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Phenoxybenzamine for pain
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ABSTRACT

The invention relates to compositions and formulations for intranasal/inhalation administration comprising phenoxybenzamine and/or related haloalkylamines, and methods of use thereof, for treatment of subjects suffering from acute and chronic pain syndromes, *e.g.*, sustained relief of local and non-regional pain initiated or maintained by the sympathetic nervous system, either peripherally or centrally in subjects suffering, *e.g.*, from reflex sympathetic dystrophy (RSD)/complex regional pain syndrome (CRPS), neuropathic and/or inflammation- associated pain.

DESCRIPTION

PHENOXYBENZAMINE FOR PAIN

FIELD OF THE INVENTION

(001) The invention relates to compositions and formulations for

intranasal/inhalation administration comprising phenoxybenzamine and/or related haloalkylamines, and methods of use thereof, for treatment of subjects suffering from acute and chronic pain syndromes, e.g., sustained relief of local and non-regional pain initiated or maintained by the sympathetic nervous system, either peripherally or centrally in subjects suffering, e.g., from reflex sympathetic dystrophy (RSD)/complex regional pain syndrome (CRPS), neuropathic and/or inflammation-associated pain. The invention further relates to an article of manufacture, e.g., apparatus/device for therapeutic delivery comprising the compositions and formulations described herein, and a method of manufacturing and using said article.

BACKGROUND OF THE INVENTION

(002) Reflex sympathetic dystrophy (RSD) is frequently categorized as a form of complex regional pain syndrome (CRPS). The term RSD/CRPS is commonly used to designate this type of chronic pain syndrome that usually follows trauma or surgery to an extremity. The pathologic mechanism of RSD/CRPS is not completely understood, however, it is considered to represent a syndrome that is maintained and exacerbated by actions of the sympathetic nervous system. A particularly insidious nature of the syndrome is that it progresses to a point where it no longer has any relationship to the initial trauma (which may have healed completely). The pain syndrome at this stage represents an altered sensory perception in the central nervous system and is self propagating, thus the term "reflex" sympathetic dystrophy.

(003) Administration of phenoxybenzamine has been reported for early stages of RSD/CRPS pain using an intravenous regional block of an affected extremity (Inchiosa M. et al., U.S. Patent No. 5,898,035). This procedure is usually carried out by physician specialists trained in this technique. Intravenous (injectable) administration of

phenoxybenzamine was also previously reported for treating high blood pressure (Ideda M. et al., Effect of phenoxybenzamine on portal venous pressure in patients hypertension; Amer. J. Gastroenterology (1979) 71:389-394).

CLAIMS (20)

What is claimed is:

1. 1. A pharmaceutical composition for intranasal and/or inhalation administration

   comprising a haloalkylamine and/or a pharmaceutically-acceptable salt thereof.

2. 2. The composition of claim 1, wherein said haloalkylamine is selected from the group consisting of phenoxybenzamine and dibenamine.

3. 3. The composition of claim 1, wherein said haloalkylamine is phenoxybenzamine.

4. 4. The composition of claim 1, wherein the composition is a selected from the group consisting of liquid, dry powder, aerosol and non-aerosol formulations.

5. 5. The composition of claim 4, wherein the composition is a dry powder formulation.

6. 6. The composition of claim 5, wherein the powder has an average particle size of about 0.1 μιη to about 50 μιη.

7. 7. The composition of claim 4, wherein the composition is a liquid formulation

   selected from the group consisting of spray and drops.

8. 8. A method for treatment of pain syndromes comprising administering to a subject in need thereof, the composition of claim 1 in an amount effective to achieve sustained pain relief of local and/or non-regional pain.

9. 9. The method of claim 8, wherein the composition is administered in an amount of less than about 10 mg per dose.

10. 10. The method of claim 8, wherein the composition is administered in an amount of about 1 mg to about 3 mg per dose.

11. 11. The method of claim 8, wherein the composition is administered as a regimen over a prolonged period of time.

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(004) Oral administration of phenoxybenzamine has also been reported for treatment of RSD/CRPS. For example, Ghostine et al. reported oral administration of 40- 120 mg of phenoxybenzamine to RSD patients for 6 to 8 weeks and showed that while the treatment was beneficial, postural hypotension was a prominent side effect in about 45% of the patients. Further, some patients also reported ejaculatory problems (Ghostine S.Y. et al., Phenoxybenzamine in the treatment of causalgia, J. Neurosurg., (1984) 60: 1263-1268).

