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(54) **METHODS AND COMPOSITIONS FOR TREATING PAIN OF THE MUCOUS MEMBRANE**

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(57) **ABSTRACT**

Compositions useful for long-lasting pain relief from mucosal damage, such as mucosal inflamation, abrasions, ulcerations, lesions, trauma and incisions, without significant systemic absorption. The compositions of the invention are particularly suitable for application to the mucous membrane of the nasal cavity and buccal cavity. To relieve pain, the compositions or the invention are topically applied directly to the affected area.

31 Claims, No Drawings

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METHODS AND COMPOSITIONS FOR TREATING PAIN OF THE MUCOUS MEMBRANE

This is a continuation of application Ser. No. 09/888,466, filed Jun. 25, 2000, now Abandon.

This application claims the benefit of U.S. Provisional patent application Ser. No. 60/222,164, filed Jun. 26, 2000, hereby incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

The invention relates to methods and compositions for treating the pain associated with mucosal damage, such as inflamation, abrasions, ulcerations, lesions, incisions, and trauma.

BACKGROUND OF THE INVENTION

The term mucous membrane refers to the moist linings of the buccal cavity, nasal cavity, gastrointestinal tract, respiratory tract, conjunctiva, vagina, colon, urinary bladder, and urethra (Forstner et al., 1973 *J. Cell. Sci.* 12:585; Peppas et al., 1985 *J. Control. Release* 2:257; Lehr et al., 1992 *J. Control Release* 18:249; Spiro, 1970 *Ann. Rev. Biochem.* 39:599; Lebat-Robert et al., 1979 *Path. Biol.* 24:241). The normally smooth, moist, and pink buccal mucosa is very sensitive and inflamation or ulceration (oral mucositis) causes severe pain. Dental surgery, such as root canal and tooth extraction can also severely damage the buccal mucosa causing severe pain. Moreover, oral mucositis and dental surgery can induce secondary conditions, such as weight loss and dehydration from reluctance to eat or drink, infection (bacterial, fungal, and viral), fever, nausea, and diarrhea.

Oral mucositis has a variety of causes, for example, bacterial infections, such as streptococci; viral infections, such as herpes simplex virus; fungal infections; side effects of systemic diseases; vitamin deficiency; iron deficiency; cheek biting; mouth breathing; jagged teeth; orthodontic appliances; ill-fitting dentures; excessive use of alcohol or tobacco; thermally-hot foods; spicy foods; and as a side effect of medication. Severely-painful oral mucositis is a symptom endured by almost all chemotherapy patients. Mucositis symptoms peak 7 to 10 days following chemotherapy, and gradually recede over the following two weeks. For a discussion of the causes and symptoms of mucositis, see *The Merck Manuel, Fifteenth Edition,* Merck Sharp & Dohme Research Laboratories, Rahway, N.J., (1987) pp. 2322–2320.

Topical application of local anesthetics can provide some relief of oral-mucositis and dental-surgery pain but absorption through the mucous membranes occurs rapidly, and pharmaceuticals applied to the mucous membrane for their local effect sometimes cause systemic toxicity (*Goodman and Gilman's The Pharmacological Basis of Therapeutics* 9th ed. J. G. Harman and L. E. Limird Eds., McGraw-Hill New York 1996 p. 8) especially with the higher doses required for adequate pain relief. Systemic absorption is even more likely when the mucous membrane is ulcerated or inflamed. Thus, with traditional anesthetic compositions for mucositis, e.g., 2 percent lidocaine oral rinse or 5% lidocaine ointment, systemic toxicity limits the dosage and so adequate pain relief is difficult to achieve. Other less toxic pain relieving compositions, such as rinses comprising hydrogen peroxide and sodium bicarbonate are less effective at reducing pain. An additional problem with oral rinses is, that following application, the action of swallowing and saliva reduces the concentration of active agent on the affected area, thus oral rinses comprising local anesthetics have a low duration of activity.

In summation, a long-lasting, non-toxic anesthetic composition effective for amelioration of the severe pain induced by mucosal damage, such as mucositis and dental surgery, is needed.

