flucytocine, itraconazole, fluconazole, clotrimazole, and econazole, to prevent or treat infections of the lesions. The antimicrobial agent can also be a polymer, such as the antimicrobial polymers disclosed in Mandeville, III *et al.*, "Ionic Polymers as Anti-Infective Agents", U.S. Patent No. 6,034,129; Kurtz and Neenan; "Antimicrobial Compositions and Methods", U.S. Serial No. 09/568,825, filed May 11, 2000; and Kurtz and Fitzpatrick, "Anionic Polymers as Toxin Binders", U.S. Serial No. 09/541,268, filed April 3, 2000.

Alternatively or additionally, the composition can further comprise an anti-inflammatory agent, such as aspirin, acetaminophen or ibuprofen, salicylic acid, salicyloyl salicylic acid (disalcid), salicylamide, diflunisal (dolobid), mefenamic acid (ponstel), mellofenamic acid (meclomen), fenoprofen (nalfon), ketoprofen (orodis), flubiprofen (ansaid), naproxen (naprosyn), diclofenas (voltaren), benorylate (benoral), caprofen (rimadyl), sulindac (clinoril), piroxicam, oxyphenylbutazone (tanderil), phenylbutazone (butazolidin), metiazinic acid, zomepirac, zomax, ketorolac (toradol), etodolac (lodine), tolmetin, tolectin, indomethacin (indocin), tenidap (enablex) and/or an anesthetic agent, such as benzydamine, dyclonine, diphenylhydramine, benzocaine, cocaine and lidocaine.

The method of the claimed invention is particularly useful in the treatment of oral mucositis resulting from anti-cancer therapy, such as radiation therapy or chemotherapy, including induction therapy in leukemia patients. "Treatment" includes prophylactic and/or therapeutic treatment. The treatment can be particularly beneficial for patients undergoing treatment for tumors of the head and neck, such as radiation patients. For prophylactic treatment of mucositis resulting from chemotherapy, treatment with the bismuth salt is initiated before the onset of the chemotherapy, during chemotherapy, after chemotherapy is completed but before symptoms appear or any combination of the above. For prophylactic treatment of mucositis resulting from radiation therapy, treatment with the bismuth salt is initiated before the onset of radiation therapy, during radiation exposure, after radiation exposure has been terminated (preferably no sooner than about one hour, more preferably five hours after termination) but before symptoms appear or any combination of the above. Prophylactic treatment includes inhibiting the onset of mucositis, delaying the onset of mucositis, reducing the severity of mucositis and/or reducing the likelihood of developing mucositis. For therapeutic treatment of mucositis resulting from radiation therapy or chemotherapy, the bismuth salt is administered after symptoms of mucusitis (e.g., mouth ulcers) have appeared.

The method is preferably used with human patients, but can also be used with other mammals, such as companion animals (e.g., dogs, cats, and the like), farm

animals (horses, cattle and the like) and laboratory animals (hamsters, mice, rats and the like).

Example 1. Synthesis of Bismuth Ascorbate Using Bismuth Acetate and Ascorbic Acid in Toluene

77.0 grams of bismuth acetate and one equivalent of ascorbic acid (35.12 grams) were added to a 2 liter round bottom flask. Toluene (1200 milliliters) was then added as the solvent. A distillation head with a 1 liter catch flask was attached to the reaction flask. The mixture was stirred vigorously and heated to reflux (about 110° C). The mixture never completely dissolved (yellow cloudy mix). After about 5 hours of refluxing (while stirring), the toluene was slowly distilled off. When about 200 milliliters were left in the reaction flask, the heat was turned off, and the reaction was allowed to cool to room temperature. A fine yellow powder precipitated and was separated by filtration. The yellow powder with then rinsed with about 3 liters of hexane, collected and then dried *in vacuo* overnight at 50° C. The final product was a fine powder with a yellowish/off-white tint that had an acetic odor. The yield was 108 grams.

Example 2. Procedure for Synthesizing Bismuth Glutathione Using Bismuth Acetate and Ascorbic Acid

9.4 grams of bismuth acetate (Aldrich) and three equivalents, 22.4 grams, of glutathione reduced (Lancaster) were added to a 1 liter one neck round bottom flask. Toluene (600 milliliters) was added as the solvent. A distillation head with a 500 milliliters catch flask was attached to the reaction flask. The mixture was stirred vigorously and heated to reflux (about 110° C). The mixture never completely dissolved (white cloud mix). After about 5 hours of refluxing (while stirring), the toluene was slowly distilled off. When 100 milliliters were left in reaction flask, the heat was turned off and the reaction was allowed to cool to room temperature. A white powder precipitated and was separated by filtration. The resulting white powder was then rinsed with about 1 liter of hexane. The powder was then collected

and placed on the speed vac overnight at 50° C. The resulting product was a white powder. This yield was 23.5 grams.