(005) The existence of serious side effects and the need to continue therapy for long periods (e.g., 6-9 weeks), substantially reduces the value of oral phenoxybenzamine for the treatment of RSD/CRPS. Thus, because of the devastating and debilitating effects of RSD/CRPS and in view of the limited and often unsuccessful options for its treatment, there is a pressing need for therapeutic approaches/agents that are safe, efficacious, well- tolerated, which can be administered more conveniently and over an extended period of time.

SUMMARY OF THE INVENTION

(006) The invention relates to compositions and formulations for

intranasal/inhalation administration comprising phenoxybenzamine and/or related haloalkylamines, and pharmaceutically-acceptable salts thereof, and methods of use thereof, e.g., for treatment of subjects suffering from pain syndromes, e.g., sustained relief of local and non-regional pain initiated or maintained by the sympathetic nervous system, either peripherally or centrally in subjects suffering from reflex sympathetic dystrophy (RSD)/complex regional pain syndrome (CRPS), neuropathic and/or inflammation- associated pain or pain related to nerve injury.

(007) In one aspect of the invention, compositions and formulations for intranasal and/or inhalation administration comprising phenoxybenxamine and/or related

haloalkylamines are provided.

(008) In another aspect of the invention, a method for treatment of pain syndromes in a subject in need thereof comprising administering compositions and formulations for intranasal and/or inhalation administration comprising phenoxybenzamine and/or related haloalkylamines in an amount effective to achieve sustained pain relief of e.g., neuropathic and/or inflammation-associated pain or pain related to nerve injury, is provided. (009) In another aspect of the invention, a method for treatment c in a subject in need thereof comprising administering compositions and formulations for intranasal and/or inhalation administration comprising phenoxybenzamine and/or related haloalkylamines, in an amount effective to inhibit glutamate release over a sustained time period, for achieving sustained pain relief of e.g., neuropathic and/or inflammation- associated pain, is provided.

(0010) In another aspect of the invention, a method for treatment of non-regional pain in a subject suffering from reflex sympathetic dystrophy (RSD) comprising administering to the subject compositions and formulations for intranasal and/or inhalation administration comprising phenoxybenzamine and/or related haloalkylamines, in an amount effective to inhibit glutamate release over a sustained time period, for achieving sustained pain relief is provided.

(0011) In another aspect of the invention, a method for treatment of pain syndromes in a subject suffering from an inflammatory condition, comprising administering to the subject compositions and formulations for intranasal and or inhalation administration comprising phenoxybenzamine and/or related haloalkylamines, in an amount effective to achieve sustained pain relief of e.g., neuropathic and/or inflammation- associated pain, is provided.

(0012) In another aspect of the invention, an article of manufacture, e.g., apparatus/device for therapeutic delivery comprising any of the compositions and formulations described herein, optionally with a label and/or instructions for use in treatment of pain syndromes, e.g., for achieving sustained relief of local and non-regional pain initiated or maintained by the sympathetic nervous system, either peripherally or centrally in subjects suffering from reflex sympathetic dystrophy (RSD)/complex regional pain syndrome (CRPS), neuropathic and/or inflammation-associated pain.

(0013) In yet another aspect of the invention, a method of manufacturing an article of manufacture, e.g. , apparatus/device

12. 12. The method of claim 8, wherein the pain is initiated or maintained

sympathetic nervous system, either peripherally or centrally.

13. 13. The method of claim 8, wherein the pain syndrome is selected from the group

consisting of reflex sympathetic dystrophy (RSD)/complex regional pain syndrome (CRPS), neuropathic pain, inflammation- associated pain and pain related to nerve injury.

14. 14. The method of claim 8, wherein the pain syndrome is reflex sympathetic dystrophy (RSD)/complex regional pain syndrome (CRPS).

15. 15. The method of claim 8, wherein the composition is administered in an amount effective to achieve irreversible antagonism of calmodulin in the nervous system.

16. 16. The method of claim 8, wherein the composition is administered in amount

effective to inhibit glutamate release in the nervous system over a sustained time period.

17. 17. An article of manufacture comprising:

(i) a container adapted for intranasal and/or inhalation administration;

(ii) a composition within the container, wherein the composition comprises a composition for intranasal and/or inhalation administration comprising a haloalkylamine and/or a pharmaceutically-acceptable salt thereof, for therapeutic delivery to a subject in need thereof, an amount effective to achieve sustained pain relief of local and/or non-regional pain.