SUMMARY OF THE INVENTION

In one aspect, the invention provides compositions and methods that provide long-lasting local anesthesia and effective pain relief. The compositions of the invention can be topically applied to the affected area, for example, via a dose-metered applicator adapted for spraying or adapted for use with a cannula. When topically applied, the compositions of the invention provide a powerful local-anesthetizing effect, in spite of low anesthetic concentration. Hence, the compositions of the invention provide significant pain relief with low systemic absorption and, therefore, low systemic toxicity. The compositions of the invention, in addition to the ability to remain on the affected area for extended periods, hydrate and soothe.

In one embodiment, the compositions of the invention can be topically applied directly to the affected area to alleviate pain in a subject on any area of a subject's body.

In another embodiment, the compositions of the invention are useful for topical application to a subject's mucous membrane, to induce a long-lasting local-anesthetic effect, thereby relieving pain from mucositis, such as mucosal inflamation, abrasions, ulcerations, and lesions, without significant systemic absorption.

In yet another embodiment, the compositions of the invention are useful for topical application to the site of dental surgery, such as root-canal or tooth-extraction surgery, to induce a long-lasting local-anesthetic effect, thereby relieving the surgical pain, without significant systemic absorption.

In one more embodiment, the invention relates to compositions comprising a mucoadhesive, a local anesthetic or a pharmaceutically-acceptable salt thereof, and an opioid or a pharmaceutically-acceptable salt thereof. In a preferred embodiment, the compositions contain water and are sterile. In a more preferred embodiment, the compositions of the invention, further comprise a chelating agent and a preservative.

In another embodiment, the invention relates to a container adapted for topical application and containing a pharmaceutically-acceptable composition comprising a mucoadhesive, a local anesthetic or a pharmaceutically-acceptable salt thereof, and an opioid or a pharmaceutically-acceptable salt thereof. Preferably, the container is adapted for dose-metered application, such as a dose-metered pump for use with a spray applicator or cannula.

In still another embodiment, the invention relates to a method of inducing local anesthesia in a subject's mucosal membrane by topically applying a pharmaceutically-acceptable composition comprising a local anesthetic or a pharmaceutically-acceptable salt thereof and an opioid or a pharmaceutically-acceptable salt thereof to the subject's mucosal membrane. Preferably, the composition is applied to an area within the subject's buccal or nasal cavity. Preferably, the composition further comprises a mucoadhesive.

In yet another embodiment, the invention relates to a method of inducing local anesthesia in a subject by topically

applying a composition comprising a mucoadhesive, a local anesthetic or a pharmaceutically-acceptable salt thereof, and an opioid or a pharmaceutically-acceptable salt thereof to a subject. Preferably, the composition is applied to a mucosal surface of the subject, for example, an area within the subject's buccal or nasal cavity.

These and other features, aspects, and advantages of the invention will become better understood with reference to the following detailed description, examples, and appended claims.

DETAILED DESCRIPTION OF THE INVENTION

The phrase "pharmaceutically-acceptable salt(s)," as used herein includes but is not limited to salts of acidic or basic groups that may be present in compounds used in the present compositions. Compounds included in the present compositions that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically-acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, including, but not limited to, sulfuric, citric, maleic, acetic, oxalic, hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts.

Compounds included in the present compositions that include an amino moiety may form pharmaceutically-acceptable salts with various amino acids, in addition to the acids mentioned above. Compounds, included in the present compositions, that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include alkali metal or alkaline earth metal salts and, particularly, calcium, magnesium, sodium, lithium, zinc, potassium, and iron salts. For a review on pharmaceutically-acceptable salts see Berge et al., 1977 *J. Pharm. Sci.,* 66:1, incorporated herein by reference.