Example 3. Synthesis of Bismuth Ascorbate Using Na^+ Ascorbate and Bismuth Nitrate

612.6 grams (10 equivalents) of sodium ascorbate (Aldrich) were dissolved in 1125 milliliters of deionized water (completely dissolved in about 15-20 minutes) in a 2 liter Erlenmeyer flask . The resulting solution was stirred at room temperature, resulting in a clear deep orange-red solution. 150 grams of bismuth nitrate pentahydrate (Aldrich) were ground into fine grains with a mortar and pestle. The ground bismuth nitrate was added as a solid a few hundred milligrams at a time over a period of approximately 3 hours. Upon addition of the bismuth nitrate, the solution became cloudy and small white undissolved particles could be seen. After all of the bismuth nitrate was added, the reaction was allowed to stir at room temperature for about 72 hours. It was then filtered by gravity filtration to remove any undissolved particles. A clear deep orange/red color remained. The filtrate was diluted with deionized water to 3750 milliliters and poured into a large 10 liter plastic bucket. The product was precipitated by adding 3750 milliliters ethanol (Aldrich, HPLC grade) to the reaction solution. It was then separated by filtration. The light orange solid that remained was dried under vacuum at room temperature. The yield was about 90 grams.

Example 4. Procedure for Synthesizing Bismuth Ascorbate with Bismuth Acetate and Ascorbic Acid in Water

Bismuth acetate (Strem Chemicals), 100 grams, was ground to a fine powder with a mortar and pestle. This fine powder was added to a 1 liter Erlenmeyer flask with 500 milliliters of deionized water with stirring, resulting in a suspension. With continuous stirring, 137 grams of ascorbic acid (Aldrich, 3 equivalents) were added as a solid. Immediately, a yellow color was observed. The total volume of the reaction was increased to1 liter by adding deionized water. The reaction was stirred at room temperature for 5 days. After 5 days, the reaction was filtered using a

Buchner funnel with suction. The isolated solid was air-dried in the Buchner funnel overnight. The final product was an orange-yellow solid. The reaction yielded 107 grams.

Example 5. Bismuth Ascorbate and Bismuth Glutathione Are Effective in Treating Mucositis in a Hamster Model Following Irradiation Therapy.

The efficacy of bismuth-containing compounds in treating oral mucositis was assayed according to a hamster model disclosed in Sonis *et al., Oral Oncology 36:*373 (2000), the entire teachings of which are incorporated herein by reference. Briefly, male Golden Syrian hamsters (Charles River Laboratories), aged 5 to 6 weeks, with body weights of approximately 90 g at project commencement, were used. Mucositis was induced using an acute radiation protocol. A single dose of radiation (35-40 Gy/dose) was administered to all animals on Day 0. Radiation was generated with a 250 kilovolt potential (15 mA) source at a focal distance of 50 cm, hardened with a 0.35 mm Cu filtration system. Irradiation targeted the left buccal pouch mucosa at a rate of 121.5 cGy/minute. Prior to irradiation, animals were anesthetized with an intraperitoneal injection of sodium pentobarbital (80 mg/kg). The left buccal pouch was everted, fixed and isolated using a lead shield.

All animals were dosed with test material three times per day. A needleless tuberculin syringe, containing 0.5 ml of the test compound was inserted into the left cheek pouch and the drug deposited into the pouch. Dosing began on Day 0 and continued until Day 20.

For the evaluation of mucositis, the animals were anesthetized with inhalation anesthetics, and the left pouch everted. Mucositis was scored visually by comparison to a validated photographic scale, ranging from 0 for normal to 5 for severe ulceration. In descriptive terms, this scale is defined as follows:

Score	Description
0	Pouch completely healthy. No erythema or vasodilation
1	Light to severe erythema and vasodilation. No erosion of mucosa
2	Severe erythema and vasodilation. Erosion of superficial aspects of mucosa leaving denuded areas. Decreased stippling of mucosa.
3	Formation of off-white ulcers in one or more places. Ulcers may have a yellow/gray appearance due to a pseudomembrane. Cumulative size of ulcers should equal about 1/4 of the pouch. Severe erythema and vasodilation.
4	Cumulative seize of ulcers should equal about 1/2 of the pouch. Loss of pliability. Severe erythema and vasodilation
5	Virtually all of pouch is ulcerated. Loss of pliability (pouch can only partially be extracted from mouth).