18. 18. The article of manufacture of claim 17, further comprising a label and/or

instructions directing use and/or administration of the composition to said subject.

19. 19. The article of manufacture of claim 17, wherein the composition is

phenoxybenzamine and/or a pharmaceutically-acceptable salt thereof.

20. 20. The article of manufacture of claim 17, wherein the composition is a dry powder.

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for therapeutic delivery comprising any of the compositions and formulations described herein, packaging the composition to obtain an article of manufacture and instructing, directing or promoting the use of the

composition/article of manufacture for any of the uses described herein. Such instructing, directing or promoting includes advertising. BRIEF DESCRIPTION OF THE DRAWINGS

(0014) Figure 1: Changes in U.V. absorbance of phenoxybenzamine following dissolution in normal saline at room temperature.

DETAILED DESCRIPTION OF THE INVENTION

(0015) The disclosure herein relates to compositions and formulations for intranasal/inhalation administration comprising phenoxybenzamine and/or related haloalkylamines, and methods of use thereof for treatment of acute and chronic pain syndromes in a subject in need thereof, e.g., in subjects suffering from pain when the pain component is initiated or maintained by the sympathetic nervous system, either

peripherally or centrally. In that respect, the compositions and formulations disclosed herein are useful for treatment of RSD/CRPS, and other pain syndromes involving neuropathic pain and/or nerve injury. The compositions and formulations disclosed herein are further useful for the treatment of inflammatory condition-associated pain syndromes.

(0016) Herein, the terms "RSD/CRPS," "pain syndrome," and "neuropathic pain" are used as per the accepted definitions in the field (Bonica J. J. et al., The Management of Pain, Second Ed., Lea and Febiger, Philadelphia, 1990, pp. 220-243), and as described in U.S. Patent No. 5,898,035, the disclosure of which is hereby incorporated herein by reference with respect to the disclosures of treatment subjects, conditions and active compounds. Diagnostic criteria used to identify a subject suffering from the above syndromes/conditions would be apparent to a person of skill in the art {see, e.g., Stanton-Hicks M. et al., Reflex sympathetic dystrophy: changing concepts and taxonomy, Pain, (1995) 63: 127-133.)

(0017) Herein, the term "inflammation- associated pain" refers to pain associated with inflammatory conditions. Inflammatory conditions are defined as per the standard medical textbook usage and diagnostic criteria for such conditions are well-known to a medical practitioner.

(0018) As used herein, the term "non-regional pain" refers to pain which has spread to areas beyond a local area of trauma or insult/injury. Typically, occurrence of non- regional pain is at later stages of a pain syndrome where pain has progressed to a point where it no longer has a discrete relationship to the initial trauma or insult/injury. Thus, non-regional pain associated with a pain syndrome at this stage represents an altered sensory perception in the central nervous system and may be self propagating. (0019) As used herein, "related haloalkylamines" include, but not compounds that have structural similarity to phenoxybenzamine, and which also share some of its adrenergic-related effects. Such compounds are known to persons of skill in the art, e.g., Iversen et al. studied a total of 21 haloalkylamine derivatives, including phenoxybenzamine, for adrenergic-related effects (Inversen L.L. et al., Inhibition of catecholamine uptake in the isolated heart by haloalkylamines related to

phenoxybenzamine, Br. J. Pharmac, (1972) 46:647-657; see, e.g., Table 1 spanning p. 650- 651). The chemical cyclization products that are formed spontaneously when

phenoxybenzamine or other haloalkylamines are placed in solution are also within the scope of the invention {see, e.g., Adams and Kostenbauder, Phenoxybenzamine stability in aqueous ethanolic solutions. II. Solvent effects on kinetics, International J of

Pharmaceutics, (1985) 25:313-327). The disclosure of compounds and their structural formulae in the above two publications is incorporated herein by reference.

(0020) Pharmaceutically-acceptable derivatives and salts thereof of

phenoxybenzamine and/or related haloalkylamines, and their use for the methods described herein are also within the scope of the present invention. Such salts may be prepared using knowledge in the pharmaceutical arts.