As used herein the term "opioid" means all agonists and antagonists of opioid receptors, such as mu (μ), kappa (κ), and delta (δ) opioid receptors and subtypes thereof. For a discussion of opioid receptors and subtypes see *Goodman and Gilman's The Pharmacological Basis of Therapeutics* 9th ed. J. G. Harman and L. E. Limird Eds., McGraw-Hill New York:1996 pp. 521–555, incorporated herein by reference. The opioid can be any opioid receptor agonist or antagonist known or to be developed. Preferred opioids interact with the μ-opioid receptor, the κ-opioid receptor, or both. Preferably, the opioid is an opioid-receptor agonist.

Examples of suitable opioids for use with the invention include, but are not limited to, alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, benzitramide, nor-binaltorphimine, bremazocine, buprenorphine, butorphanol, clonitazene, codeine, CTOP, DAMGO, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydrocodeine enol acetate, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, diprenorphine, DPDPE, eptazocine, ethoheptazine, ethylketocyclazocine, ethylmethylthiambutene, etonitazene, etorphine, fentanyl, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, lofentanil, loperamide, meperidine, meptazinol, metazocaine, methadone, metopon, morphine, myrophine, nalbuphine, naltrindole, benzoylhydrazone, naltrexone, narceine, nicomorphine, norlevorphanol, normethadone, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, papaverine, pentazocine, phenadoxone, phenazocine, phenoperidine, piminodine, pirtramide, proheptazine, promedol, propiram, propoxyphene, remifentanil, spiradoline, sufentanil, tilidine, U50,488, and U69,593, amiphenazole, cyclazocine, levallorphan, nalmefene, nalorphine, naloxone, and naltrexone or pharmaceutically-acceptable salts thereof, or mixtures thereof.

Examples of peptide opioids include, but are not limited to, Tyr-Gly-Gly-Phe-Leu ([Leu^5]enkephalin), Tyr-Gly-Gly-Phe-Met ([Met^5]enkephalin), Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Gln (DynorphinA), Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Gln-Phe-Lys-Val-Val-Thr (Dynorphin B), Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-Pro-Lys (α-Neoendorphin), Tyr-Gly-Gly-Phe-Leu-Arg-Lsy-Tyr-Pro (β-Neoendorphin), Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Asn-Ala-Ile-Ile-Lys-Asn-Ala-Tyr-Lys-Lys-Gly-Glu (β_h-Endorphin), [D-Ala^2,MePhe^{4}Gly(ol)^5]enkephalin (DAMGO), [D-Pen^{2,}D-Pen^5]enkephalin (DPDPE), [D-Ser^{2,}Leu^5]enkephalin-Thr^6 (DSLET), [D-Ala^{2,}D-Leu^5] enkephalin (DADL), D-Phe-Cys-Tyr-D-Trp-Orn-Thr-Pen-Thr-NH_2(CTOP), [D-Ala^2,N-MePhe^4,Met(O)^5-ol] enkephalin (FK-33824), Tyr-D-Ala-Phe-Asp-Val-Val-Gly-NH_2 ([D-Ala^2]Deltorphin 1), Tyr-D-Ala-Phe-Glu-Val-Val-Gly-NH_2 ([D-Ala^{2}Glu^4]Deltorphin (Deltorphin II)), Tyr-Pro-Phe-Pro-NH^2 (Morphiceptin), Tyr-Pro-MePhe-D-Pro-NH^2 (PL-017), [D-Ala^2,Leu^5,Cys^6]enkephalin (DALCE) or pharmaceutically-acceptable salts thereof, or mixtures thereof Preferred opioids include morphine, loperamide and loperamide derivatives such as those disclosed in U.S. Pat. Nos. 5,763,445; 5,981,513; 5,869,521; 5,744,458; 5,760,023; 5,798,093; 5,849,762; 5,811,078; 6,004,964; 5,962,477; 5,688,955; 5,888,494; 5,646,151; and 5,667,773 (all of which patents are incorporated by reference herein), or pharmaceutically-acceptable salts thereof, or mixtures thereof. The most preferred opioid is morphine or a pharmaceutically-acceptable salt thereof.