A score of 1-2 is considered to represent a mild stage of the disease, whereas a score of 3-5 is considered to indicate moderate to severe mucositis. Following visual scoring, a photograph was taken of each animal's mucosa using a standardized technique. At the conclusion of the experiment, all films were developed and the photographs randomly numbered. At least two independent trained-observers graded the photographs in blinded fashion using the above-described scale (blinded scoring). A score of 1-2 is considered to represent a mild stage of the disease, whereas a score of 3-5 is considered to indicate moderate to severe mucositis in which frank ulceration of the cheek pouch is evident. Treatment efficacy was measured by the reduction in time that the animals experienced ulcerative mucositis (a score < 3) expressed as a percentage of the time that the animals in the control group experienced ulcerative mucositis (a score ≥ 3).

Animals treated with solutions containing 1.75 mg/ml of bismuth ascorbate showed significant improvement in their mucositis scores; and animals treated with solutions containing 17.5 mg/ml of bismuth glutathione showed significant

improvement in their mucositis scores. Animals treated with solutions containing 17.5 mg/ml ascorbic acid showed no improvement in their scores.

Example 6. Hamster Model with or prior to irradiation therapy.

Groups of 5 animals each (n = 5). Dosing begins before irradiation and test compound can be applied with swabs according to the instructions below. No treatment is given after irradiation. Animals are scored for mucositis through day 20.

The hamsters are dosed with test compound 20 minutes prior to irradiation and then again 10 minutes prior to irradiation. Each dosing involves two applications of test compound. Twenty minutes before irradiation the applicator swab is dipped into the solution and allowed to soak for a few seconds and then is applied to the solution into the cheek pouch by liberally smearing the solution over the area to be irradiated as well as the surrounding areas that typically get mucositis. Thirty seconds - 1 minute later the solution is reapplied. A fresh swab is used for each application. After 10 minutes the procedure is repeated. Ten minutes later the animals are irradiated. After irradiation the animals are not dosed again.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

What is claimed is:

1. A method of treating oral mucositis in a mammal comprising administering an effective amount of a bismuth salt of an antioxidant or free radical scavenger to the mammal.

2. The method of Claim 1 wherein a bismuth salt of an antioxidant is administered to the mammal.

3. The method of Claim 2 wherein the antioxidant is a thiol-containing, a phenol containing or a double bond containing antioxidant.

4. The method of Claim 2 wherein the bismuth salt is bismuth *N*-acetylcysteine, bismuth mercaptoethylamine or bismuth dehydroascorbic acid.

5. The method of Claim 2 wherein the bismuth salt is bismuth ascorbate.

6. The method of Claim 2 wherein the bismuth salt is bismuth glutathione.

7. The method of Claim 1 wherein the bismuth salt is administered in an aqueous suspension.

8. The method of Claim 7 wherein the suspension further comprises a non-ionic cellulose ether and magnesium aluminum silicate.

9. The method of Claim 7 further comprising a xanthum gum and magnesium aluminum silicate.

10. The method of Claim 7 further comprising one or more preservatives, colorants, sweeteners and flavorants.

11. The method of Claim 7 wherein the composition further comprises an antimicrobial agent.

12. The method of Claim 7 wherein the composition further comprises an anti inflammatory agent.

13. The method of Claim 7 wherein the composition further comprises an anesthetic agent.

14. The method of Claim 7 wherein the oral mucositis is a side-effect of anti-cancer therapy.

15. The method of Claim 7 wherein the bismuth salt is bismuth ascorbate.

16. The method of Claim 7 wherein the bismuth salt is bismuth glutathione.

17. The method of Claim 7 wherein the oral mucositis is a side-effect of anti-cancer chemotherapy.

18. The method of Claim 7 wherein the bismuth salt is administered after the onset of the symptoms of mucositis.

19. The method of Claim 7 wherein the oral mucositis is a side-effect of radiation therapy and the bismuth salt is administered after termination of radiation exposure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/18034

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/29, 31/555
US CL :514/184, 503
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/184, 503

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3,651,208 (LAUSTER) 21 March 1972 (21.03.72), see the entire document.	1-19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 25 JULY 2002	Date of mailing of the international search report 20 AUG 2002
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