(0021) As used herein, "treatment" or "treating" refers to obtaining a desired pharmacologic effect. The effect may be therapeutic in terms of improving pain in a subject suffering from a pain syndrome, slowing down or reducing severity/intensity of pain, arresting progression of pain, reducing the frequency of pain episodes, increasing/delaying the duration between pain episodes, reducing/ameliorating the risk of progression and/or adverse symptoms/effects attributable to the disease including inflammatory and/or neurological and/or neuromuscular symptoms, and/or inducing a measurable reduction of morbidity associated with the pain syndrome and to stabilize the condition to improve quality of life.

(0022) Compositions and formulations for intranasal/inhalation administration comprising phenoxybenzamine and/or related haloalkylamines may be administered prophylactically. As used herein, "prophylactic" administration refers to preemptive administration in conjunction with surgeries that are known to have a relatively high risk of development of a chronic neuropathic pain syndrome. This includes, e.g., hand/foot surgery and amputations. Prophylactic administration of the therapeutic composition(s) of the invention may also be provided during the early period following an injury that is

viewed as high risk for development of a chronic neuropathic syndrome. (0023) The advantage of administering phenoxybenzamine and/or haloalkylamines via intranasal and inhalation routes is that they are non-invasive, can be self-administered by the patient, and represent efficient routes for rapid and complete plasma delivery. Moreover, administration via intranasal and inhalation routes results in systemic distribution of the drug, and are therefore useful for treatment of pain syndromes, e.g., RSD/CRPS at early stages (where the pathology is localized to an extremity), as well as for advanced stages (where the pathology has spread to multiple sites in the body). Additionally, intranasal/inhalation routes of administration allows for a rapid onset of effect because venous drainage from the nasal mucosa and the pulmonary alveoli passes completely and directly into the circulation to the heart. Rapid onset of effect facilitates the opportunity for the physician and/or the patient to more effectively titrate the dose needed for an adequate therapeutic effect.

(0024) Chemically, phenoxybenzamine is a weak base with a pka (dissociation constant) of 6.58 and an octanol/water logP partition coefficient of 4.6. Thus, it is highly lipophilic and would pass across cell membranes readily. Therefore, intranasal/inhalation routes of administration represent efficient routes for the rapid and complete delivery of phenoxybenzamine to the plasma. Further, while oral phenoxybenzamine has relatively low oral bioavailability (20%-30%), administration via intranasal and inhalation routes bypasses first-pass metabolism by the liver (where it is primarily metabolized), thus resulting in increased bioavailability while avoiding unwanted side effects of oral administration. A further advantage of the present invention is that intranasal and inhalation routes allow for administration of lower dosages (e.g., less than 10 mg, e.g., about 1 mg - about 3mg per administration) of compound(s) disclosed herein.

(0025) Inchiosa M. et al. reported a favorable therapeutic response in CRPS I patients using Dibenzyline® (at a maximum dose of 10 mg/day), an FDA-approved oral preparation of phenoxybenzamine (Inchiosa et al., Treatment of complex regional pain syndrome type I with oral phenoxybenzamine: rationale and case reports; Pain Practice, (2008) 8(2): 125-132). These studies focused on role of phenoxybenzamine as a noncompetitive (irreversible; long-lasting) a-adrenergic antagonist via blockade of

adrenergically- sensitized blood vessels and sensory fibers in the affected region of pain. Such administration is not within the scope of the present invention.

(0026) Action of phenoxybenzamine in non-competitive (irreversible) antagonism of calmodulin has been studied (Cinimo et al., Characteristics of the binding of phenoxybenzamine to calmodulin., 1988, Biochem. Pharmacol. 37:2739-45; Lukas T. J. et al., Drug-protein interactions: isolation and characterization of covalent a(phenoxybenzamine and calmodulin, 1985, Biochemistry, 24: 151-7; Earl C. Q. et al., Interactions of alpha adrenergic antagonist with calmodulin. 1984, Life Sci. 35:525-34). Calmodulin plays a critical role in synaptic transmission. In association with

depolarization of the presynaptic nerve ending, Ca ++ enters the nerve terminal, combines with calmodulin, which then activates a Ca ++/calmodulin-dependent protein kinase; this kinase then phosphorylates synapsin I, which mediates the mobilization of vesicles containing neuromediator, allowing for their release into the synaptic cleft. This process is believed to operate in release of glutamate, and in central sensitization to pain mediated via action of glutamate on N-methyl-D-aspartate (NMD A) receptors. In central neurons, Ca ++/calmodulin-dependent protein kinase can be autophosphorylated to a form that is no longer dependent upon Ca++ to maintain its active state. This results in a persistence of its effects, e.g., sustained glutamate release and may thus contribute to amplification of pain perception in certain syndromes (Siegelbaum S. A. et al., Modulation of synaptic transmission: second messengers; in Principles of Neural Science, 4th Ed., E. R. Kandel, J. H. Schwartz, and T. M. Jessell, eds. McGraw-Hill, New York, 2000; pp.229-52).