As used herein, the term "local anesthetic" means any drug that provides local numbness or analgesia or any drug that provides a regional blockage of nociceptive pathways (afferent and/or efferent) and that is not an agonist or an antagonist of an opioid receptors. The local anesthetic can be any local anesthetic known or to be developed. Examples of local anesthetics suitable for use with the invention include: ambucaine, amolanone, amylcaine, benoxinate, benzocaine, betoxycaine, biphenamine, bupivacaine, butacaine, butamben, butanilicaine, butethamine, butoxycaine, carticaine, chloroprocaine, cocaethylene, cocaine, cyclomethycaine, dibucaine, dimethisoquin, dimethocaine, diperodon, dyclonine, ecogonidine, ecogonine, euprocin, fenalcomine, formocaine, hexylcaine, hydroxyteteracaine, isobutyl p-aminobenzoate, leucinocaine, levoxadrol, lidocaine, mepivacaine, meprylcaine, metabutoxycaine, methyl chloride, myrtecaine, naepaine, octacaine, orthocaine, oxethazaine, parenthoxycaine, phenacaine, phenol, piperocaine, piridocaine, polidocanol, pramoxine, prilocaine, procaine, propanocaine, proparacaine, propipocaine, propoxycaine, pseudococaine, pyrrocaine,

ropivacaine, salicyl alcohol, tetracaine, tolycaine, trimecaine, zolamine, or pharmaceutically-acceptable salts thereof, or mixtures thereof.

The amide and ester type local anesthetics are preferred. Amide type local anesthetics are characterized by an amide functionality, while ester type local anesthetics contain an ester functionality. Preferred amide type local anesthetics, include lidocaine, bupivacaine, prilocaine, mepivacaine, etidocaine, ropivacaine, dibucaine, and pharmaceutically-acceptable salts thereof and mixtures thereof. Preferred ester type local anesthetics include tetracaine, procaine, benzocaine, chloroprocaine, and pharmaceutically-acceptable salts thereof and mixtures thereof. The most preferred local anesthetic is lidocaine. The meaning of "local anesthetic" also encompasses drugs not traditionally associated with local anesthetic properties but which have a local-anesthetic effect, for example, non-narcotic analgesics, such as, acetylsalicylic acid, ketoprofen, piroxicam, diclofenac, indomethacin, ketorolac, Vioxx®, and Celebrex®. Furthermore, in order to improve the effectiveness and tolerance of the present topically-effective therapy, local anesthetics with different pharmacodynamics and pharmacokinetics may be combined in a composition of the invention. A preferred combination of local anesthetics is lidocaine and prilocaine and another preferred combination is lidocaine and tetracaine.

As used herein, the term "local delivery" of a therapeutic, means topical application of the therapeutic to a subject, whereafter a therapeutically-effective amount of the therapeutic is absorbed in the immediate application area, preferably, without significant absorption into the blood stream.

As used herein, a "therapeutically-effective amount" of the compositions of the invention means the amount required to induce a local-anesthetic effect or numbness sufficient to ameliorate pain induced by ulceration, inflamation, or lesions of the buccal or nasal membrane or other mucous membranes or the pain associated with mucosal trauma, such as dental surgery. Preferably, the active agents of the composition are not absorbed systemically.

As used herein, the term "subject" means any animal, preferably a mammal, more preferably a human.