(0027) The non-competitive (irreversible) antagonism of calmodulin, by phenoxybenzamine provides a long duration block of the sensitized pain pathways, and helps mediate gradual reversal of the sensitized state and a return to basal levels of transmission, i.e., to levels of sensory input that are more consistent with the degree of healing that has taken place at the initial source of afferent input. Thus, the present invention relates to Ca ++/calmodulin-dependent protein kinase as a therapeutic molecular target for treatment of pain by phenoxybenzamine, or other compounds described herein.

(0028) The compositions and formulations for intranasal and/or inhalation administration comprising phenoxybenzamine and/or related haloalkylamines are also useful for treatment of subjects suffering from neuropathic conditions as well as for treatment of subjects suffering from pain syndromes that are not considered to have a sympathetic nervous system component, e.g., subjects suffering from diabetic peripheral neuropathy; postherpetic neuralgia; trigeminal neuralgia; phantom limb pain; carpal tunnel syndrome; multiple sclerosis-associated central neuropathic pain; and spinal cord injury-associated neuropathic pain.

(0029) Phenoxybezamine has been shown to block a -adrenergic receptors on immune cells, and additionally, to block calmodulin-mediated release of inflammatory cytokines from these cells. Phenoxybenzamine has also been tested in an animal model of inflammatory pain (Chang M. et al., Evaluation of phenoxybenzamine in pain following gene expression studies and connectivity mapping. Molecular Pain, 2010, 6:56). However, based on such disclosure, effectiveness of intranasal or inhalation administraton of the compositions disclosed herein would not be apparent.

(0030) In certain embodiments, the compositions and formulations disclosed herein are also useful for treatment of pain syndromes in a subject suffering from an inflammatory condition e.g., arthritic conditions, ankylosing spondylitis, systemic sclerotic conditions, etc. In certain other embodiments, the subject is not suffering from an inflammatory condition.

(0031) The compositions and formulations for intranasal and inhalation

administration are also useful for some of the established indications of

phenoxybenzamine, i.e., to control episodes of hypertension and sweating in

pheochromocytoma patients (pheochromocytoma is a tumor of the adrenal medulla, which results in high circulating levels of the endogenous catecholamines, norepinephrine and epinephrine). Phenoxybenzamine produces long-lasting insurmountable block of a- adrenergic receptors, thereby preventing the surges of blood pressure that would occur when large quantities of catecholamines are released from the tumor. When circulating levels of catecholamines are low, the drug produces a vasodilation, relative to basal vessel tone, due to blockade of sympathetic nerve transmission to blood vessels.

Phenoxybenzamine also has an accepted off-label oral use for treatment of urinary symptoms associated with benign prostatic hypertrophy, and is also accepted as having potential value in the treatment of peripheral vascular diseases, such as Raynaud's syndrome (Drug information for the health care professional (USP DI), 21st Edition, Vol. 1, Micormedex, Englewood, CO; 2001: 00. 2416-7), thus the compositions and

formulations for intranasal and inhalation administration disclosed herein are also useful for treatment of these conditions.

(0032) The active agents {i.e., phenoxybenzamine and/or related haloakylamines) of the compositions and formulations of the invention may be administered intranasally or by inhalation. Further, a composition and/or formulation of the invention may contain one or more of said active agents.

(0033) Phenoxybenzamine is approved for oral administration (Dibenzyline®), however, only approximately 20% of a given dose is absorbed into the plasma {i.e., 20% bioavailability). In some embodiments of the present invention the dose delivered by intranasal or inhalation spray is adjusted to 20% of the accepted oral dose range in humans. Compositions for nasal/inhalation administration are generally liquid fora aqueous solutions) for administration as a spray or in the form of drops. Suspension and powder formulations for intranasal/inhalation administration, e.g., insufflations, may be also used (with longer shelf-life). The powdered form, protected from exposure to water vapor, is stable over extended periods of time.

(0034) Because of its noncompetitive (irreversible) mechanism of antagonism of a- adrenergic receptors, the drug does not have a true half time of elimination. The half time of its action is best described as the half time of re-synthesis of a-adrenergic receptors, or the slow spontaneous hydrolytic cleavage of the covalent linkage, which is a matter of days. The half time of re-synthesis of calmodulin is another factor that determines the duration of action of phenoxybenzamine. A person of skill in the art would be able to determine the dosage amounts in view of this and other disclosure herein.

(0035) Depending on the delivery device that is used, the drug may be admixed with an essentially inert carrier, such as lactose, so that a metered unit of administration would deliver the desired dose of drug.

(0036) Formulations for inhalation may be prepared as an aerosol, either a solution aerosol in which the active agent is solubilized in a carrier (e.g., propellant) or a dispersion aerosol in which the active agent is suspended or dispersed throughout a carrier and an optional solvent. Non-aerosol formulations for inhalation may take the form of a liquid, typically an aqueous suspension, although aqueous solutions may be used as well. In such a case, the carrier is typically a sodium chloride solution having a concentration such that the formulation is isotonic relative to normal body fluid. In addition to the carrier, the liquid formulations may contain water and/or excipients including an antimicrobial preservative (e.g., benzalkonium chloride, benzethonium chloride, chlorobutanol, phenylethyl alcohol, thimerosal and combinations thereof), a buffering agent (e.g., citric acid, potassium metaphosphate, potassium phosphate, sodium acetate, sodium citrate, and combinations thereof), a surfactant (e.g., polysorbate 80, sodium lauryl sulfate, sorbitan monopalmitate and combinations thereof), and/or a suspending agent (e.g., agar, bentonite,

microcrystalline cellulose, sodium carboxymethylcellulose, hydroxypropyl

methylcellulose, tragacanth, veegum and combinations thereof). Non-aerosol formulations for inhalation may also comprise dry powder formulations, particularly insufflations in which the powder has an average particle size of, for example about 0.1 pm to 50 pm, preferably 1 m to about 25 pm. (0037) The compounds and compositions of the invention may be least once a day. They may be administered over extended periods of time, as a regimen, e.g., for several days or for several weeks, for example, from two to four weeks, and may be administered, for example, once a day to once a week to once a month, e.g., daily, weekly or monthly. For example, for initial treatment, administration can be carried out daily for a number of days (e.g., 5 to 20 days) and then continued in a once a week, or once a month, regimen for a period of weeks, as needed (e.g., 4 to 12 weeks or more).

(0038) A daily effective amount of the composition of the invention may be provided, for example, in a single dose. The amount per administered dose, and duration and frequency will depend on factors such as the nature and severity of the condition, age and general health of the subject, the tolerance of the subject to the composition, the response of the disease to therapy and duration and profile of the symptoms experienced by the subject and can be assessed by a person of skill in the art.

(0039) The effective amount of phenoxybenzamine and/or a related haloalkyamine to be administered according to the methods recited herein may be determined by a person of skill in the art using the guidance provided herein and general knowledge in the art. For example, the effective amount may be such as to achieve a physiologically relevant concentration in the body of a mammal, e.g., human, and/or to achieve any of the therapeutic or prophylactic effects described herein. Relevant doses may include from at least 1 mg and above, e.g. from 2 mg and above, e.g., less than 40 mg, or e.g., less than 20 mg, or less than 10 mg, e.g. from 2 mg to 20 mg, e.g. 2 mg to 10 mg or e.g. 2 mg to 5mg or e.g. 2 mg to 4 mg or e.g., 2 mg to 3 mg. Other doses higher than, intermediate to or less than these doses may also be used and may be determined by one skilled in the art following the methods of this invention.

(0040) The invention is further described in the following non-limiting examples.

EXAMPLES

(0041) Example 1: Stability of phenoxybenzamine in normal saline.

(0042) Stability of phenoxybenzamine solutions is dependent upon the nature of the vehicle that is used to dissolve the drug (Lim, L-Y. et ah, Stability of phenoxybenzamine hydrochloride in various vehicles. Am. J. Health-Syst Pharm. 54:2073-2078, 1997). (0043) A phenoxybenzamine solution was prepared by dissolving phenoxybenzamine (U.S. Pharmacopeia, reference standard, 12601 Twinbrook Parkway, Rockville, MD 20852) in normal saline at room temperature. Stability of the

phenoxybenzamine solution was tested by studying changes in U.V. absorbance at several time points e.g., 10 minutes, 3 days, 29 days and 117 days after dissolution.