As used herein the term "mucoadhesive" means a natural or synthetic substance, e.g., gels, pastes, macromolecules, polymers, and oligomers, or mixtures thereof, that can adhere to a subject's mucous membrane for a period of time sufficient to locally deliver a therapeutically-effective amount of a composition of the invention to a subject. Adhesion of mucoadhesives to the mucous membrane occurs primarily via secondary chemical bonds, such as hydrogen bonding and Van der Waal forces (Tabor et al., 1977 *J. Colloid Interface Sci.* 58:2 and Good 1977 *J. Colloid Interface Sci.* 59:398). Mucoadhesive substances often form viscous aqueous solutions. The composition itself does not need to be mucoadhesive, as long as it can form a mucoadhesive gel upon on the contact with the mucous membrane. For example, gellan gum itself is a very weak mucoadhesive. On contact with the buccal membrane, gellan gum can interact with the ions in the mucous membrane and form an adhesive gel layer. According to the invention, mucoadhesives possess binding properties that may be distinguished from non-mucoadhesives by comparing the degree of adhesion to a mucosal surface. For example, comparison of a potential mucoadhesive with a control emulsion of comparable viscosity prepared without mucoadhesive properties, e.g., a starch solution. At similar viscosities, the emulsion prepared with the mucoadhesive will bind to the mucosal surface more strongly than will the control emulsion, preferably at least 25% greater mucosal binding than the control emulsion, more preferably at least 50% greater, still more preferably at least 100% greater mucosal binding. Either mechanical binding to mucous membrane per se or the degree of biological effect of a drug delivered may be used as a measurement parameter for mucoadhesion. This test may be used to distinguish preferred mucoadhesives. Substances can be screened for their ability to be used as mucoadhesives for local delivery of compositions of the invention according to the methodology described in Smart et al., 1982 *J. Pharm. Pharmacol.* 34:70P and Smart et al., 1984 J. Pharm. Pharmacol. 36:295, which methodology comprises estimating values of adhesive strength between the substance and the mucous membrane. Preferably, the mucoadhesive is water soluble, such that at least 1% by weight of the mucoadhesive is soluble in water at 25° C. In a preferred embodiment, the mucoadhesive will exhibit non-Newtonian fluid properties, i.e., the viscosity decreases with increasing shear forces. Accordingly, the viscosity of the composition can be modulated by altering the shear forces present when the composition is applied to a surface. A composition with non-Newtonian fluid properties, becomes less viscous when shaken or atomized, then, upon standing, returns to its original viscosity.

Examples of mucoadhesives for use in the present invention include, but are not limited to, pectin, alginic acid, chitosan, hyaluronic acid, polysorbates, such as polysorbate-20, -21, -40, -60, -61, -65, -80, -81, -85; poly (ethyleneglycol), such as PEG-7, -14, -16, -18, -55, -90, -100, -135, -180, -4, -240, -6, -8, -9, -10, -12, -20, or -32; oligosaccharides and polysaccharides, such as gellan, carrageenan, xanthan gum, gum Arabic, and dextran; cellulose esters and cellulose ethers; modified cellulose polymers, such as carboxymethylcellulose, hydroxyethylcellulose, hydroxypropyl methylcellulose, hydroxyethyl ethylcellulose; polyether polymers and oligomers, such as polyoxyethylene; condensation products of poly(ethyleneoxide) with various reactive hydrogen containing compounds having long hydrophobic chains (e.g. aliphatic chains of about 12 to 20 carbon atoms), for example, condensation products of poly(ethylene oxide) with fatty acids, fatty alcohols, fatty amides, polyhydric alcohols; polyether compounds, such as poly(methyl vinyl ether), polyoxypropylene of less than 10 repeating units; polyether compounds, such as block copolymers of ethylene oxide and propylene oxide; mixtures of block copolymers of ethylene oxide and propylene oxide with other excipients, for example, pluronic lethicin organogel (see 1997 *International Journal of Pharmaceutical Compounding* 1:71); poly (vinyl alcohol); polyacrylamide; hydrolyzed polyacrylamide; poly(vinyl pyrrolidone); poly(methacrylic acid); poly (acrylic acid) or cosslinked polyacrylic acid, such as carbomer, i.e., a homopolymer of acrylic acid crosslinked with either an allyl ether of pentaerythritol, an allyl ether of sucrose, or an allyl ether of propylene (e.g., Acrisint® 400, 410, or 430 commercially available from 3V Inc. Weehawkin, N.J.); Orabase® (i.e., a mixture of gelatine, pectin and sodium carboxymethyl cellulose in a plasticized hydrocarbon gel, commercially available from Hoyt laboratories, Needhm, Mass.); Carafate® (sulfated sucrose and aluminum hydroxide, commercially available from Marion Laboratories, Inc., Kansas City, Mont.). The block copolymers of ethylene oxide and propylene oxide are particularly preferred. Preferred block copolymers of ethyl-

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Sync your system to PACER to automate legal marketing.