(0044) As shown in Figure 1, (readings after 10 minutes (solid line) is "time 0"), there were some minor changes after 3 days (dotted line). There were marked changes after 29 days (dashed line which largely overlaps the spectrum after 117 days, the grey line). The transformation (apparently, cyliczation; Adams and Kostenbauder, Phenoxybenzamine stability in aqueous ethanolic solutions. II. Solvent effects on kinetics, International J of Pharmaceutics, (1985) 25:313-327) appears to have been complete by 29 days except for the fact that the grey and dashed lines do not overlap at the very low wavelengths. Thus, there may be some additional changes in the breakdown products after the longest period (117 days). It is apparent that storage requirements of phenoxybenzamine in solution are an important consideration, and demonstrates the advantages of therapeutic delivery of the drug in a dry powder form.

(0045) Example 2: Inhibition of calmodulin by phenoxybenzamine.

(0046) In these studies, the potency of phenoxybenzamine and other known inhibitors of calmodulin, as well as possible potential inhibitors (other haloalkylamine derivatives) is compared.

(0047) Phenoxybenzamine and dibenamine, an analog of phenoxybenzamine are tested for calmodulin inhibition. Also tested for calmodulin-inhibition are amitriptyline (an anti-depressant) and thalidomide, both of which are used in treatment of pain syndromes.

(0048) Calmodulin activity is assayed by detection of conversion of [3H] cyclic adenosine 3',5'-monophosphate to [3H]5' adenosine monophosphate by calmodulin stimulated cAMP phosphodiesterase (Wallace R. W. et al., Assay of calmodulin by Ca^{2+}dependent phosphodiesterase. In: Methods in Enzymology, Vol 102, Means, A.R., and O'Malley, B., eds. New York, Academic Press, 1983; pp.39-47).

(0049) Example 3: Effect of phenoxybenzamine on glutamate release.

(0050) The effect of injected phenoxybenzamine on the release of glutamate into the cerebrospinal fluid (CSF) of rats that are exposed to a mild noxious thermal stimulus (controlled hot plate exposure) is tested. The phenoxybenzamine is inject animals for these experiments to ensure precise dose administration.

(0051) The objective of these experiments is to study in vivo effect of calmodulin inhibition to reduce glutamate release into the CSF. The use of a hot plate exposure as a sensory stimulus is well- acknowledged as a suitable model for testing, e.g., anesthetics (Kizelshteyn G. et al., Enhancement of bupivacine sensory blockade of rat sciatic nerve by combination with phenol. Anes Analg 74:499-502, 1992). CSF levels of glutamate in rats prior to and following controlled hot plate exposure in animals that receive injections of phenoxybenzamine or the vehicle control is tested. Glutamate is also an important sensory mediator at supraspinal sites, but it is more convenient to sample CSF in the spinal canal rather than in the brain.

(0052) Further, the analgesic effect of phenoxybenzamine in this model is tested by evaluating whether phenoxybenzamine prolongs the latency time for the animals to respond to the thermal stimulus. The licking of the hind paws by rats is considered a characteristic behavioral response to the thermal stimulus. A prolongation of latency time is indicative of a direct analgesic effect of phenoxybenzamine. If the sensory blocking effect of the drug is so strong as to put the animal at risk of burn injury to the paws, a defined time limit that mandates the removal of the animal from the hot plate, is strictly followed. Amitriptyline and thalidomide are also tested for their effects on CSF glutamate concentrations and behavioral responses to stimuli. This model is also used to study the efficacy of other haloalkylamines.

(0053) Glutamate CSF levels respond to various insults and has been studied for example in brain hypoxia-ischemia models (Castillo J. et al., Progression of ischaemic stroke and excitotoxic aminoacids. Lancet 349(9045):79-83, 1997). CSF glutamate concentration is analyzed using a glutamate dehydrogenase-based assay of L-glutamic acid. The assay involves the formation of a fluorescent derivative of NAD+, which is

proportional to the amount of glutamate that is reacted by glutamate dehydrogenase (Perez- de la Mora M et al., A glutamate dehydrogenase-based method for the assay of L-glutamic acid: Formation of pyridine nucleotide fluorescent derivatives. Anal Biochem 180:248- 252, 1989.) This assay has substantially more sensitivity than that required for the measurement of glutamate in CSF. The assay is linear down to 250 pmol of glutamate per assay tube. A 250 µl sample of normal rat CSF contains approximately 600 pmol of glutamate (van-Landeghem F. K. et al., Glia 35: 167-179, 2001).
(0054) Example 4: Intranasal and/or Inhalation administration of phenoxybenzamine for CRPS treatment.

(0055) Human subjects are selected based on known clinically defined criteria for CRPS (Inchiosa M. et al., Treatment of complex regional pain syndrome type I with oral phenoxybenzamine: rationale and case reports; Pain Practice, (2007) 8(2): 125- 132). Study subjects include those with localized pain as well as those with advanced stages wherein the pathology has spread to multiple sites in the body.

(0056) The compositions and formulations disclosed herein are administered once or more than once daily. The following tests are performed as outcome measures of treatment (i.e., assessment of sustained pain relief) as described in Malik et al., 1998 (Mailk V. K. et al., Intravenous regional phenoxybenzamine in the treatment of reflex sympathetic dystrophy., Anesthesiology, 1998, 88:823:827). Changes in the visual analog pain scale (VAS) after treatment is a primary outcome measure. Additionally, quantitative assessments of changes in muscle work (indirect measure of pain), and changes in skin temperature of an affected area, are carried out. The measures of muscle work include hand-grip strength of an upper extremity, or foot pressure on a scaling device for a lower extremity. Range of motion evaluation is carried out for more diffuse pain syndromes. Finally, the ability of an individual to return to work or regain performance of physical activities is also rated.

(0057) Additional outcome measures include analysis of changes in inflammatory cytokine levels (local and/or plasma) in treated subjects. In pathologies that are largely restricted to an extremity, pre- and post-treatment cytokine levels are measured in the venous effluent from that limb. In cases of diffuse pathology, plasma levels are studied. The pro-inflammatory cytokine, tumor necrosis factor alpha (TNF-a), interleukins IB and 6 are analyzed using quantification methods available, e.g., Luminex-100 bead-based fluorescence flow cytometry assays.

PATENT CITATIONS

Cited Patent	Filing date	Publication date	Applicant	Title
US5070084 *	Feb 26, 1990	Dec 3, 1991	Campbell James N	Treatment of sympathetically maintained pain
US5898035 *	Aug 28, 1996	Apr 27, 1999	New York Medical College	Formulations of haloalkylamines and local anesthetic and methods for the treatment of reflex sympathetic dystrophy (RSD)
US20010000261 *	Dec 7, 2000	Apr 12, 2001	Redano Richard T.	Method for accelerating the delivery of a vasodilating agent to the penis
US20020161016 *	Nov 21, 2001	Oct 31, 2002	Peter Tam	As-needed administration of tricyclic and other non-SRI antidepressant drugs to treat premature ejaculation
US20070298999 *	Jun 26, 2007	Dec 27, 2007	Zaijie Wang	Method for treating pain with a calmodulin inhibitor
US20090156581 *	Apr 14, 2006	Jun 18, 2009	Board Of Trustrees Of Michigan State University	Aminergic pharmaceutical compositions and methods
US20100113563 *	Dec 23, 2009	May 6, 2010	Zaijie Wang	Method for Treating Pain with a Calmodulin Inhibitor

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Citing Patent	Filing date	Publication date	Applicant	Title
WO2015035308A3 *	Sep 8, 2014	Oct 29, 2015	The University Of Montana	Method of reducing neuronal cell death with haloalkylamines

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CLASSIFICATIONS

International Classification	A61K31/13, A01N33/14
Cooperative Classification	A61K31/137, A61K9/0073, A61K9/0043, A61K31/138

LEGAL EVENTS

Date	Code	Event	Description
Jan 16, 2013	121	Ep: the epo has been informed by wipo that ep was designated in this application	**Ref document number:** 12790100 **Country of ref document:** EP **Kind code of ref document:** A1

RHC-0080

Date	Code	Event	Description
Nov 25, 2013	NENP	Non-entry into the national phase in:	**Ref country code:** DE
			Ref document number: 12790100
Jun 11, 2014	122	Ep: pct app. not ent. europ. phase	**Country of ref document:** EP
			Kind code of ref document: A1